

Steven M. Donn
Sunil K. Sinha *Editors*

Manual of Neonatal Respiratory Care

Third Edition

 Springer

Manual of Neonatal Respiratory Care

Steven M. Donn • Sunil K. Sinha
Editors

Manual of Neonatal Respiratory Care

Third Edition

 Springer

Editors

Steven M. Donn, MD, FAAP
Professor of Pediatrics
Division of Neonatal–Perinatal Medicine
C.S. Mott Children’s Hospital
Faculty Associate, Center for Global Health
School of Public Health
University of Michigan Health System
Ann Arbor, MI, USA

Sunil K. Sinha, MD, PhD, FRCP, FRCPCH
Professor of Pediatrics
University of Durham
Consultant in Pediatrics and Neonatal
Medicine
The James Cook University Hospital
Department of Neonatal Medicine
Middlesbrough, Marton-in-Cleveland, UK

ISBN 978-1-4614-2154-2 e-ISBN 978-1-4614-2155-9
DOI 10.1007/978-1-4614-2155-9
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2012930134

© Springer Science+Business Media, LLC 2012

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, LLC, 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

While the advice and information in this book are believed to be true and accurate at the date of going to press, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

*To all those parents in the past 30 years
who have entrusted me with the care
of their most precious possessions*

Steven M. Donn

*To all those who have pursued careers
in the care of newborn infants*

Sunil K. Sinha

Foreword

A successful transition from fetal to neonatal life is dependent upon the profound cardiorespiratory adaptations occurring at this time. Unfortunately, these events frequently require medical intervention, especially in preterm infants. The consequences of the resultant pathophysiologic changes and therapeutic interventions in such neonates may have long lasting effects on the developing respiratory system and even the neurodevelopmental outcome of this high-risk population.

Recognition of the importance of neonatal respiratory management was an early milestone in the history of neonatology. The role of surfactant deficiency in the etiology of neonatal respiratory distress syndrome was sealed over 50 years ago, and this paved the way for the introduction of assisted ventilation for this population in the 1960s. I was privileged to be introduced to neonatal pediatrics in the early 1970s at a time when the advent of continuous positive airway pressure demonstrated how physiologic insight can be translated into effective therapy. The decade of the 1970s offered so many other innovations in neonatal respiratory care. These included noninvasive blood gas monitoring, xanthine therapy for apnea, and our first real understanding of the pathogenesis and management of meconium aspiration syndrome, group B streptococcal pneumonia, and persistent fetal circulation or primary pulmonary hypertension of the newborn, three frequently interrelated conditions. The decade ended in remarkable fashion with the introduction of exogenous surfactant therapy and recognition that the novel new technique of high-frequency ventilation allows effective gas exchange in sick neonates.

The last 30 years have enabled us to build drastically on the foundation of this earlier period in neonatal respiratory management. The improved survival of extremely low birth weight infants has been nothing short of spectacular. For preterm infants, the focus is now clearly to reduce the unacceptably high incidence of bronchopulmonary dysplasia. However, many key questions in neonatal respiratory care still need to be addressed. What constitutes optimal ventilatory strategy and optimal targets for gas exchange as reflected in levels of PaO_2 and PaCO_2 ? What is the risk/benefit ratio of current and future pharmacologic adjuncts to ventilatory

support, such as inhaled nitric oxide, xanthine, or antioxidant therapy, to name a few? How can we safely support ventilation and provide pharmacotherapy in the most noninvasive manner?

For preterm or term infants with malformations of the respiratory system, advances in pre- and postnatal imaging and surgical techniques hold promise for improved outcome. Great strides are being made simultaneously in our understanding of the molecular basis for normal and abnormal lung development. Furthermore, it is being increasingly recognized that genotypic characteristics may greatly influence the consequences of subsequent environmental exposures on lung development. These scientific advances need to be translated into improving adverse neonatal outcomes, such as the unacceptably high rate of wheezing disorders and asthma in the survivors of neonatal intensive care. As care providers to neonates, it is our responsibility to encourage clinical trials and other patient-based investigation that will allow us to optimize the outcome of neonatal respiratory care.

The third edition of the *Manual of Neonatal Respiratory Care* is comprehensive and provides an important educational tool to address many of these challenges. It is, again, thoroughly edited by the accomplished trans-Atlantic team of Steven Donn and Sunil Sinha. Once again, they have assembled physician/scientist leaders in the field of Developmental Pulmonology who provide a true international perspective to neonatal respiratory care. Both prior and new contributors provide a concise overview that spans neonatal physiology, pathogenesis of disease, and unique approaches to management of both simple and complex neonatal respiratory disorders. The result is a comprehensive text that provides a strongly international insight into neonatal respiratory care in a user-friendly, practical format.

Cleveland, OH, USA

Richard J. Martin, MBBS, FRACP

Preface

It is indeed a privilege for us to edit the third edition of the *Manual of Neonatal Respiratory Care*, and we were honored when Springer Science+Business Media approached us to do this.

In the years that have passed since the second edition, much has transpired, some technological and some philosophical. Microprocessor-based technology continues to refine the equipment at our disposal and to offer us almost limitless ways to manage neonatal respiratory failure. At the same time, there has been a resurgence in the philosophy of minimal intervention, giving rise to the new popularity of continuous positive airway pressure and noninvasive ventilation. We have entered the age of evidence-based medicine, emphasizing the importance of the randomized, controlled trial. We have seen enormous growth in information technology and worldwide access to it. Therapeutic options also continue to expand, but greater care must be taken as survival of even more premature babies accentuates their toxicities and complications.

We have maintained the same outline format for the third edition, appreciating the positive feedback we have received from many that this is conducive to bedside use. We have not only updated previous chapters, we have added newer ones to reflect changes in practice, equipment, and science. Some of these include an expanded focus on oxygen toxicity, control of oxygen delivery, use of nasal cannula therapy, noninvasive ventilation, newer ventilators, management of hemodynamics, home ventilation, interpreting medical literature, medico-legal issues, and an expansive contemporary bibliography on neonatal respiratory care.

Our list of contributors represents a world-class group of scientists, clinicians, and experts in their respective fields. We are indebted to them for taking the time and effort to provide their insights and knowledge. The *Manual of Neonatal Respiratory Care* would also not have been possible without the efforts of many “behind the scenes” individuals, including our development editor, Mike Griffin, and our acquisitions editor, Shelley Reinhardt, both of Springer; Vicky Hall in Middlesbrough; and Susan Peterson in Ann Arbor, who coordinated the efforts of more than 50 contributors,

and somehow managed to get all 85 chapters formatted the same way (an incredible feat!). Lastly, we acknowledge our wives, Paula Donn, and Lalita Dean, for their patience and sacrifices while we put the *Manual* together.

Change will continue to occur at a rapid pace. What we hope this edition accomplishes is the establishment of fundamentals that will enable the clinician to develop the ability to assimilate change in a physiologically sound way while providing the best possible care to his or her patients.

Ann Arbor, MI, USA
Middlesbrough, UK

Steven M. Donn
Sunil K. Sinha

Contents

List of Abbreviations	xxv
Part I Lung Development and Maldevelopment	
1 Development of the Respiratory System.....	3
Vinod K. Bhutani	
2 Developmental Lung Anomalies.....	17
Mohammad A. Attar and Subrata Sarkar	
Part II Principles of Mechanical Ventilation	
3 Spontaneous Breathing.....	27
Emidio M. Sivieri and Vinod K. Bhutani	
4 Pulmonary Gas Exchange	39
Vinod K. Bhutani	
5 Oxygen Therapy.....	49
Win Tin	
6 Oxygen Toxicity.....	55
Ola Didrik Saugstad	
7 Pulmonary Mechanics	61
Emidio M. Sivieri and Vinod K. Bhutani	
8 Basic Principles of Mechanical Ventilation	73
Waldemar A. Carlo, Namasivayam Ambalavanan, and Robert L. Chatburn	
9 Classification of Mechanical Ventilation Devices.....	87
Waldemar A. Carlo, Namasivayam Ambalavanan, and Robert L. Chatburn	

10 Ventilator Parameters..... 93
 Waldemar A. Carlo, Namasivayam Ambalavanan,
 and Robert L. Chatburn

11 Respiratory Gas Conditioning and Humidification..... 99
 Andreas Schulze

Part III Procedures and Techniques

12 Clinical Examination 109
 Avroy A. Fanaroff and Jonathan M. Fanaroff

13 Neonatal Resuscitation 121
 Janet M. Rennie

14 Laryngoscopy and Endotracheal Intubation..... 129
 Karen Wiseman and Steven M. Donn

15 Vascular Access 137
 Steven M. Donn

16 Tracheostomy 143
 Steven M. Donn

Part IV Monitoring the Ventilated Patient

17 Continuous Monitoring Techniques 149
 Christian F. Poets

18 Pulse Oximetry 155
 Win Tin and Samir Gupta

19 Interpretation of Blood Gases..... 159
 David J. Durand

20 Neonatal Pulmonary Graphics 167
 Joanne Nicks

21 Radiography 181
 Ramon Sanchez and Peter J. Strouse

22 Transillumination..... 211
 Steven M. Donn

23 Echocardiography..... 213
 Jonathan Wyllie

24 Bronchoscopy 225
 Neil N. Finer

Part V Non-invasive Ventilatory Techniques

25 Nasal Cannula Therapy..... 231
 Andrea L. Lampland and Mark C. Mammel

26 Continuous Positive Airway Pressure 237
 Colin J. Morley

27 Non-invasive Ventilation..... 247
 Brigitte Lemyre and Haresh Kirpalani

Part VI Ventilatory Modes and Modalities

28 Positive End-Expiratory Pressure 255
 Sarvin Ghavam and Haresh Kirpalani

29 Intermittent Mandatory Ventilation 261
 Steven M. Donn and Sunil K. Sinha

30 Synchronized Intermittent Mandatory Ventilation 267
 Steven M. Donn and Sunil K. Sinha

31 Assist/Control Ventilation 271
 Steven M. Donn and Sunil K. Sinha

32 Volume-Targeted Ventilation 275
 Steven M. Donn and Sunil K. Sinha

33 Pressure Control Ventilation..... 281
 Steven M. Donn

34 Pressure Support Ventilation 285
 Sunil K. Sinha and Steven M. Donn

35 Proportional Assist Ventilation..... 291
 Andreas Schulze

Part VII High-Frequency Ventilation

36 High-Frequency Ventilation: General Concepts..... 301
 J. Bert Bunnell

37 High-Frequency Jet Ventilation..... 319
 Martin Keszler

38 High-Frequency Oscillatory Ventilation..... 327
 Reese H. Clark

Part VIII Commonly Used Neonatal Ventilators

39	VIP Bird Gold Ventilator	341
	Michael A. Becker and Steven M. Donn	
40	AVEA Ventilator	349
	Michael A. Becker and Steven M. Donn	
41	Bear Cub 750_{psy}	357
	Joanne Nicks	
42	Newport Wave	363
	Robert L. Chatburn and Teresa A. Volsko	
43	Newport e360	369
	Cyndy Miller	
44	Dräger Babylog VN500 Infant and Pediatric Ventilator	379
	Donald M. Null, Jr.	
45	SERVO-i Ventilator and Neurally Adjusted Ventilatory Assist (NAVA)	387
	Jennifer Beck and Louis Fuentes	
46	SLE5000 and SLE4000 Infant Ventilators	397
	Barbara Pilgrim and Sunil K. Sinha	
47	Bunnell Life Pulse High-Frequency Jet Ventilator	403
	Martin Keszler	
48	Sensormedics 3100A High-Frequency Oscillatory Ventilator	407
	David J. Durand and Jeanette M. Asselin	

Part IX Adjunctive Therapies

49	Hemodynamic Support	417
	Keith J. Barrington	
50	Nutritional Support of the Ventilated Infant	425
	David Adamkin	
51	Surfactant Replacement Therapy	443
	Fernando Moya and Maria-Cristina Javier	
52	Pharmacologic Agents	455
	Varsha Bhatt-Mehta and Steven M. Donn	
53	Automatic Control of Oxygen Delivery	469
	Nelson Claure and Eduardo Bancalari	
54	Sedation and Analgesia	473
	Elaine M. Boyle and Neil McIntosh	

55 Inhaled Nitric Oxide Therapy..... 485
 John P. Kinsella

56 Extracorporeal Membrane Oxygenation..... 497
 Robert E. Schumacher

57 Liquid Ventilation for Neonatal Respiratory Failure 505
 Ronald B. Hirschl

Part X Management of Common Neonatal Respiratory Diseases

58 Mechanisms of Respiratory Failure 513
 Anne Greenough and Anthony D. Milner

59 Tissue Hypoxia 517
 Anne Greenough and Anthony D. Milner

60 Indications for Mechanical Ventilation..... 521
 Anne Greenough and Anthony D. Milner

61 Respiratory Distress Syndrome 523
 Steven M. Donn and Sunil K. Sinha
 (Case Study by Brooke D. Vergales and Jay P. Goldsmith)

62 Pneumonia 533
 Elvira Parravicini and Richard A. Polin

63 Meconium Aspiration Syndrome..... 555
 Thomas E. Wiswell
 (Case Study by Brooke D. Vergales and Jay P. Goldsmith)

64 Persistent Pulmonary Hypertension of the Newborn 565
 Robert E. Schumacher and Steven M. Donn
 (Case Study by Brooke D. Vergales and Jay P. Goldsmith)

65 Congenital Diaphragmatic Hernia 577
 Deepak Kalbigiri Vasudev and David Field
 (Case Study by Brooke D. Vergales and Jay P. Goldsmith)

66 Pulmonary Hypoplasia/Agensis..... 587
 Deepak Kalbigiri Vasudev and David Field

67 Apnea Syndromes 593
 Alan R. Spitzer

68 Weaning and Extubation..... 609
 Steven M. Donn and Sunil K. Sinha
 (Case Study by Brooke D. Vergales and Jay P. Goldsmith)

Part XI Bronchopulmonary Dysplasia

- 69 Etiology and Pathogenesis** 625
Natasha Henner and Jonathan M. Davis
- 70 Management** 633
Eduardo Bancalari
- 71 Long-Term Outcome of Newborns
with Bronchopulmonary Dysplasia** 639
Sumesh Thomas, Prashanth Murthy, and Saroj Saigal

Part XII Complications Associated with Mechanical Ventilation

- 72 Thoracic Air Leaks** 647
Jennifer Dalton and Steven M. Donn
- 73 Patent Ductus Arteriosus** 659
Jonathan Wyllie
- 74 Neonatal Pulmonary Hemorrhage** 665
Tonse N.K. Raju
- 75 Retinopathy of Prematurity** 675
Alistair R. Fielder
- 76 Neurologic Complications of Mechanical Ventilation** 685
Gillian Brennan and Jeffrey M. Perlman

Part XIII Other Considerations

- 77 Nursing Care of the Ventilated Infant** 693
Kimberly LaMar
- 78 Transport of Ventilated Babies** 705
Steven M. Donn and Molly R. Gates
- 79 Home Ventilation** 717
Wan Chong Tsai
- 80 Discharge Planning and Follow-Up of the NICU Graduate** 723
Win Tin and Mithilesh Lal

Part XIV Ethical and Legal Considerations

- 81 Initiation of Life Support at the Border of Viability** 733
Naomi Laventhal, Joanne Lagatta, and William Meadow
- 82 Withdrawal of Ventilatory Support** 739
Malcolm L. Chiswick

Contents	xvii
83 Medical Liability, Documentation, and Risk Management	747
Steven M. Donn and Jonathan M. Fanaroff	
 Part XV Research and the Literature	
84 Interpreting Medical Literature	753
Omar Kamlin and Peter Davis	
85 Contemporary Classics in Neonatal Respiratory Care	759
Rachel L. Chapman and Lorelei Woody	
 Appendix	767
 Index	769

List of Contributors

David Adamkin, MD Neonatal Department, University of Louisville Hospital, Louisville, KY, USA

Namasivayam Ambalavanan, MBBS, MD Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA

Jeanette M. Asselin, RRT, MS Neonatal/Pediatric Research Group, Children's Hospital & Research Center Oakland, Oakland, CA, USA

Mohammad A. Attar, MD Department of Pediatrics, University of Michigan Health System, Ann Arbor, MI, USA

Eduardo Bancalari, MD Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, Miami, FL, USA

Keith J. Barrington, MB, ChB Department of Neonatology, CHU Sainte Justine, Montreal, QC, Canada

Jennifer Beck, PhD Keenan Research Centre in the Li Ka Shing Knowledge Institute of St-Michael's Hospital, Toronto, ON, Canada

Michael A. Becker, RRT Department of Critical Care Support Services, C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI, USA

Varsha Bhatt-Mehta, MS (CRDSA), PharmD, FCCP Department of Pediatrics, C.S. Mott Children's Hospital, College of Pharmacy, University of Michigan, Ann Arbor, MI, USA

Vinod K. Bhutani, MD Department of Pediatrics, Stanford University, Lucile Packard Children's Hospital, Palo Alto, CA, USA

Elaine M. Boyle, MBChB, MSc, PhD Department of Health Sciences, University of Leicester, Leicester, Leicestershire, UK

Gillian Brennan, MB, BCh, BAO Division of Newborn Medicine, Weill Cornell Medical Center, New York-Presbyterian Hospital, New York, NY, USA

J. Bert Bunnell, ScD Bunnell Inc., Department of Bioengineering, University of Utah, Salt Lake City, UT, USA

Waldemar A. Carlo, MD Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA

Rachel L. Chapman, MD Division of Neonatal-Perinatal Medicine, Department of Pediatrics, C.S. Mott Children's Hospital, University of Michigan School of Medicine, Ann Arbor, MI, USA

Robert L. Chatburn, MHHS, RRT-NPS, FAARC Cleveland Clinic, Respiratory Institute, Cleveland, OH, USA

Malcolm L. Chiswick, MD, FRCP(Lond), FRCPCH, FRCOG, DCH University of Manchester, Manchester, UK
Newborn Intensive Care Unit, St. Mary's Hospital, Oxford Road, Manchester, UK

Reese H. Clark, MD Pediatrix Medical Group, Department of Pediatrics, Greenville Memorial Hospital, Greenville, SC, USA

Nelson Claure, MSc, PhD Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, Miami, FL, USA

Jennifer Dalton, MD Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI, USA

Jonathan M. Davis, MD Department of Pediatrics, The Floating Hospital for Children at Tufts Medical Center, Boston, MA, USA

Peter Davis, MBBS, MD, FRACP Newborn Research, The Royal Women's Hospital, Parkville, VIC, Australia

Steven M. Donn, MD, FAAP Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital, F5790 Mott Hospital/5254, University of Michigan Health System, Ann Arbor, MI, USA

David J. Durand, MD Division of Neonatology, Department of Neonatology, Children's Hospital & Research Center Oakland, Oakland, CA, USA

Avroy A. Fanaroff, MD, FRCPE, FRCPCH, FAAP Department of Pediatrics, Rainbow Babies and Children's Hospital, Cleveland, OH, USA

Jonathan M. Fanaroff, MD, JD Division of Neonatology, Department of Pediatrics, Rainbow Babies & Children's Hospital, Cleveland, OH, USA

David Field, MBBS, FRCPCH, FRCP(Ed), DM Leicester Royal Infirmary, Neonatal Unit, Infirmary Square, Leicester, UK

Alistair R. Fielder, FRCP, FRCS, FRCOphth Optometry & Visual Science, City University, Northampton Square, London, UK

Neil N. Finer, MD Pediatrics, Division of Neonatology, San Diego Medical Center, University of California, Hillcrest, San Diego, CA, USA

Louis Fuentes, RRT Maquet Critical Care, Wayne, NJ, USA

Molly R. Gates, MA, MSN, RN-C Perinatal Nursing, C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI, USA

Sarvin Ghavam, MD Department of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Jay P. Goldsmith, MD Women's and Children's Hospital, Lafayette, LA, USA
Department of Neonatology, Tulane University, New Orleans, LA, USA

Anne Greenough, MD Division of Asthma, Allergy and Lung Biology, King's College London, London, UK

Samir Gupta, DM, MRCP, MD, FRCPCH, FRCPI Department of Neonatal Paediatrics, University Hospital of North Tees, Stockton-on-Tees, Cleveland, UK

Natasha Henner, MD Department of Pediatrics, The Floating Hospital for Children at Tufts Medical Center, Boston, MA, USA

Ronald B. Hirschl, MD Department of Pediatric Surgery, C.S. Mott Children's Hospital, Ann Arbor, MI, USA

Maria-Cristina Javier, MD Department of Neonatology, New Hanover Regional Medical Center, Coastal Carolina Neonatology, PLLC, Wilmington, NC, USA

Omar Kamlin, MRCP, MRCPCH, FRACP The Royal Women's Hospital, Neonatal Services, Parkville, VIC, Australia

Martin Keszler, MBBS, FRACP MD Department of Pediatrics, Women and Infants' Hospital of Rhode Island, Brown University, Providence, RI, USA

John P. Kinsella, MD Children's Hospital of Colorado, Aurora, CO, USA

Haresh Kirpalani, BM, MRCP, FRCP, MSc The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Joanne Lagatta, MD, MS Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA

Mithilesh Lal, FRCPCH Department of Neonatal Medicine, The James Cook University Hospital, Middlesbrough, UK

Kimberly LaMar, ND, NPD-BC Chamberlain College of Nursing,
Phoenix Campus, Phoenix, AZ, USA

Andrea L. Lampland, MD Department of Newborn Medicine, Children's
Hospitals and Clinics of Minnesota, St. Paul, MN, USA

Naomi Laventhal, MD, MA Department of Pediatrics, University of Michigan
C.S. Mott Children's Hospital, Ann Arbor, MI, USA

Brigitte Lemyre, MD, FRCP University of Ottawa, Division of Neonatology,
Department of Pediatrics, Children's Hospital of Eastern Ontario,
Ottawa, ON, Canada

Mark C. Mammel, MD Department of Newborn Medicine,
Children's Hospitals and Clinics of Minnesota, University of Minnesota,
St. Paul, MN, USA

Richard J. Martin, MBBS, FRACP Case Western Reserve University,
Cleveland, OH, USA

Division of Neonatology, Rainbow Babies & Children's Hospital,
Cleveland, OH, USA

Neil McIntosh, DSc(Med), FRCP, FRCPE, FRCPCH University of Edinburgh,
Child Life and Health, Edinburgh, UK

William Meadow, MD, PhD Department of Pediatrics, The University
of Chicago, Chicago, IL, USA

Cyndy Miller, RRT, AS/AA Department of Clinical Education,
Newport Medical Instruments, Costa Mesa, CA, USA

Anthony D. Milner, MD Division of Asthma, Allergy and Lung Biology,
King's College London, London, UK

Colin J. Morley, MB Bchir, DCH, MD, FRCPCH, FRACP Neonatal Research,
The Royal Women's Hospital, Melbourne, VIC, Australia
The Rosie Maternity Hospital, Cambridge, UK

Fernando Moya, MD Department of Neonatology, New Hanover Regional
Medical Center, Coastal Carolina Neonatology, PLLC, Wilmington, NC, USA

Prashanth Murthy, MBBS, MD, MRCPCH Department of Pediatrics,
McMaster Children's Hospital, Hamilton, ON, Canada

Joanne Nicks, RRT, AAS Pediatric Respiratory Care, C.S. Mott Children's
Hospital, Ann Arbor, MI, USA

Donald M. Null, Jr., MD Primary Children's Medical Center, Newborn Intensive
Care Unit, Salt Lake City, UT, USA

Elvira Parravicini, MD Division of Neonatology, Department of Pediatrics,
NY Presbyterian Morgan Stanley Children's Hospital, New York, NY, USA

Jeffrey M. Perlman, MB, ChB Division of Newborn Medicine,
Weill Cornell Medical Center, New York-Presbyterian Hospital,
New York, NY, USA

Barbara Pilgrim SLE Ltd, Twin Bridges Office Park, Croydon,
Surrey, UK

Christian F. Poets, MD Department of Neonatology, Tuebingen University
Hospital, Tuebingen, Germany

Richard A. Polin, MD Division of Neonatology, Department of Pediatrics,
NY Presbyterian Morgan Stanley Children's Hospital, New York, NY, USA

Tonse N.K. Raju, MD, DCH Eunice Kennedy Shriver National Institute
of Child Health and Human Development, Bethesda, MD, USA

Janet M. Rennie, MA, MD, FRCP, FRCPC, FRCOG Institute of Women's
Health, University College London Hospitals, London, UK

Ramon Sanchez, MD Section of Pediatric Radiology, University of Michigan,
C.S. Mott Children Hospital, Ann Arbor, MI, USA

Subrata Sarkar, MD Division of Neonatal-Perinatal Medicine,
Department of Pediatrics, C.S. Mott Children's Hospital, University of Michigan
Health System, Ann Arbor, MI, USA

Saroj Saigal, MD, FRCPC Department of Pediatrics, McMaster Children's
Hospital, Hamilton, ON, Canada

Ola Didrik Saugstad, MD, PhD Department of Pediatric Research,
Oslo University Hospital, Rikshospitalet, Oslo, Norway

Andreas Schulze, MD, PhD Division of Neonatology, Dr. von Hauner Children's
Hospital, Munich, Germany

Department of Pediatrics, Klinikum Grosshadern, Ludwig Maximilian University,
Munich, Germany

Robert E. Schumacher, MD Department of Pediatrics, C.S. Mott Children's
Hospital, University of Michigan Health System, Ann Arbor, MI, USA

Sunil K. Sinha, MD, PhD, FRCP, FRCPC Department of Neonatal Medicine,
The James Cook University Hospital, University of Durham,
Marton-in-Cleveland, Middlesbrough, UK

Emidio M. Sivieri, MS Neonatal Pulmonary Function Laboratory,
Pennsylvania Hospital, Philadelphia, PA, USA

Alan R. Spitzer, MD Department of Research, Education, and Quality,
MEDNAX, Inc., Sunrise, FL, USA

Peter J. Strouse, MD Section of Pediatric Radiology, University of Michigan,
C.S. Mott Children Hospital, Ann Arbor, MI, USA

Sumesh Thomas, MBBS, DCH, FRCP, FRCPC, FRCPC

Department of Pediatrics, McMaster Children's Hospital, Hamilton, ON, Canada

Win Tin, FRCPC Department of Neonatal Medicine, The James Cook University Hospital, Middlesbrough, UK

Wan Chong Tsai, MD, MS Department of Pediatric Pulmonology, Promedica Toledo Children's Hospital and University of Toledo, Toledo, OH, USA

Deepak Kalbigiri Vasudev, MBBS, DCH, MRCPCH Leicester Royal Infirmary, Neonatal Unit, Infirmary Square, Leicester, UK

Brooke D. Vergales, MD Department of Pediatrics, University of Virginia, Charlottesville, VA, USA

Teresa A. Volsko, MHHS, RRT, FAARC Respiratory Care and Polysomnography Programs, Youngstown State University, Youngstown, OH, USA

Karen Wiseman, MD Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI, USA

Thomas E. Wiswell, MD Department of Pediatrics, Florida Children's Hospital, Orlando, FL, USA

Lorelei Woody, MLIS Alfred A. Taubman Health Sciences Library, University of Michigan, Ann Arbor, MI, USA

Jonathan Wyllie, BSc(Hons), MB ChB, FRCPC, FRCP, FERC Department of Neonatology, The James Cook University Hospital, Middlesbrough, Cleveland, UK

List of Abbreviations

μm	Micrometer
$^{\circ}\text{C}$	Degrees Celsius (Centigrade)
$^{\circ}\text{K}$	Degrees, Kelvin
A	Alveolar
a	Arterial
a/A	Arterial/alveolar ratio
A/C	Assist/control
AAC	Automatic airway compensation
A-aDO ₂	Alveolar–arterial oxygen gradient
ABG	Arterial blood gas
ACT	Activated clotting time
ADP	Adenosine diphosphate
AH	Absolute humidity
ALTE	Apparent life-threatening event
AM	Morning
AMP	Adenosine monophosphate
Ao	Aortic
AOI	Apnea of infancy
AOP	Apnea of prematurity
AP	Anteroposterior
ARDS	Adult (or acute) respiratory distress syndrome
ASD	Atrial septal defect
ATP	Adenosine triphosphate
ATPS	Ambient temperature and pressure, saturated with water vapor
BAER	Brainstem audiometric-evoked responses
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
BPM (bpm)	Beats or breaths per minute
BR	Breath rate
BTPS	Body temperature and pressure, saturated with water vapor

C	Compliance
C20	Compliance over last 20% of inflation
CCAM	congenital cystic adenomatoid malformation
cAMP	Cyclic adenosine monophosphate
CBF	Cerebral blood flow
CBG	Capillary blood gas
cc	Cubic centimeter
C_D or C_{DYN}	Dynamic compliance
CDH	Congenital diaphragmatic hernia
CDP	Constant distending pressure
CF	Cystic fibrosis
cGMP	Cyclic guanosine monophosphate
CHAOS	Congenital high airway obstruction syndrome
CHD	Congenital heart disease
C_L	Compliance
CLD	Chronic lung disease
CLE	Congenital lobar emphysema
cm	Centimeter
CMV	Conventional mechanical ventilation
CMV	Cytomegalovirus
CNS	Central nervous system
CO	Cardiac output
CO_2	Carbon dioxide
CO-Hb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPL	Congenital pulmonary lymphangiectasia
CPR	Cardiopulmonary resuscitation
CPT	Chest physiotherapy
CRP	C-reactive protein
CSF	Cerebrospinal fluid
C_{ST}	Static compliance
CT	Computed tomography
CVP	Central venous pressure
CXR	Chest X-ray (radiograph)
D	End-diastole
D5W	Dextrose 5% in water
DCO_2	Gas transport coefficient for carbon dioxide
DIC	Disseminated intravascular coagulation
dL	Deciliter
DNA	Deoxyribonucleic acid
DPG	Diphosphoglycerate
DPPC	Dipalmitoyl phosphatidyl choline
DR	Delivery room

E	Elastance
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDRF	Endothelial-derived relaxing factor
EEG	Electroencephalogram
EF	Ejection fraction
ELBW	Extremely low birth weight
EMG	Electromyogram
EMLA	Eutectic mixture of Lidocaine and Prilocaine
ERV	Expiratory reserve volume
ET	Endotracheal
ETCO ₂	End-tidal carbon dioxide
ETCPAP	Endotracheal continuous positive airway pressure
ETT	Endotracheal tube
F or f	Frequency
F or Fr	French
FCV	Flow control valve, flow-cycled ventilation
FDA	Food and Drug Administration (US)
FDP	Fibrin degradation products
FGF	Fibroblast growth factor
FIO ₂	Fraction of inspired oxygen
FiO ₂	Fraction of inspired oxygen
FOE	Fractional oxygen extraction
FRC	Functional residual capacity
FSP	Fibrin split products
FTA	Fluorescent treponemal antibody
g	Gauge
g	Gram
G	Gravida
GA	Gestational age
GBS	Group B streptococcus
GER	Gastro-esophageal reflux
GERD	Gastro-esophageal reflux disease
GIR	Glucose infusion rate
gm	Gram
GNP	Gross national product
GTP	Guanosine triphosphate
GUI	Graphics user interface
h or hr	Hour
H ₂ O	Water
Hb	Hemoglobin
HCH	Hygroscopic condenser humidifier
HCO ₃ ⁻	Bicarbonate

HFJV	High-frequency jet ventilation
HFNC	High flow nasal cannula
HFO	High-frequency oscillation
HFOV	High-frequency oscillatory ventilation
HFV	High-frequency ventilation
Hg	Mercury
Hgb	Hemoglobin
HME	Heat and moisture exchanger
HR	Heart rate
HSV	Herpes simplex virus
Hz	Hertz
I	Inertance
I:E	Inspiratory:expiratory ratio
IC	Inspiratory capacity
Ig	Immunoglobulin
IL	Interleukin
IMV	Intermittent mandatory ventilation
INO	Inhaled nitric oxide
IO	Intraosseous
IP	Inspiratory pressure
IPPV	Intermittent positive pressure ventilation
IRV	Inspiratory reserve volume
IUGR	Intrauterine growth restriction
IV	Intravenous
IVC	Inferior vena cava(I)
IVH	Intraventricular hemorrhage
IVS	Interventricular septum
<i>K</i>	Constant
kDa	Kilodalton
kg	Kilogram
kPa	Kilopascal
L	Liter
LA	Left atrium
LBW	Low birth weight
LCD	Liquid crystalline display
LED	Light emitting diode
LHR	Ratio of lung diameter to head circumference
LOS	Length of stay
LPM (lpm)	Liters per minute
LVEDD	Left ventricular end-diastolic dimension
LVID	Left ventricular internal diameter
LVIDD	Left ventricular internal diameter at diastole
LVIDS	Left ventricular internal diameter at systole
LVO	Left ventricular output

m	Meter
MAP	Mean arterial pressure
MAS	Meconium aspiration syndrome
mcg	Microgram
MD	Minute distance
mEq	Milliequivalent
MetHb	Methemoglobin
mg	Milligram
MIC	Mean inhibitory concentration
min	Minute
mL (ml)	Milliliter
mm	Millimeter
MMV	Mandatory minute ventilation
mOsm	Milliosmoles
MRI	Magnetic resonance imaging
MSAF	Meconium-stained amniotic fluid
MV	Minute ventilation
NAVA	Neurally adjusted ventilatory assist
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NIPPV	Noninvasive positive pressure ventilation
NIRS	Near-infrared spectroscopy
NO	Nitric oxide
NO ₂	Nitrogen dioxide
NOS	Nitric oxide synthase
O ₂	Oxygen
OI	Oxygenation index
P	Para
P	Pressure
P50	Point of 50% saturation of hemoglobin with oxygen
PACO ₂	Partial pressure of carbon dioxide, alveolar
PaCO ₂	Partial pressure of carbon dioxide, arterial
PAO ₂	Partial pressure of oxygen, alveolar
PaO ₂	Partial pressure of oxygen, arterial
PAV	Proportional assist ventilation
Paw	Airway pressure
Pāw	Mean airway pressure
PB	Periodic breathing
PC	Pressure control
PCA	Postconceptional age
PCR	Polymerase chain reaction
PDA	Patent ductus arteriosus
PE	Elastic pressure

PEEP	Positive end-expiratory pressure
PFC	Persistent fetal circulation, perfluorocarbon
PG	Prostaglandin
PH ₂ O	Partial pressure of water vapor
PI	Inspiratory pressure
P _i	Pressure, inertial
PICC	Percutaneous intravenous central catheter
PIE	Pulmonary interstitial emphysema
PIP	Intrapleural pressure
PIP	Peak inspiratory pressure
PL	Pressure limit
PL	Pressure limit
PLV	Partial liquid ventilation
PMA	Postmenstrual age
PMA	Premarket approval (US)
PN ₂	Partial pressure of nitrogen
PPHN	Persistent pulmonary hypertension of the newborn
ppm	Parts per million
PR	Resistive pressure
prbc	Packed red blood cells
PRVC	Pressure-regulated volume control
PSI	Pounds per square inch
PSIG	Pounds force per square inch gauge
PST	Static pressure
PSV	Pressure support ventilation
PT	Prothrombin time
PTP	Transpulmonary pressure
PTT	Partial thromboplastin time
PTV	Patient-triggered ventilation
PUFA	Polyunsaturated fatty acids
PV-IVH	Periventricular–intraventricular hemorrhage
PVL	Periventricular leukomalacia
PvO ₂	Mixed central venous oxygen tension
PvO ₂	Partial pressure of oxygen, venous
PVR	Pulmonary vascular resistance
q	Every
Q	Perfusion
<i>r</i>	Radius
<i>R</i>	Resistance
<i>R</i> _{AW}	Airway resistance
RBC	Red blood cell
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
RE	Expiratory resistance

REM	Rapid eye movement
RH	Relative humidity
RI	Inspiratory resistance
ROP	Retinopathy of prematurity
ROS	Reactive oxygen species
RR	Respiratory rate, relative risk
RSV	Respiratory syncytial virus
RV	Reserve volume
RVO	Right ventricular output
S	End-systole
S1 (2,3,4)	First (second, third, fourth) heart sound
SaO ₂	Arterial oxygen saturation
s	Second
sGC	Soluble guanylate cyclase
SIDS	Sudden infant death syndrome
SIMV	Synchronized intermittent mandatory ventilation
SNAP	Score for neonatal acute physiology
SOD	Superoxide dismutase
SP	Surfactant protein
SpO ₂	Pulse oximetry saturation
sq	Square
STPD	Standard temperature and pressure, dry
SV	Stroke volume
SVC	Superior vena cava(l)
SvO ₂	Venous oxygen saturation
SVR	Systemic vascular resistance
T	Temperature
TBW	Total body water
TcPCO ₂	Transcutaneous carbon dioxide tension
TCPL(V)	Time-cycled, pressure-limited (ventilation)
TcPO ₂	Transcutaneous oxygen tension
TCT	Total cycle time
T _E or T _e	Expiratory time
TEF	Tracheo-esophageal fistula
TGF	Transforming growth factor
TGV	Total or thoracic gas volume
THAM	Tris-hydroxyaminomethane
T _i or T _i	Inspiratory time
TLC	Total lung capacity
TLV	Total liquid ventilation
TPN	Total parenteral nutrition
TPV	Time to peak velocity
TRH	Thyroid releasing hormone
TTN, TTNB	Transient tachypnea of the newborn
TTV	Targeted tidal volume

U	Units
UAC	Umbilical artery catheter
V	Volume, velocity
\dot{V}	Flow
\ddot{V}	Rate of change of flow
V/Q	Ventilation/perfusion
V_A	Alveolar ventilation
VA	Anatomic volume
V-A	Veno-arterial
VAP	Ventilator-associated pneumonia
VAPS	Volume-assured pressure support
VC	Vital capacity
VCF	Velocity of circumferential fiber shortening
VCO_2	Carbon dioxide elimination
VCV	Volume-controlled ventilation
VD	Deadspace volume
VDRL	Venereal disease research laboratory
VEGF	Vascular endothelial growth factor
VILI	Ventilator-induced lung injury
VLBW	Very low birthweight
VS	Volume support
VSD	Ventricular septal defect
V_T	Tidal volume
V_{TE}	Expired tidal volume
V_{TI}	Inspired tidal volume
VTI	Velocity time interval
V-V	Venovenous
WBC	White blood cell

Part I
Lung Development and Maldevelopment

Chapter 1

Development of the Respiratory System

Vinod K. Bhutani

I. Introduction

- A. The neonatal respiratory system is a complex organ whose life-sustaining function on the initiation and maintenance of an ongoing dynamic interaction among multiple tissue types of diverse embryonic origins.
- B. It has two functional areas: the conducting system and the gas exchange system.
 - 1. Nasal passages, pharynx, larynx, trachea, bronchi, and bronchioles are generally supported by cartilage until the terminal bronchioles and prevent airway collapse during expiration.
 - 2. The surrounding tissues include airway smooth muscle that regulates airway resistance, whereas the fibroelastic supportive tissue offers elasticity during both respiratory cycles.
 - 3. The structural mucosal layers are lined by motile ciliary cells, mucus-producing goblet cells, and basal cells that provide for regeneration and healing.
 - 4. The submucosal layers contain sero-mucous glands and Clara cells.
 - 5. The gas exchange system comprises respiratory noncartilaginous bronchioles that lead to alveolar ducts, sacs, and alveoli. These are areas lined by squamous type I pneumocytes (that produce prenatal lung fluid in utero) and the cuboidal type II pneumocytes that manufacture and secrete surfactant. The gas exchange areas interface through the blood/air barrier with pulmonary vasculature.
 - 6. Our understanding of the genetic, molecular, and cellular developmental processes that continue during lifetime are perturbed by maturation, disease, environmental factors, and recovery.

V.K. Bhutani, MD (✉)
Department of Pediatrics, Stanford University, Lucile Packard Children's Hospital,
750 Welch Road, 3315, Palo Alto, CA 94305, USA
e-mail: bhutani@stanford.edu

- C. The complex process of mammalian lung development includes lung airway branching morphogenesis and alveolarization, together with angiogenesis and vasculogenesis.
1. Severe defects of any of these developmental events will lead to neonatal respiratory failure and death in infants. However, the impact of milder structural or functional defects, occurring as a result of aberrant lung development, have been neglected in the past because of a relative lack of early respiratory signs, plus the technical difficulties of making an anatomic or physiologic diagnosis *in vivo*.
 2. Accumulated data obtained as a result of significant advancements in human genomic studies and rodent genetic manipulation indicate that early abnormal lung development may indeed be a significant susceptibility factor in certain respiratory diseases that become clinically detectable during childhood or even during later life, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and asthma.
- D. The lung arises from the floor of the primitive foregut as the laryngotracheal groove at about the 26th day of fetal life (approximately 4–6 weeks gestation in humans).
1. The proximal portion of this primitive structure gives rise to the larynx and trachea, which becomes separated from the esophagus, while progenitor cells located at the distal part of the primitive trachea give rise to the left and right main stem bronchi.
 2. Branching morphogenesis of the left and right bronchi forms specific lobar, segmental, and lobular branches. This process extends through the canalicular stage of lung development up to approximately 20 weeks' gestation in humans.
 3. The first 16 of these 23 airway generations are stereo-specific in humans, the remainder being fractal in geometry, but with a distinct proximal–distal pattern of diameter and epithelial differentiation that are genetically “hard wired.”
 4. Alveolarization begins at approximately 20 weeks in humans and continues at least up to 7 years of age, giving rise to an eventual alveolar gas diffusion surface 70 m^2 in area by $1 \text{ }\mu\text{m}$ in thickness.
 5. This enormous surface is closely apposed to an alveolar capillary network capable of accommodating a blood flow between 5 L/min at rest and 25 L/min at maximal oxygen consumption in the young and fit adult.
 6. The entire developmental process of the lung is orchestrated by finely integrated and mutually regulated networks of transcriptional factors, growth factors, matrix components, and physical forces.
 7. Factors that adversely impact the developing lung include human prematurity, oxygen exposure, early corticosteroid exposure, incorrect amounts of growth factor (platelet-derived growth factor, fibroblast growth factor [FGF], vascular endothelial growth factor, transforming growth factor [TGF]- β family, and Wnt) signaling, abnormal regulation, or injury of the

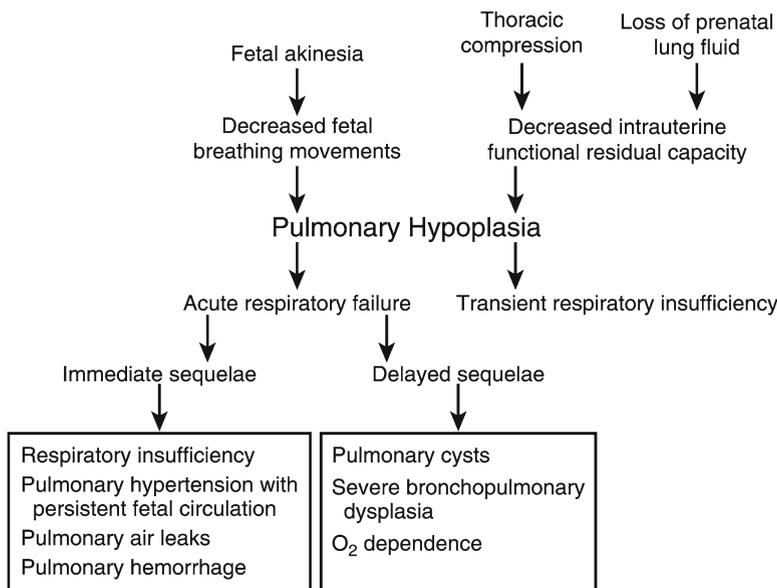


Fig. 1.1 Probable mechanisms and sequelae of pulmonary development during prolonged amniotic leak (modified from Bhutani VK, Abbasi S, Weiner S. Neonatal pulmonary manifestations due to prolonged amniotic leak. *Am J Perinatol.* 1986;3:225, © Thieme Medical Publishers, with permission)

pulmonary capillary vasculature. Individually and cumulatively, these all result in hypoplasia of the alveolar epithelial surface, with a resulting deficiency in gas transport, particularly during exercise. For example, survivors of human prematurity with bronchopulmonary dysplasia (BPD) desaturate on maximal exercise during childhood, and some are now entering young adulthood with increasingly severe gas diffusion problems.

8. In addition, physical forces play an important role in regulating lung formation.
 - a. In utero, the lung is a hydraulic, fluid-filled system.
 - b. Secretion of fluid into the airway lumen is osmotically driven by active chloride secretion through chloride channels. This gives rise to a continuous forward flow of lung liquid that drains into the amniotic fluid.
 - c. The larynx acts as a hydraulic pinchcock valve and maintains and intraluminal hydraulic pressure of approximately 1.5 cm water in the airways.
 - d. Excess fluid drainage during fetal life results in hypoplasia of the lung (Fig. 1.1).
 - e. Conversely, obstruction of the trachea in embryonic lung in culture can result in a doubling of the rate of airway branching.
 - f. Moreover, physiologic fluctuations in intraluminal pressure caused by coordinated peristaltic contractions of airway smooth muscle have

Table 1.1 Magnitude of lung development: from fetal age to adulthood

	30 weeks	Term	Adult	Fold increase after term PCA
Surface area (m ²)	0.3	4.0	100	23
Lung volume (mL)	25	200	5,000	23
Lung weight (g)	25	50	800	16
Alveoli (number)	Few	50 m	300 m	6
Alveolar diameter (μm)	32	150	300	10
Airway branching (number)	24	24	24	0

been shown to play an important role in embryonic lung branching morphogenesis.

- g. Fetal breathing movements cause cyclic fluctuation of intratracheal pressure during fetal life.
 - h. Following cord clamping and the resulting rush of catecholamines at birth, the lung lumen dries out and rapidly switches to air breathing.
 - i. Clearance of lung intraluminal liquid is mediated by cessation of chloride secretion into the lumen and activation of active sodium transport out of the lumen. Null mutation of sodium transporter channel genes (α -epithelial sodium channel, α -EnaC) is lethal neonatally because it abrogates this net osmotically driven fluid uptake.
 - j. “Erection” of alveolar septa is relatively poorly understood. Nevertheless, correct organization of the elastin matrix niche is important, as is remodeling of the alveolar capillary network. This suggests that vascular hydraulic perfusion pressure may play a key role in the emergence of septal structures into the alveolar space.
 - k. This concept is further supported by a requirement for vascular endothelial growth factor secretion by the alveolar epithelium to maintain vascular integrity and remodeling, and hence correct epithelial branching as well as alveolar morphogenesis.
- E. Prenatal development of the respiratory system is not complete until sufficient gas exchange surface has formed to support the newborn at birth.
 - F. Pulmonary vasculature must also achieve sufficient capacity to transport carbon dioxide and oxygen through the lungs.
 - G. Gas exchange surface must be structurally stable, functional, and elastic to require minimal effort for ventilation and to be responsive to the metabolic needs of the infant.
 - H. Structural maturation of the airways, chest wall, and respiratory muscles and neural maturation of respiratory control are integral to the optimal function of the gas exchange “unit.”
 - I. Respiratory system development continues after birth and well into childhood (Table 1.1).
 - J. Fundamental processes that impact on respiratory function.

Table 1.2 Stages of prenatal and postnatal structural lung development

Phase	Postconceptional age	Length: terminal bronchiole to pleura (mm)	Lung development
Embryonic	0–7 weeks	<0.1	Budding from the foregut
Pseudoglandular	8–16 weeks	0.1	Airway division commences and terminal bronchioles formed
Canalicular	17–27 weeks	0.2 mm	<ul style="list-style-type: none"> • Three generations of respiratory bronchioles • Primitive saccules formation with type I and II epithelial cells • Capillarization
Saccular	28–35 weeks	0.6	Transitional saccules formed
Alveolar	>36 weeks	11	<ul style="list-style-type: none"> • True alveoli appear
Postnatal	2 months	175	Terminal saccules formed
Early Childhood	6–7 years	400	<ul style="list-style-type: none"> • True alveoli appear
			<ul style="list-style-type: none"> • Five generations of alveolar ducts • Alveoli form with septation
			<ul style="list-style-type: none"> • Airways remodeled • Alveolar sac budding occurs

1. Ventilation and distribution of gas volumes
2. Gas exchange and transport
3. Pulmonary circulation
4. Mechanical forces that initiate breathing and those that impede airflow
5. Organization and control of breathing

II. Lung development

A. Background. The lung’s developmental design is based upon the functional goal of allowing air and blood to interface over a vast surface area and an extremely thin yet intricately organized tissue barrier. The developmental maturation is such that growth (a quantitative phenomenon) progresses separately from maturation (a qualitative phenomenon). A tension skeleton comprises connective tissue fibers and determines the mechanical properties of the lungs: axial, peripheral, and alveolar septal.

1. Axial connective tissue fibers have a centrifugal distribution from the hilum to the branching airways.
2. Peripheral fibers have a centripetal distribution from the pleura to within the lungs.
3. Alveolar septal fibers connect the axial and peripheral fibers.

B. Functional anatomy (Table 1.2).

1. Fetal lung development takes place in seven phases.
2. Demarcations are not exact but arbitrary with transition and progression occurring between each.

Table 1.3 Factors that influence fetal lung maturation

Physical	Hormonal	Local
Fetal respiration	Glucocorticoids	cAMP
Fetal lung fluid	Prolactin	Methylxanthines
Thoracic volume (FRC)	Insulin	
	Sex hormones	

Table 1.4 Chemical features of fetal fluids

	Osmolality (mOsm/L)	Protein (g/dL)	pH	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)
Fetal lung fluid	300	0.03	6.27	140	6.3	144	2.8
Fetal plasma	290	4.1	7.34	140	4.8	107	24
Amniotic fluid	270	0.1–0.7	7.07	110	7.1	94	18

3. Little is known about the effects of antenatal steroids on the transition and maturation of fetal lung development.

C. Factors that impact fetal lung growth.

1. Physical, hormonal, and local factors play a significant role (Table 1.3).
2. The physical factors play a crucial role in the structural development and influence size and capacity of the lungs.
3. Hormonal influences may be either stimulatory or inhibitory.

D. Fetal lung fluid and variations in lung development. Production, effluence, and physiology are dependent on physiologic control of fetal lung fluid.

1. Production—secretion commences in mid-gestation, during the canalicular phase, and composition distinctly differs from fetal plasma and amniotic fluid (Table 1.4).
2. Distending pressure—daily production rates of 250–300 mL/24 h result in distending pressure of 3–5 cm H₂O within the respiratory system. This hydrostatic pressure seems to be crucial for fetal lung development and the progressive bifurcations of the airways and development of terminal saccules.
3. Fetal breathing—during fetal breathing movements, tracheal egress of lung fluid (up to 15 mL/h) during expiration (compared to minimal loss during fetal apnea) ensures that lung volume remains at about 30 mL/kg (equivalent to the functional residual capacity, FRC). Excessive egress has been associated with pulmonary hypoplasia (Fig. 1.1), whereas tracheal ligation has been associated with pulmonary hyperplasia.

III. Upper airway development

- A. Airways are heterogeneous, conduct airflow, and do not participate in gas exchange.

Table 1.5 Classification, branching, and lumen size of adult human airways

Branch order	Name	Number	Diameter (mm)	Cross-sectional area (cm ²)
0	Trachea	1	18	2.54
1	Main bronchi	2	12.2	2.33
2	Lobar bronchi	4	8.3	2.13
3	Segmental bronchi	8	5.6	2.00
4	Subsegmental bronchi	16	4.5	2.48
5–10	Small bronchi	32–1,025	3.5 - 1.3	3.11–13.4
11–14	Bronchioles	2,048–8,192	1.99 - 0.74	19.6–69.4
15	Terminal bronchiole	32,768	0.66	113
16–18	Respiratory bronchioles	65,536–262,144	0.54 - 0.47	180–534
19–23	Alveolar ducts	524,288–8,388,608	0.43	944–11,800
24	Alveoli	300,000,000	0.2	

1. Starting as the upper airways (nose, mouth, pharynx, and larynx), they lead to the trachea. From here, the cartilaginous airways taper to the small bronchi and then to the membranous airways and the last branching, the terminal bronchioles (Table 1.5).
 2. The lower airways and the gas exchange area commence with the respiratory bronchioles.
 3. The upper airways are not rigid, but are distensible, extensible, and compressible. The branching is not symmetrical and dichotomous but irregular. The lumen is not circular and subject to rapid changes in cross-sectional area and diameter because of a variety of extramural, mural, and intramural factors.
- B. Anatomy includes the nose, oral cavity, palate, pharynx, larynx, hyoid bone, and extrathoracic trachea.
- C. Function is to conduct, humidify, warm (or cool) to body temperature, filter air into the lungs. Also help to separate functions of respiration and feeding as well as share in the process of vocalization.
- D. Patency control—stable pressure balance between collapsing forces (inherent viscoelastic properties of the structures and that of the constricting tone) and the dilator forces of supporting musculature help to maintain upper airway patency. Negative pressure in the airways, neck flexion, and changes in the head and neck posture narrow the airways. Both intrinsic and extrinsic muscles of the upper airway can generate dilator forces, such as flaring of the ala nasi.

IV. Lower airway development

A. Anatomy

1. Conducting airways of the intrathoracic trachea.

Table 1.6 Clinical conditions associated with narrowing of the airways

Airway inflammation	<ul style="list-style-type: none"> • Mucosal edema • Excessive secretions • Inspissation of secretions • Tracheitis
Bronchoconstriction	<ul style="list-style-type: none"> • Reactive airways • Exposure to cold, dry air • Exposure to bronchoconstricting agents
Bronchomalacia	<ul style="list-style-type: none"> • Prolonged mechanical ventilation • Congenital • Secondary to vascular abnormality
Trauma	<ul style="list-style-type: none"> • Foreign body • Mucosal damage from ventilation, suction catheters • Subglottic stenosis
Congenital	<ul style="list-style-type: none"> • Choanal stenosis • High arched palate
Chemical	<ul style="list-style-type: none"> • Aspiration of gastric contents • Hyper-/hypo-osmolar fluid in the airways

2. Respiratory gas exchange portions of terminal and respiratory bronchioles and alveolar ducts.

B. Function of airway smooth muscle

1. Tone is evident early in fetal life and plays significant role in controlling airway lumen.
2. In the presence of respiratory barotrauma, there appears to be a propensity for airway reactivity, perhaps a component of the smooth muscle hyperplasia seen in BPD.
3. Patency control. Excitatory and inhibitory innervations lead to bronchoconstriction or dilatation, respectively.
4. Narrow airways. Narrowing of the airways leads to increased resistance to airflow, an increased resistive load during breathing, and thereby an increased work of breathing and wasted caloric expenditure. Clinical factors associated with airway narrowing are listed in Table 1.6.

V. Thoracic and respiratory muscle development

A. Anatomy

1. Three groups of skeletal muscles are involved in respiratory function.
 - a. Diaphragm
 - b. Intercostal and accessory muscles
 - c. Abdominal muscles
2. These comprise the respiratory pump that helps conduct the air in and out of the lungs.
3. During quiet breathing, the primary muscle for ventilation is the diaphragm.
4. The diaphragm is defined by its attachments to the skeleton.

- a. That part attached to the lumbar vertebral regions is the crural diaphragm.
 - b. That part attached to the lower six ribs is the costal diaphragm.
 - c. Both converge and form a single tendon of insertion.
5. Innervation of the diaphragm is by alpha motor neurons of the third through fifth cervical segments, the phrenic nerve.
 6. Attached to the circumference of the lower thoracic cage, its contraction pulls the muscle downward, displaces the abdomen outward, and lifts up the thoracic cage.
 7. In the presence of a compliant thoracic cage, relative to the lungs, the thoracic cage is pulled inward (sternal retraction).
 8. The concomitant pressure changes during inspiration are reduction of intrapleural pressure and an increase in the intra-abdominal pressure.

B. Respiratory contractile function

1. Strength, endurance, and the inherent ability to resist fatigue may assess the performance of the respiratory muscles.
2. Strength is determined by the intrinsic properties of the muscle (such as its morphologic characteristics and types of fibers).
3. Clinically, strength may be measured by the pressures generated at the mouth or across the diaphragm at specific lung volumes during a static inspiratory or expiratory maneuver.
4. Endurance capacity of a respiratory muscle depends upon the properties of the system as well as the energy availability of the muscles.
5. Clinically, endurance is defined as the capacity to maintain either maximal or submaximal levels of ventilation under isocapnic conditions. It may be standardized either as maximal ventilation for duration of time, or ventilation maintained against a known resistive load, or sustained ventilation at a specific lung volume (elastic load). It is also determined with respect to a specific ventilatory target and the time to exhaustion (fatigue).
6. Respiratory muscles fatigue when energy consumption exceeds energy supply.
7. Fatigue is likely to occur when work of breathing is increased, strength reduced, or inefficiency results so that energy consumption is affected.
8. Hypoxemia, anemia, decreased blood flow to muscles, and depletion of energy reserves alter energy availability.
9. Clinical manifestations of respiratory muscle fatigue are progressive hypercapnia or apnea.

C. Postnatal maturation

1. Lung size, surface area, and volume grow in an exponential manner for about 2 months after term gestation.

Table 1.7 Postnatal maturation of the lung

	Number of alveoli	Surface area (m ²)	Respiratory rate (per minute)
Birth	24,000,000	2.8	45 (35–55)
5–6 months	112,000,000	8.4	27 (22–31)
~1 year	129,000,000	12.2	19 (17–23)
~3 year	257,000,000	22.2	19 (16–25)
~5 year	280,000,000	32.0	18 (14–23)
Adult	300,000,000	75	15 (12–18)

2. Control of breathing (feedback control through chemoreceptors and stretch receptors), and the neural maturation of the respiratory centers also appear to coincide with maturation at about two months postnatal age.
3. Beyond this age, lung volumes continue to increase during infancy, slowing during childhood but still continuing to grow structurally into early adolescence (Table 1.7).
4. It is this biologic phenomenon that provides a scope of recovery for infants with BPD.
5. In health, the increasing lung volume and cross-sectional area of the airways is associated with a reduction in the normal respiratory rate.

VI. Descriptive embryology of the lung

The following paragraphs briefly describe the anatomical changes which occur during lung development. Changes in gene expression can be found at <http://www.ana.ed.ac.uk/database/lungbase/lunghome.html>.

- A. The anatomical development of the lung can be regarded as a continuous process from the advent of the laryngotracheal groove until adulthood, although obvious radical physiological changes occur at birth. The description below is based on human respiratory development, though other mammals follow a very similar developmental program, especially during the early phases.
- B. The respiratory system begins as a ventral outgrowth (laryngotracheal groove) from the wall of the foregut, close to the fourth and sixth pharyngeal pouches. The groove deepens and grows downward to form a pouch-like evagination, fully open to the foregut. Two longitudinal folds of tissue (tracheo-esophageal folds) on either side of the groove grow together and fuse, forming a new tube (laryngotracheal tube) distinct from the foregut.
- C. Communication with the foregut is maintained via a longitudinally oriented slit-like opening (laryngeal orifice).
- D. Proliferation of the underlying mesenchyme forms swellings around the laryngeal orifice (epiglottal swelling and arytenoid swellings) from which the epiglottis, glottis, laryngeal cartilages, and musculature will develop.

- E. At the same time, the laryngeotracheal tube elongates downward and penetrates the underlying splanchnopleuric mesoderm. A distinct swelling develops at the distal end and is termed the *lung bud* (respiratory diverticulum).
- F. Approximately 28 days after fertilization, the lung bud branches to form the left and right primary bronchial buds, which will ultimately develop into the left and right lungs. Branching is in part directed by the interaction of the epithelium with the underlying splanchnic mesoderm.
- G. By the fifth week, elongation, branching, and budding of the two bronchial buds gives rise to three bronchial stems on the right and two on the left—these are the foundation for the lobular organization of the mature lung.
- H. Dichotomous branching continues for approximately ten weeks, establishing the conducting portion of the airways. Up to 24 orders of branches are generated, the final level being the prospective terminal bronchioles. New branches are being formed within a rapidly proliferating, homogeneous mesenchyme.
- I. Differentiation of the mesenchyme and epithelia begins in the more proximal regions of the airways and progresses distally, beginning during week 10 when mesenchymal cells condense around the larynx and trachea. These form smooth muscle and supporting cartilages. The pulmonary arteries and veins develop in parallel with the conducting portion of the lungs and follow the same branching pattern.
- J. Initially, the airway lumina are very narrow, with a thick pseudostratified epithelial lining. From week 13 onward, the lumina enlarge and the epithelium thins to a more columnar structure. The pluripotent epithelial cells differentiate to ciliated cells and goblet cells, initially in the proximal regions of the developing lung and progressing distally.
- K. From weeks 16–24, the primordia of the respiratory portions of the lungs are formed. The terminal bronchioles divide to form two respiratory bronchioles, which in turn branch to form three to six primitive alveolar ducts, ending in terminal sacs.
- L. At the same time, extensive angiogenesis within the peripheral mesenchyme leads to vascularization of the developing respiratory structures. The cuboidal intermediate cells of the lower airways differentiate to form ciliated cells and clara cells. Peripheral mesenchymal cells differentiate to form the visceral pleura; the remaining mesenchymal cells gain the characteristics of stromal fibroblasts.
- M. By week 26, the terminal sacs have started to dilate, and will eventually differentiate into alveolar complexes. The stroma thins, bringing the growing capillary network into close association with the immature alveoli. The cuboidal cells of the terminal sac epithelium differentiate into alveolar

type II cells, which secrete low levels of surfactant. Where cells with type II phenotype juxtapose a capillary, they differentiate into type I cells, which flatten and can provide a functional though inefficient blood/air barrier if the infant is born prematurely.

- N. During subsequent weeks, there is a rapid expansion of the respiratory portion of the lung. Terminal saccules dilate and branch to form further generations of terminal saccules, vascularized septa form within growing terminal sacs, and type I cells continue to flatten and spread, increasing the surface area available for gas exchange. The parenchyma of the lung continues to thin, and fibroblasts lay down the collagen and elastin fiber components of the stroma.
- O. The composition of pulmonary surfactant is developmentally regulated. By week 30, there is a significant rise in the amount of surfactant secreted from the type II cells.
- P. By week 36, the stroma of the lung has thinned to the extent that capillaries may protrude into the prospective alveolar airspaces.
- Q. The final stages of maturation of the respiratory system occur after 36 weeks' gestation and continue into adulthood. At around 36 weeks, the first mature alveoli appear, characterized by thin-walled interalveolar septa with a single layered capillary network. The diameter of the capillaries is sufficiently large that they may span the alveolar walls and interact with the airspaces on both sides.
- R. New alveoli are generated by a process of septal subdivision of existing immature alveoli. There is a growth spurt soon after birth, though new alveoli continue to form at a high rate for up to 3 years.
- S. As the alveoli mature and the walls thin, there is a decrease in the relative proportion of stroma to total lung volume, which contributes significantly to growth for 1–2 years after birth. By 3 years, the overall morphology of the lung has been established and subsequent expansion occurs through a proportional growth of all lung components until adulthood.

VII. Developmental stages (*Human*)

- A. Embryonic phase (3–7 weeks). Initial budding and branching of the lung buds from the primitive foregut. Ends with the development of the presumptive bronchopulmonary segments.
- B. Pseudoglandular phase (7–16 weeks). Further branching of the duct system (up to 21 further orders) generates the presumptive conducting portion of the respiratory system up to the level of the terminal bronchioles. At this time, the future airways are narrow with few lumina and a pseudostratified squamous epithelium. They are embedded within a rapidly proliferating mesenchyme. The structure has a glandular appearance.
- C. Canalicular phase (16–24 weeks). The onset of this phase is marked by extensive angiogenesis within the mesenchyme that surrounds the more distal reaches of the embryonic respiratory system to form a dense capillary network. The diameter of the airways increases with a consequent

decrease in epithelial thickness to a more cuboidal structure. The terminal bronchioles branch to form several orders of respiratory bronchioles. Differentiation of the mesenchyme progresses down the developing respiratory tree, giving rise to chondrocytes, fibroblasts, and myoblasts.

- D. Terminal sac phase (24–36 weeks). Branching and growth of the terminal sacs or primitive alveolar ducts. Continued thinning of the stroma brings the capillaries into apposition with the prospective alveoli. Functional type II pneumocytes differentiate via several intermediate stages from pluripotent epithelial cells in the prospective alveoli. Type I pneumocytes differentiate from cells with a type II-like phenotype. These cells then flatten, increasing the epithelial surface area by dilation of the saccules, giving rise to immature alveoli. By 26 weeks, a rudimentary though functional blood/gas barrier has formed. Maturation of the alveoli continues by further enlargement of the terminal sacs, deposition of elastin foci and development of vascularized septae around these foci. The stroma continues to thin until the capillaries protrude into the alveolar spaces.
- E. Alveolar phase (36 weeks—term/adult). Maturation of the lung indicated by the appearance of fully mature alveoli begins at 36 weeks, though new alveoli will continue to form for approximately three years. A decrease in the relative proportion of parenchyma to total lung volume still contributes significantly to growth for 1–2 years after birth; thereafter, all components grow proportionately until adulthood.

Chapter 2

Developmental Lung Anomalies

Mohammad A. Attar and Subrata Sarkar

I. Introduction

- A. Most pulmonary malformations arise during the embryonic and the pseudoglandular stages of lung development.
- B. The spectrum of developmental malformations related to lung bud formation, branching morphogenesis, and separation of the trachea from the esophagus includes laryngeal, tracheal, and esophageal atresia; tracheoesophageal fistula; pulmonary aplasia; and bronchogenic cysts.
- C. Development abnormalities related to the pseudoglandular stage of lung development and failure of the pleuroperitoneal cavity to close properly include intralobar pulmonary sequestration, cystic adenomatoid malformation, tracheomalacia and bronchomalacia, and congenital diaphragmatic hernia (CDH).
- D. The spectrum of abnormalities arising at the canalicular and the sacular stage of lung development are related to growth and maturation of the respiratory parenchyma and its vasculature and include acinar dysplasia, alveolar capillary dysplasia, and pulmonary hypoplasia.
- E. Acute lung injury in the neonatal period may alter subsequent alveolar and airway growth and development.

M.A. Attar, MD (✉)

Department of Pediatrics, University of Michigan Health System, F5790 Mott Hospital,
1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA
e-mail: mattar@med.umich.edu

S. Sarkar, MD

Division of Neonatal-Perinatal Medicine, Department of Pediatrics,
C.S. Mott Children's Hospital, University of Michigan Health System,
1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA

II. Categorizations of lung anomalies

- A. Lung anomalies can be localized to the lung or be part of multiple organ involvement.
- B. Lung anomalies may be associated with other congenital anomalies that could be part of a syndrome.
- C. Congenital anomalies in the lung can be categorized as malformations in:
 - 1. The tracheobronchial tree.
 - 2. Distal lung parenchyma.
 - 3. Abnormalities in the pulmonary arterial and venous trees and the lymphatics.

III. Malformations of the tracheobronchial tree

A. Tracheoesophageal fistula

- 1. Occurs in one in 3,000–4,500 live births.
- 2. May result from failure of the process of separation of the primitive foregut into the respiratory and alimentary tracts at 3–6 weeks of gestation.
- 3. Usually found in combination with various forms of esophageal atresia. The most common combination is esophageal atresia with a distal tracheoesophageal fistula (TEF) (about 85% of the cases).
- 4. Infants often present with respiratory distress secondary to airway obstruction from excess secretions or aspiration of gastric contents into the lung through the fistula.
- 5. Excessive salivation and vomiting soon after feedings are often the first clue to diagnosis.
- 6. Esophageal atresia itself is diagnosed by the inability to pass a catheter into the stomach. The diagnosis is confirmed by radiographic studies showing a distended blind upper esophageal pouch filled with air and the catheter coiled in the pouch.
- 7. TEF without esophageal atresia (H-type fistula) is extremely rare and usually presents after the neonatal period.

B. Laryngotracheoesophageal cleft

- 1. There is a long connection between the airway and the esophagus caused by the failure of dorsal fusion of the cricoid, normally completed by the eighth week of gestation. Several subtypes have been described.
- 2. Affected infants have chronic aspiration, gag during feeding, and develop pneumonia.
- 3. The diagnosis is made by bronchoscopy.

C. Congenital high airway obstruction syndrome (CHAOS)

- 1. May be caused by laryngeal atresia, subglottic stenosis, a laryngeal web, or a completely occluding laryngeal cyst.

2. Prenatal diagnosis of upper airway obstruction could be inferred from secondary changes, such as enlarged echogenic lung, flattened or inverted diaphragm, fetal ascites, or hydrops.
3. Antenatal MRI may be helpful in localizing the level of obstruction.

D. Tracheal agenesis

1. Rare, but fatal, anomaly caused by displacement of the tracheoesophageal septum.
2. The length of the agenetic segment is variable.
3. Usually present with TEF and most are associated with other anomalies.
4. At birth, this anomaly is suspected when attempts at intubation are unsuccessful.

E. Tracheal stenosis

1. A malformation where the trachea is narrow, either because of intrinsic abnormality in cartilage formation or by external compression from abnormal vessel formation or vascular rings.
2. The major cause for intrinsic tracheal stenosis is an abnormality in cartilaginous ring formation, either from posterior fusion of the normal C-shaped rings or from the formation of a complete cartilaginous sleeve as reported in children with craniosynostosis syndromes, including Crouzon, Apert, and Pfeiffer syndromes.
3. Clinical manifestations: Biphasic stridor or expiratory wheezing.
4. Diagnosis is by bronchoscopy.

F. Tracheomalacia and bronchomalacia

1. There is absence or softening in the cartilaginous rings that cause the trachea to collapse on expiration. There is a reduction in the cartilage:soft tissue ratio.
2. The anomaly may be segmental or diffuse.
3. Infants with laryngomalacia present with variable inspiratory stridor that worsens with crying, feeding, and upper respiratory infections.
4. The tracheomalacia may be associated with other congenital anomalies like vascular rings and TEF.

G. Congenital bronchogenic cysts

1. Caused by abnormal budding and branching of the tracheobronchial tree.
2. Tend to lie in the posterior mediastinum, near the carina, but may be found in the anterior space.
3. Cysts are filled with a clear, serous fluid unless they become infected. The walls of these cysts generally contain smooth muscle and cartilage.
4. It may be considered if a space-occupying lesion is detected on a chest radiograph obtained for investigation of respiratory distress.

H. Congenital lobar emphysema

1. Can be divided into lobar overinflation, or regional or segmental, pulmonary overinflation.
2. Congenital lobar emphysema (CLE) may result from malformation in the bronchial cartilage with absent or incomplete rings, a cyst in the bronchus, a mucus or meconium plug in the bronchus, or from extrinsic bronchial obstruction caused by dilated vessels, or intrathoracic masses, such as bronchogenic cysts, extralobar sequestration, enlarged lymph nodes, and neoplasms.
3. CLE usually affects the upper and middle lobes on the right, and the upper lobe on the left.
4. These lesions cause air trapping, compression of the remaining ipsilateral lung or lobes, and respiratory distress.
5. Age at the time of diagnosis is closely related to the severity of the respiratory distress and the amount of functioning lung.
6. Diagnosis is by radiography, which reveals the lobar distribution of the hyperaeration with compression of adjacent pulmonary parenchyma.

IV. Malformations of the distal lung parenchyma

A. Pulmonary agenesis and aplasia (see also Chap. 66)

1. A form of arrested lung development that results in the absence of the distal lung parenchyma.
2. Pulmonary agenesis is the complete absence of one or both lungs, including bronchi, bronchioles, vasculature, and respiratory parenchyma.
3. Pulmonary aplasia occurs when only rudimentary bronchi are present; each ends in a blind pouch, with no pulmonary vessels or respiratory parenchyma.
4. This defect arises early in lung development when the respiratory primordium bifurcates into the right and left primitive lung buds.
5. Unilateral pulmonary agenesis is more common than bilateral.
6. Some infants may have severe respiratory distress that does not respond to mechanical ventilation.
7. Radiography shows homogeneous density in place of the lung, the ribs appear crowded on the involved side, and there is mediastinal shift. A CT scan of the chest confirms the absence of lung tissue.

B. Pulmonary hypoplasia

1. Develops as a result of other anomalies in the developing fetus. Many of these anomalies physically restrict growth or expansion of the peripheral lung.
2. It occurs in infants with renal agenesis or dysplasia, urinary outlet obstruction, loss or reduction of the amniotic fluid from premature rupture of membranes, diaphragmatic hernia, large pleural effusions, congenital anomalies of the neuromuscular system, and chromosomal anomalies, including trisomy 13, 18, and 21.

C. Congenital diaphragmatic hernia (Chap. 65)

1. CDH occurs in one per 2,000–3,000 births.
2. Fifty percent are associated with other malformations, especially neural tube defects, cardiac defects, and malrotation of the gut.
3. In CDH, the pleuroperitoneal canal fails to close. This allows the developing abdominal viscera to bulge into the pleural cavity and stunts the growth of the lung.
4. The most common site is the left hemithorax, with the defect in the diaphragm being posterior (foramen of Bochdalek) in 70% of infants.
5. The left side of the diaphragm is involved more frequently than the right.
6. The severity of the resulting pulmonary hypoplasia varies, probably depending upon the timing of the onset of compression, with early, severe compression of the lungs associated with more hypoplasia.
7. There is a decrease in the alveolar number and size and a decrease in the pulmonary vasculature.
8. Infants with a large CDH present at birth with cyanosis, respiratory distress, a scaphoid abdomen, decreased breath sounds on the side of hernia, and displacement of heart sounds to the opposite side.
9. The diagnosis is often made by antenatal ultrasonography, which is often precipitated by the occurrence of polyhydramnios.
10. Often there is severe pulmonary hypertension, likely because of the increased proportion of muscular arteries in the periphery of the lung, which results in increased pulmonary vascular resistance.

D. Congenital bronchiolar cysts

1. Unlike bronchogenic cysts, bronchiolar cysts are in communication with the more proximal parts of the bronchial tree and with distal alveolar ducts and alveoli.
2. These cysts are usually multiple and are restricted to a single lobe.
3. They may be filled with air, fluid, or both.

E. Congenital cystic adenomatoid malformation

1. Congenital cystic adenomatoid malformation (CCAM) is a pulmonary maldevelopment with cystic replacement of small airways and distal lung parenchyma. It is also called congenital pulmonary airway malformation (CPAM).
2. There are five types of CCAM, classified on the basis of the gross appearance and histologic features, but a simpler classification based on anatomic and ultrasonographic findings includes two major types: macrocystic and microcystic.
 - a. In the macrocystic type, the cysts are more than 5 mm in diameter, visible on fetal ultrasonography, and the prognosis is better.
 - b. In the microcystic type, the cysts are smaller, and the mass has a solid appearance.

3. Prognosis is worse if the cystic mass is large and associated with mediastinal shift, polyhydramnios, pulmonary hypoplasia, or hydrops fetalis.
4. After birth, because they are connected to the airways, cysts fill with air, produce further compression of the adjacent lung, and result in respiratory distress.
5. Spontaneous regression of CCAM with normal lungs at birth can occur.

F. Bronchopulmonary sequestration

1. Develops as a mass of nonfunctioning lung tissue, not connected to the tracheobronchial tree and receives its blood supply from one or more anomalous systemic arteries arising from the aorta.
2. There are two forms of bronchopulmonary sequestration depending on whether it is within (intralobar) or outside (extralobar) the visceral pleural lining.
3. Most infants with bronchopulmonary sequestration are asymptomatic in the neonatal period.
4. If the sequestration is sufficiently large, there may be persistent cyanosis and respiratory distress.
5. Some cases may present with large unilateral hydrothorax, possibly secondary to lymphatic obstruction or congestive heart failure secondary to large left-to-right shunting through the sequestration.
6. The classic appearance on chest radiography consists of a triangular or oval-shaped basal lung mass on one side of the chest, usually the left.
7. Diagnosis is confirmed with chest CT and magnetic resonance angiography.

G. Alveolar capillary dysplasia

1. There is misalignment of the pulmonary veins.
2. Characterized by inadequate vascularization of the alveolar parenchyma resulting in reduced number of capillaries in the alveolar wall.
3. This malformation causes persistent pulmonary hypertension in the newborn and is uniformly fatal.

H. Congenital pulmonary lymphangiectasia (CPL)

1. Extremely rare condition consists of markedly distended or dilated pulmonary lymphatics, which are found in the bronchovascular connective tissue, along the interlobular septae, and in the pleura. It may be primary, secondary, or generalized.
2. This condition has been associated with Noonan, Ulrich-Turner, and Down syndromes.
3. Primary lymphangiectasia is a fatal developmental defect in which the pulmonary lymphatics fail to communicate with the systemic lymphatics. Affected infants present with respiratory distress and pleural effusions and die shortly after birth.

4. Secondary lymphangiectasia is associated with cardiovascular malformations.
5. Generalized lymphangiectasia is characterized by proliferation of the lymphatic spaces and occurs in the lung as part of a systemic abnormality, in which multiple lymphangiomas are also found in the bones, viscera, and soft tissues.
6. Patients with pulmonary lymphangiectasia present with nonimmune hydrops fetalis and pleural effusions. Pleural effusions are typically chylous. Pleural effusions in the neonatal period may be serous with minimal triglycerides, particularly before enteral feeding is established.

I. Other conditions that manifest as interstitial lung disease

1. Disorders of surfactant protein (SP) B and C (deficiencies and dysfunction) that are associated with lamellar body anomalies related to ABCA3 gene deficiency, thyroid transcription factor 1 (TTF1) deficiency, or alveolar epithelia cell granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor deficiency.
2. Lung injury related to cystic fibrosis and alpha-1 antitrypsin deficiency may also present as pulmonary dysfunction and emphysema.
3. Diagnostic evaluation for these conditions is usually attempted because of persistent severe respiratory failure in the neonatal period that does not respond to conventional therapy or extracorporeal membrane oxygenation support.

Suggested Reading

- Devine PC, Malone FD. Noncardiac thoracic anomalies. *Clin Perinatol*. 2000;27:865–99.
- Hansen T, Corbet A, Avery ME. Malformations of the mediastinum and lung parenchyma. In: Taesch WH, Ballard RA, Gleason CA, editors. *Avery's diseases of the newborn*. 8th ed. Philadelphia: Elsevier/Saunders; 2005. p. 737–57.
- Nogee LM. Genetic basis of children's interstitial lung disease. *Pediatr Allergy Immunol Pulmonol*. 2010;23:15–24.
- Sandu K, Monnier P. Congenital tracheal anomalies. *Otolaryngol Clin N Am*. 2007;40:193–217.
- Wert SE. Normal and abnormal structural development of the lung. In: Polin RA, Fox WW, Abman SH, editors. *Fetal and neonatal physiology*. 3rd ed. Philadelphia: WB Saunders; 2004. p. 783–94.

Part II
Principles of Mechanical Ventilation

Chapter 3

Spontaneous Breathing

Emidio M. Sivieri and Vinod K. Bhutani

I. Introduction

- A. Air, like liquid, moves from a region of higher pressure to one with lower pressure.
- B. During breathing and just prior to inspiration, no gas flows because the gas pressure within the alveoli is equal to atmospheric pressure.
- C. For inspiration to occur, alveolar pressure must be less than atmospheric pressure.
- D. For expiration to occur, alveolar pressure must be higher than atmospheric pressure.
- E. Thus, for inspiration to occur, the gradient in pressures can be achieved either, by lowering the alveolar pressure (“negative,” “natural,” spontaneous breathing) or, raising the atmospheric pressure (“positive,” “pressure,” mechanical breathing).
- F. The clinical and physiologic implications of forces that influence inspiration and expiration are discussed in this section.

II. Signals of respiration

- A. Each respiratory cycle can be described by the measurement of three signals: driving pressure (P), volume (V), and time (Fig. 3.1).
- B. The rate of change in volume over time defines flow (\dot{V}).
- C. The fundamental act of spontaneous breathing results from the generation of P , the inspiratory driving force needed to overcome the elastic, flow-resistive, and inertial properties of the entire respiratory system in order to initiate airflow.

E.M. Sivieri, MS (✉)
Neonatal Pulmonary Function Laboratory, Pennsylvania Hospital,
800 Spruce Street, Philadelphia, PA 19107, USA
e-mail: siverie@pahosp.com

V.K. Bhutani, MD
Department of Pediatrics, Stanford University, Lucile Packard Children’s Hospital,
750 Welch Road, 3315, Palo Alto, CA 94305, USA

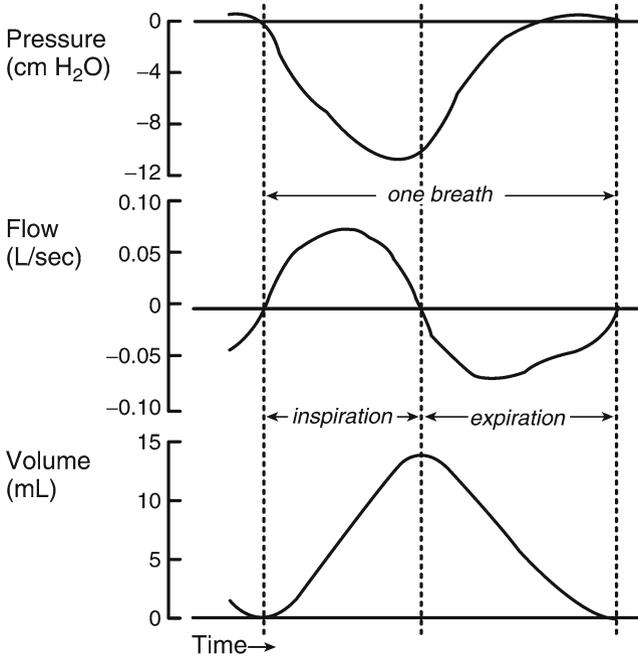


Fig. 3.1 Graphic representation of a respiratory cycle demonstrating pressure, flow, and volume waveforms. Volume is obtained by integration (area under the curve) of the flow signal (Modified from Bhutani VK, Sivieri EM, Abbasi S. Evaluation of pulmonary function in the neonate. In: Polin RA, Fox WW [Eds.]: *Fetal and Neonatal Physiology*, second edition, Philadelphia, W.B. Saunders, 1998, p. 1144, with permission)

1. This relationship has been best described by Röhler using an equation of motion in which the driving pressure (P) is equal to the sum of elastic (P_E), resistive (P_R), and inertial pressure (P_I) components, thus:

$$P = P_E + P_R + P_I$$

2. In this relationship, the elastic pressure is assumed to be proportional to volume change by an elastic constant (E) representing the elastance (or elastic resistance) of the system.
3. The resistive pressure is assumed proportional to airflow by a resistive constant (R) representing inelastic airway and tissue resistances.
4. In addition, the inertial component of pressure is assumed to be proportional to gas and tissue acceleration (\ddot{V}) by an inertial constant (I). Therefore,

$$P = EV + R\dot{V} + I\ddot{V}$$

5. This is a linear, first-order model in which the respiratory system is treated as a simple mechanical system (Fig. 3.2), where applied pressure

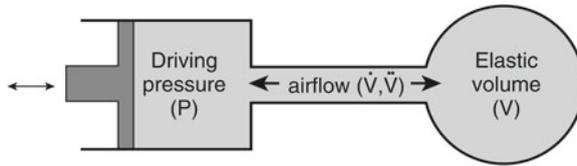


Fig. 3.2 Linear, first-order model of the respiratory system, where applied pressure causes gas to flow through a tube

P causes gas to flow through a tube (the respiratory airways) which is connected to a closed elastic chamber (alveoli) of volume V . In this ideal model E , R , and I are assumed to be constants in a linear relationship between driving pressure and volume.

6. Under conditions of normal breathing frequencies (relatively low air-flow and tissue acceleration) the inertance term is traditionally considered negligible, therefore:

$$P = EV + R\dot{V}$$

7. In respiratory terminology, elastance is usually replaced by compliance (C), which is a term used to represent the expandability or distensibility of the system. Since compliance is simply the reciprocal of elastance, the equation of motion can be rewritten as:

$$P = \frac{V}{C} + R\dot{V}$$

8. This simplified form of the Röhler equation is the basis for most evaluations of pulmonary mechanics, where measurements of P , V , and \dot{V} are used to compute the various components of respiratory system compliance, resistance, and work of breathing.
- D. One can further study the nonlinear nature of the respiratory system using more advanced nonlinear models and by analyzing two-dimensional graphic plots of P - V , V - \dot{V} , and P - \dot{V} relationships.
 - E. Because the inherent nature of the respiratory signals is to be variable (especially in premature infants), it is imperative that the signals are measured in as steady state as feasible and over a protracted period of time (usually 2–3 min).

III. Driving pressure

- A. During spontaneous breathing, the driving pressure required to overcome elastic, airflow-resistive, and inertial properties of the respiratory system is the result of intrapleural pressure (P_{ip}) changes generated by the respiratory muscles (Fig. 3.3).
- B. During a respiratory cycle, both the intrapleural and alveolar pressures change.
 1. Just before the commencement of an inspiratory cycle, the intrapleural pressure is subatmospheric (-3 to -6 cm H_2O) because of the elastic recoil effect of the lung.

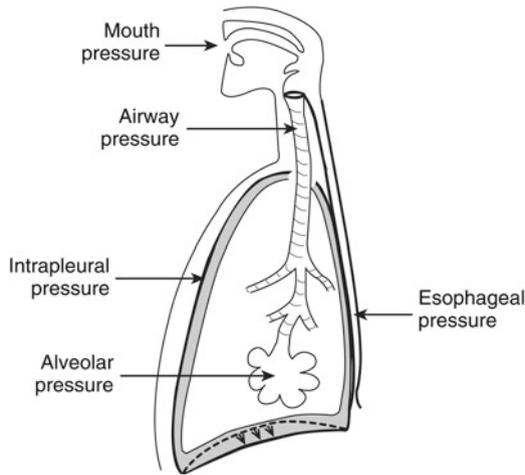


Fig. 3.3 Schematic representation of components of respiratory pressures used in pulmonary function studies. Esophageal pressure approximates intrapleural pressure (Modified from Bhutani VK, Sivieri EM, Abbasi S: Evaluation of pulmonary function in the neonate. In Polin RA, Fox WW [Eds.]: *Fetal and Neonatal Physiology*, second edition, Philadelphia, W.B. Saunders, 1998, p. 1153, with permission)

2. At this time, the alveolar pressure is atmospheric (zero) because there is no airflow and thus no pressure drop along the conducting airways.
3. During a spontaneous inspiration, forces generated by the respiratory muscles cause the intrapleural pressure to further decrease producing a concomitant fall in alveolar pressure so as to initiate a driving pressure gradient which forces airflow into the lung.
4. During a passive expiration, the respiratory muscles are relaxed and the intrapleural pressure becomes less negative.
5. Elastic recoil forces in the now expanded lung and thorax cause alveolar pressure to become positive and thus the net driving pressure forces air to flow out of the lungs.
6. With forced expiration, the intrapleural pressure rises above atmospheric pressure.
7. The magnitude of the change in the alveolar pressure depends on the airflow rate and the airway resistance but usually varies between 1 and 2 cm H₂O below and above atmospheric pressure during inspiration and expiration, respectively.
8. This range of alveolar pressure change can be markedly increased with air trapping or airway obstruction.

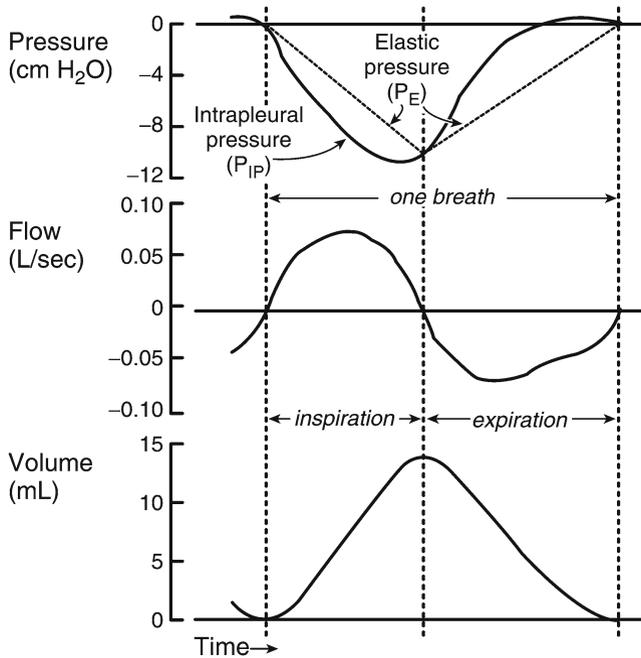


Fig. 3.4 During tidal breathing, airflow is zero at end-inspiration and end-expiration, where it reverses direction. The pressure difference between these two points represents the net elastic pressure at end-inspiration. The elastic component of intrapleural pressure at other points can be approximated by a straight line connecting points of zero flow

- C. Following are some physiologic observations of changes in intrapleural pressure during spontaneous breathing:
1. Under some conditions, respiratory airflow is zero or very close to zero:
 - a. During tidal breathing, airflow is zero at end-inspiration and end-expiration, where it reverses direction (Fig. 3.4).
 - b. During slow static inflation, airflow can be approximated as zero.
 - c. In both cases, the resistive component of driving pressure as described above is zero or $R\dot{V}=0$ and P_{IP} is equal to elastic pressure only:

$$P_{IP} = P_E = \frac{V}{C}$$

2. The elastic component of intrapleural pressure can be estimated on the pressure tracing by connecting with straight lines the points of zero flow at end-expiration and end-inspiration. The vertical segment between this estimated elastic pressure line and the measured intrapleural pressure (solid line) represents the resistive pressure component (Fig. 3.5).

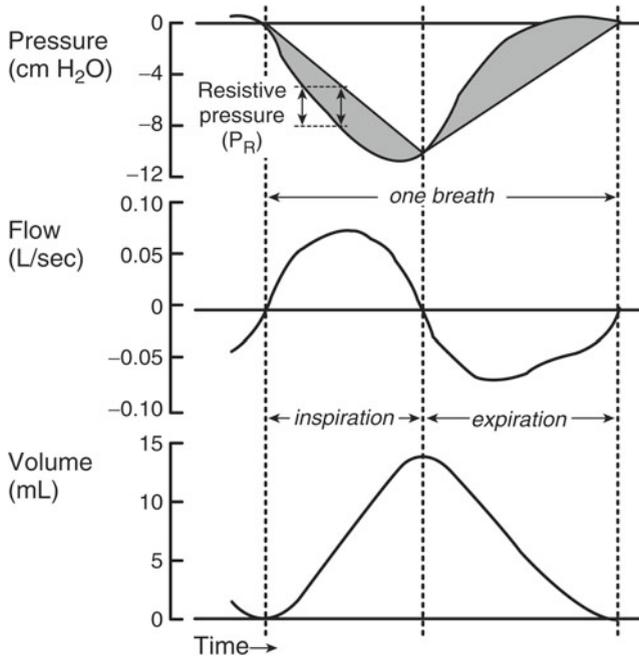


Fig. 3.5 The elastic component of intrapleural pressure can be estimated on the pressure tracing by connecting points of zero flow at end-expiration and end-inspiration with a straight line. The vertical distance between this estimate and the measured intrapleural pressure is the resistive pressure component (*solid line*)

3. Resistive pressure is usually maximum at points of peak airflow, which usually occurs during mid inspiration and mid expiration.
 4. Transpulmonary pressure (P_{TP}) is the differential between intrapleural pressure and alveolar pressure. This is the portion of the total respiratory driving pressure which is attributed to inflation and deflation of the lung specifically.
- D. With mechanical ventilation, of course, the driving pressure is provided by the ventilator. In contrast to spontaneous breathing, where a negative change in intrapleural pressure is the driving pressure for inspiration, the mechanical ventilator applies a positive pressure to an endotracheal tube. Nonetheless, in both cases there is a positive pressure gradient from the mouth to the alveoli. In both cases, the transpulmonary pressure gradient is in the same direction.
- IV. Factors that impact mechanics of airflow
- Factors that influence the respiratory muscles and respiratory mechanics have an effect on how air flows in and out of the lungs. These are characterized by physical, physiologic, and pathophysiologic considerations.

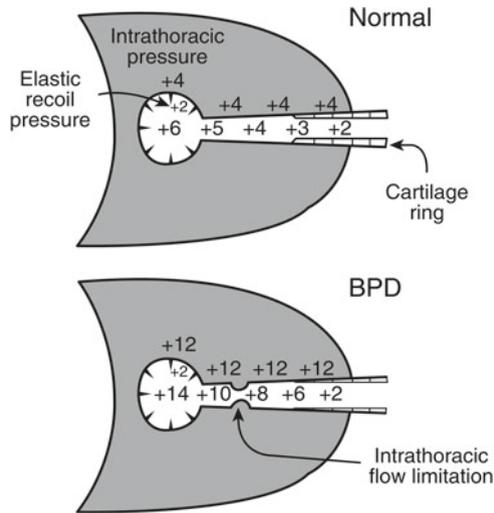


Fig. 3.6 Schematic comparison of normal and abnormal airflow. Infant with bronchopulmonary dysplasia (BPD) has higher transmural pressure generated during tidal breathing and thoracic airways are likely to be compressed during expiration, resulting in a flow limitation (Modified from Bhutani VK, Sivieri EM: *Physiological principles for bedside assessment of pulmonary graphics*. In Donn SM [Ed.]: *Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications*. Armonk, NY, Futura Publishing Co., 1998, p. 63, with permission)

A. Physical factors

1. The pattern of airflow is affected by the physical properties of the gas molecules, the laminar or turbulent nature of airflow, and the dimensions of the airways, as well as the other effects described by the Poiseuille equation (Chap. 7).
2. The elastic properties of the airway, the transmural pressure on the airway wall, and structural features of the airway wall also determine the mechanics of airflow.
3. In preterm newborns, the airways are narrower in diameter and result in a higher resistance to airflow. The increased airway compliance increases the propensity for airway collapse or distension. If a higher transmural pressure is generated during tidal breathing (as in infants with bronchopulmonary dysplasia, or, during positive pressure ventilation), the intrathoracic airways are likely to be compressed during expiration (Fig. 3.6).
4. During forced expiration, the more compliant airways are also likely to be compressed in the presence of a high intrathoracic pressure.
5. Increased distensibility of airways, as when exposed to excessive end-distending pressure, can result in increased and wasted dead space ventilation.

6. Turbulence of gas flow, generally not an issue in a healthy individual, can lead to a need for a higher driving pressure in the sick preterm infant with structural airway deformations as encountered in those with BPD.

B. Physiologic

1. The tone of the tracheobronchial smooth muscle provides a mechanism to stabilize the airways and prevent collapse.
2. An increased tone as a result of smooth muscle hyperplasia or a hyper-responsive smooth muscle should lead to a bronchospastic basis of air-flow limitation.
3. The bronchomalactic airway may be destabilized in the presence of tracheal smooth muscle relaxants.
4. The effect of some of the other physiologic factors, such as the alveolar duct sphincter tone, is not yet fully understood.

C. Pathophysiologic states

1. Plugging of the airway lumen, mucosal edema, cohesion, and compression of the airway wall lead to alterations in tracheobronchial airflow.
2. Weakening of the airway walls secondary to the structural airway barotrauma and the consequent changes of tracheobronchomalacia also result in abnormal airflow patterns.
3. BPD-related airflow effects have also been previously described.

V. Lung volumes

Ventilation is a cyclic process of inspiration and expiration. Total or minute ventilation (MV) is the volume of air expired each minute. The volume of air moved in or out during each cycle of ventilation is the tidal volume (V_T) and is a sum of the air in the conducting zone (V_D , or dead space) and the respiratory zone (V_A , or alveolar space). Thus,

$$MV = (V_A + V_D) \times \text{Frequency}$$

The process of spontaneous breathing generally occurs at about mid total lung capacity (TLC) such that about two-thirds of the total capacity is available as reserve.

A. Ventilatory volume:

1. Tidal volume (V_T): volume of air inspired with each breath.
2. Minute ventilation: product of frequency (F , the number of tidal volumes taken per minute) and V_T .
3. Dead space (V_D): volume in which there is no gas exchange.
 - a. Dead space refers to the volume within the respiratory system that does not participate in gas exchange and is often the most frequent and unrecognized cause for hypercapnia.
 - b. It is composed of several components.

- (1) Anatomic dead space is the volume of gas contained in the conducting airway.
 - (2) Alveolar dead space refers to the volume of gas in areas of “wasted ventilation,” that is, in alveoli that are ventilated poorly or are under-perfused.
 - (3) The total volume of gas that is not involved in gas exchange is called the physiologic dead space. It is the sum of the anatomic and alveolar dead space.
- c. In a normal person, the physiologic dead space should be equal to the anatomic dead space. For this reason, some investigators refer to physiologic dead space as pathological dead space.
- d. Several factors can modify the dead space volume.
- (1) Anatomic dead space increases as a function of airway size and the airway compliance. Because of the interdependence of the alveoli and airways, anatomic dead space increases as a function of lung volume. Similarly, dead space increases as a function of body height, bronchodilator drugs, and diseases, such as BPD, tracheomegaly, and oversized artificial airways.
 - (2) Anatomic dead space is decreased by reduction of the size of the airways, as occurs with bronchoconstriction, tracheomalacia, or a tracheostomy.

4. Alveolar Volume (V_A): volume in which gas exchange occurs:

$$V_A = V_T - V_D$$

5. Alveolar ventilation (V_A): product of frequency and V_A .

B. Lung reserve volumes

Reserve volumes represent the maximal volume of gas that can be moved above or below a normal tidal volume (Fig. 3.7). These values reflect the balance between lung and chest wall elasticity, respiratory strength, and thoracic mobility.

1. Inspiratory reserve volume (IRV) is the maximum volume of gas that can be inspired from the peak of tidal volume.
2. Expiratory reserve volume (ERV) is the maximum volume of gas that can be expired after a normal tidal expiration. Therefore, the reserve volumes are associated with the ability to increase or decrease tidal volume. Normal lungs do not collapse at the end of the maximum expiration.
3. The volume of gas that remains is called the residual volume (RV).

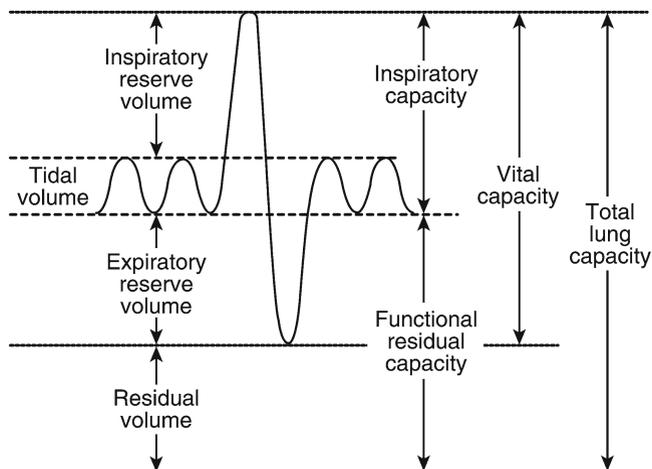


Fig. 3.7 Graphic representation of lung volumes and capacities (Modified from Bhutani VK, Sivieri EM: *Physiological principles for bedside assessment of pulmonary graphics*. In Donn SM [Ed.]: *Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications*. Armonk, NY, Futura Publishing Co., 1998, p. 67, with permission)

Table 3.1 Lung volumes in term newborns

Ventilatory volumes		Static lung volumes	
Normal values for term newborns		Normal values for term newborns	
V_T	5–8 mL/kg	RV	10–15 mL/kg
F	40–60 b/min	FRC	25–30 mL/kg
V_D	2–2.5 mL/kg	TGV	30–40 mL/kg
MV	200–480 mL/min/kg	TLC	50–90 mL/kg
V_A	60–320 mL/min/kg	VC	35–80 mL/kg

C. Lung capacities

The capacity of the lungs can be represented in four different ways: total lung capacity, vital capacity, inspiratory capacity, and functional residual capacity (FRC) (Fig. 3.7).

1. TLC is the amount of gas in the respiratory system after a maximal inspiration. It is the sum of all four lung volumes. The normal values as well as the values of static lung volumes for term newborns are shown in Table 3.1.
2. Vital capacity (VC) is the maximal volume of gas that can be expelled from the lungs after a maximal inspiration. As such, the vital capacity is the sum of IRV + TV + ERV. Inspiratory capacity (IC) is the maximal volume of gas that can be inspired from the resting end-expiration level; therefore, it is the sum of TV + IRV.

3. FRC is the volume of gas in the lung when the respiratory system is at rest; that is, the volume in the lung at the end of a normal expiration that is in continuity with the airways. The size of the FRC is determined by the balance of two opposing forces:
 - a. Inward elastic recoil of the lung tending to collapse the lung.
 - b. Outward elastic recoil of the chest wall tending to expand the lung.Functional residual capacity is the volume of gas above which a normal tidal volume oscillates. A normal FRC avails optimum lung mechanics and alveolar surface area for efficient ventilation and gas exchange.
4. Residual volume (RV): volume of air remaining in the respiratory system at the end of the maximum possible expiration.

$$\text{Expiratory reserve volume (ERV)} = \text{FRC} - \text{RV}.$$

- D. It is important to note that thoracic gas volume (TGV) is the total amount of gas in the lung (or thorax) at end-expiration. This value differs from FRC and the difference would indicate the magnitude of air trapping.

Chapter 4

Pulmonary Gas Exchange

Vinod K. Bhutani

I. Introduction

- A. Pulmonary circulation plays a critical gas exchange function of the lung.
- B. Processes governing pulmonary vascular development, especially with regard to the origin, differentiation, and maturation of the various cell types within the pulmonary vascular wall. Include factors which control development and also provide insight into the genetic diversity of pulmonary vascular wall cells.
- C. These findings begin to provide explanations for the tremendous functional heterogeneity of the pulmonary vascular cells under both normal and pathophysiologic conditions. In the future, we will need to focus more attention on understanding from where and when endothelial and smooth muscle cells arise in the course of pulmonary arterial, bronchial, and pulmonary venous development.
- D. We will need to identify the environmental signals and signaling molecules that contribute to the terminal differentiation of specific vascular cells at the local level, and which confer unique properties to these cells.
- E. We will need to use model systems that allow us to accurately mark and follow cell fates within the complex environment that obviously contributes to the ultimate phenotype of the pulmonary vascular cell of interest, as well as model systems where cell migration, cell–cell interaction, and proper environmental cues remain intact.
- F. We will need to take into account the fact that angioblasts may arise from many distant sites, and at certain stages of lung development could even come from the bone marrow-derived pool of circulating stem cells.

V.K. Bhutani, MD (✉)

Department of Pediatrics, Stanford University, Lucile Packard Children's Hospital,
750 Welch Road, 3315, Palo Alto, CA 94305, USA

e-mail: bhutani@stanford.edu

- G. Because it is clear that oxygen tension plays such a critical role in directing the development of many organs, we need to take into account the oxygen tension at which experiments are performed.
 - H. Further, we need to address the role that the nervous system may play in directing vascular development within the lung.
 - I. In doing all of the above, we will come to a better understanding of the unique origins of the macro- and microcirculations of the lung, and may also provide new insight into the unique expansion and function of the selective cell types that play critical roles in many pulmonary diseases.
- II. Transition at birth
- A. Independent pulmonary gas exchange to replace the maternal placental gas exchange mechanism needs to be established within the first few minutes after birth.
 - B. In order to effect this transition, several physiologic changes occur.
 - 1. Adjustments in circulation
 - 2. Pulmonary mechanics
 - 3. Gas exchange
 - 4. Acid–base status
 - 5. Respiratory control
 - C. Upon transition, gas exchange takes place through an air–liquid interface of alveolar epithelium with alveolar gas in one compartment and blood in the other (vascular) compartment. An understanding of gas laws, alveolar ventilation, and pulmonary vasculature are important in facilitating optimal pulmonary gas exchange.
- III. Brief outline of cardiopulmonary adaptations
- A. Prior to birth, the fetus is totally dependent on the placenta (Fig. 4.1) and has made cardiopulmonary adjustments for optimal delivery of oxygen, whereas, the maternal physiology has been adapted to maintain fetal normocapnia.
 - B. The salient features and sequence of events that occur during fetal to neonatal transition are listed in Table 4.1.
- IV. Application of gas laws for pulmonary gas exchange
- A. There are fundamental laws of physics that pertain to the behavior of gases and thereby impact gas exchange.
 - B. An understanding of these laws is also specifically pertinent to the clinician in his/her ability not only to measure and interpret blood gas values, but also to evaluate the impact on gas exchange during clinical conditions of hypothermia, high altitude, and use of gas mixtures of varying viscosities and densities.
 - C. A brief description of the pertinent and clinically relevant gas laws is listed in Table 4.2.

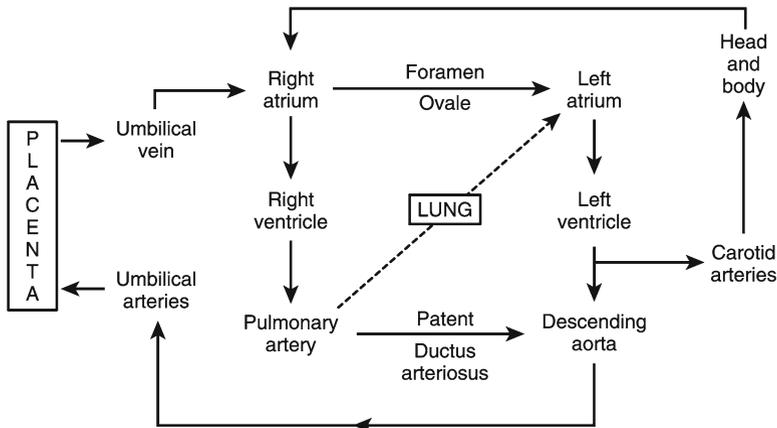


Fig. 4.1 Schematic representation of fetal circulation (From Bhutani VK: Extraterine adaptations in the newborn. *Sem Perinatol.* 1997; 1:1–12, with permission)

- D. One of the most fundamental and widely used relationships to describe pulmonary gas exchange is summarized as:

$$\text{PaCO}_2 = 863 \left(\frac{V_{\text{CO}_2}}{V_A} \right)$$

where, in a steady state and with negligible inspired carbon dioxide, the alveolar pressure of carbon dioxide (PaCO_2) is proportional to the ratio of the rates of carbon dioxide elimination (V_{CO_2}) and alveolar ventilation (V_A). This equation helps to summarize several of the gas laws. The applications of the laws are thus:

1. PaCO_2 : when measured in dry gas as a percentage, Dalton's law needs to be applied to convert the value to partial pressure. The partial pressure of carbon dioxide, rather than its percentage composition, is the significant variable because Henry's law of solubility states that the gas is physically dissolved in liquid and in equilibrium with the gas phase at the same partial pressure.
2. 863: this peculiar number is derived from the need to standardize measurements from body temperature (310°K) to standard pressure and temperature (760mmHg , 273°K). Based on the product $310 \times (760/273)$, we obtain the value 863 (in mmHg) providing the constant for the relationship in the above equation.
3. V_{CO_2} / V_A : These values are measured at ambient temperature and pressure, saturated with water vapor (ATPS). Carbon dioxide output needs to be converted to standard temperature, pressure, dry (STPD) using Boyle's and Charles's laws while alveolar ventilation has to be corrected to body temperature, pressure and saturated with water vapor (BTPS).

Table 4.1 Salient features of extrauterine cardiopulmonary adaptations

Parameter	Mother (second trimester)	Fetus (before labor)	Newborn (before first breath)	Newborn (at about 6 h)
PaO ₂	80–95 torr	<25 torr in pulmonary artery	16–18 torr	80–95 torr
PaCO ₂	~34 torr	40–42 torr	45–65 torr	34 torr
pH	~7.45	7.35–7.40	7.10–7.30	7.35–7.40
Pulmonary blood flow	Equivalent to cardiac output	13–25% Cardiac output	~25% Cardiac output	90–100% Cardiac output
Shunts	Placental shunts	– Placental shunts – Foramen ovale – Ductus arteriosus	– Foramen ovale – Ductus arteriosus – Intrapulmonary shunts	– Foramen ovale closed – Ductus arteriosus usually closed – Intrapulmonary shunts
Pulmonary mechanics	– Air-filled lungs – Hyperventilation	– Liquid-filled – FRC at 30 mL/kg	– Air and fluid (16–19 mL/kg) in the lungs	– Air-filled – FRC at 30 mL/kg
Control of respiration	Progesterone-mediated hyperventilation	Fetal breathing dependent more on stretch	First breath initiated by nonspecific respiratory	Rhythmic respiratory cycles based on chemoreceptors

Table 4.2 Laws that describe gas behavior

Law	Description
Boyle's law	At constant temperature (T), a given volume (V) of gas varies inversely to the pressure (P) to which it is subjected
Charles's law	Gas expands as it is warmed and shrinks as it is cooled
Dalton's law	The total pressure exerted by a mixture of gases is equal to the sum of the partial pressure of each gas
Amagat's law	The total volume of a mixture of gases is equal to the sum of the partial volume of each gas at the same temperature and pressure
Henry's law	At constant temperature, any gas physically dissolves in a liquid in proportion to its partial pressure, although the solubility coefficient decreases with increasing temperature and differs from one gas to another
Graham's law	The rate of diffusion of a gas is inversely proportional to the square root of its density
Fick's law	The transfer of solute by diffusion is directly proportional to the cross-sectional area available for diffusion and to the difference in concentration per unit distance perpendicular to that cross-section
Ideal gas equation	Summation of above laws: $PV=nRT$, where R is a numerical constant
Van der Waals's equation	Refinement of the ideal gas equation based upon the attractive forces between molecules and upon the volume occupied by the molecules
Barometric pressure and altitude	The decrease in barometric pressure is not linear with increasing altitude, weather, temperature, density of atmosphere, acceleration of gravity, etc., influence it

V. Development of pulmonary vasculature

- A. The main pulmonary artery develops from the embryonic left sixth arch.
 1. The sixth arches appear at about 32 days after conception (5 mm embryo stage) and give branches to the developing lung bud.
 2. Branches from the aorta that supply the lung bud and the right arch disappear subsequently.
 3. By 50 days (18 mm embryo stage), the adult pattern of vascularization has commenced.
- B. Before the main pulmonary veins are developed, the vessels drain into the systemic circulation of the foregut and trachea.
 1. These connections are lost as the main pulmonary vein develops.
 2. A primitive pulmonary vein appears as a bud from the left side of the atrial chamber at about 35 days.
 3. Starting as a blind capillary, it bifurcates several times to connect with the developing lung bud.
 4. Subsequently, the first two branches are resorbed to form the left atrium at about the seventh week.
- C. The branches of the pulmonary arterial system maintain a position next to the bronchial structures as both develop during the glandular and canalicular stages of lung development.

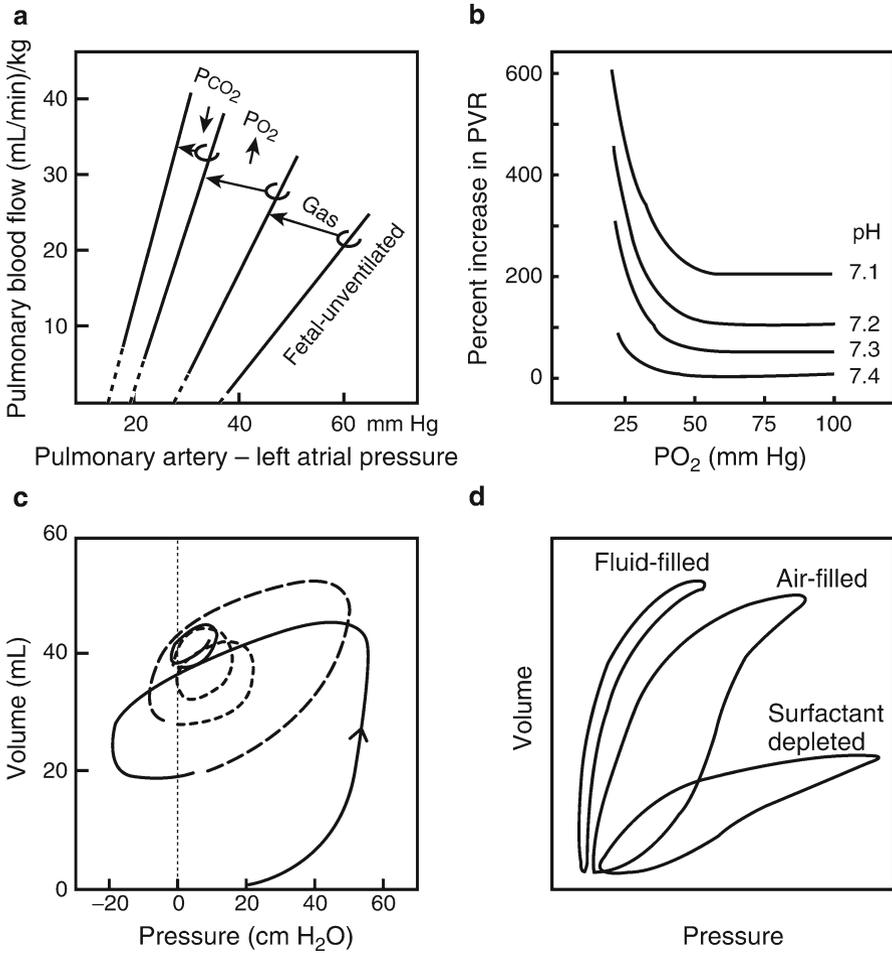


Fig. 4.2 Physiologic processes that facilitate onset of postnatal pulmonary gas exchange. (a) Effect of ventilation on reducing pulmonary vascular resistance (PVR). (b) Effects of acidosis correction on reducing PVR. (c) First breaths and establishment of optimal functional residual capacity. (d) Effect of driving pressure to maintain optimal tidal volume and work of breathing (Modified from Bhutani VK: Differential diagnosis of neonatal respiratory disorders. In Spitzer AR [Ed.]: *Intensive Care of the Fetus and Neonate*. St. Louis, Mosby-Year Book, 1996, p. 500, with permission)

D. By 16 weeks, there is a complete set of vessels that lead to the respiratory bronchioles, terminal bronchioles, and the terminal sacs.

VI. Onset of pulmonary gas exchange

A. The physiologic processes that facilitate the onset of postnatal pulmonary gas exchange (described in the series of events depicted in Fig. 4.2).

1. The effect of ventilation on reducing pulmonary vascular resistance (A).
 2. The effect of acidosis correction to enhance pulmonary blood flow (B).
 3. The effect of driving pressure and successful establishment of respiration during first breaths to achieve an optimal functional residual capacity (C).
 4. The effect of driving pressure to maintain optimal tidal volume and achieve the least work of breathing (D).
- B. These events highlight the other series of biochemical and physiologic events that concurrently occur to successfully establish and maintain the matching of ventilation to perfusion.
- C. Maladaptations delay transition to adequate pulmonary gas exchange. (Maladaptation may result from central/peripheral nervous system abnormalities as well as cardiopulmonary problems).
- D. Though it has been well established that a newborn is more likely to have events that lead to hypoxemia or maintain adequate oxygenation with an inability to compensate hemodynamically, it has also been realized that a newborn is more tolerant of hypoxemia than an adult. Reasons for occurrences of hypoxemic events:
1. Reduced FRC relative to the oxygen consumption
 2. Presence of intrapulmonary shunts that lead to V/Q mismatching
 3. A high alveolar–arterial oxygen gradient
- E. Hypercapnia that results from an inability to maintain adequate alveolar ventilation in the face of mechanical loads also results in lower alveolar oxygen tension.
- F. From a hemodynamic perspective, impaired oxygen delivery may occur because of:
1. Low P_{50} values because of high oxygen affinity of the fetal hemoglobin
 2. Increased blood viscosity
 3. Lower myocardial response to a volume or pressure load
 4. Inadequate regional redistribution of the cardiac output
- G. The relationship between arterial oxygen and carbon dioxide values and how these relate to hypoxemia and respiratory failure are shown in Fig. 4.3.
- H. The effect of oxygen inhalation on the composition of alveolar and blood gas tensions is shown in Table 4.3.
- VII. Optimal pulmonary gas exchange
- A. Failure to establish optimal pulmonary gas exchange leads to either oxygenation or ventilation failure.
 - B. Factors that impact on adequacy of neonatal gas exchange (especially a preterm newborn) are listed in Table 4.4.
 - C. Respiratory failure can initially lead to increased respiratory effort in an attempt at compensation, followed by an inability to ventilate, or apnea.

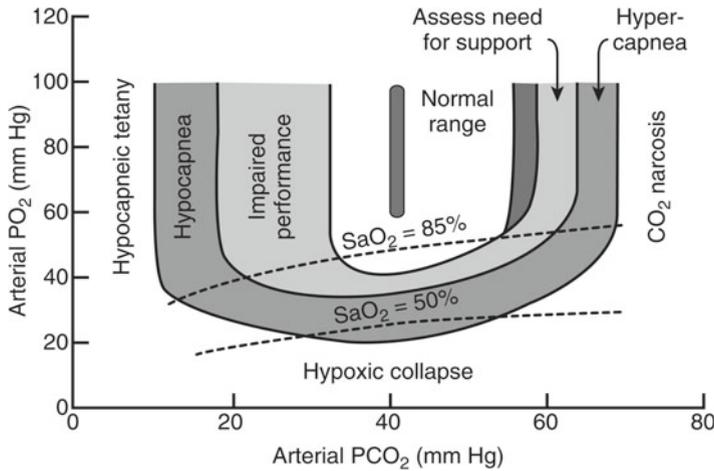


Fig. 4.3 The relationship between alveolar oxygen and carbon dioxide values and how these relate to hypoxemia and respiratory failure (Modified from Bhutani VK: Differential diagnosis of neonatal respiratory disorders. In Spitzer AR [Ed.]: *Intensive Care of the Fetus and Neonate*. St. Louis, Mosby-Year Book, 1996, p. 501, with permission)

Table 4.3 Effect of oxygen inhalation (100%) on composition of alveolar and blood gas tensions

	Inspired dry gas		Alveolar gas		End pulmonary capillary blood		Arterial blood		End-systemic capillary blood	
	Air	O ₂	Air	O ₂	Air	O ₂	Air	O ₂	Air	O ₂
P _{O₂} , torr	1,591	760	104	673	104	673	100	640	40	53.5
P _{CO₂} , torr	0.3	0	40	40	40	40	40	40	46	46
P _{H₂O} , torr	0.0	0	47	47	47	47	47	47	47	47
P _{N₂} , torr	600.6	0	569	0	569	0	573	0	573	0
P _{total} ^a , torr	760	760	760	760	760	760	760	727	706	146.5 ^a
O ₂ Sat (%)					98	100	98	100	75	85.5

^aWhat happens to the total gas tension when a baby breathes 100% oxygen: the total venous gas tension is now at 146.5 torr

Table 4.4 Factors that impact on adequacy of neonatal gas exchange

Factors for gas exchange	Impact of prematurity
Neural control of respiration	Immaturity
Mechanical loads: elastic and resistive	High chest wall to lung compliance ratio
Stability of end-expiratory lung volume	Compliant airways with pre-end-expiratory closure of airways
Ventilation-perfusion matching	Reactive pulmonary vasculature
Hemoglobin dissociation curve properties	Fetal hemoglobin characteristics
Match cardiac output to oxygen consumption	High neonatal oxygen consumption
Ability to maintain alveolar ventilation	Propensity for respiratory muscle fatigue

- D. The concurrent changes in arterial oxygen and carbon dioxide gas tensions during both health and disease are shown in Fig. 4.3.

VIII. Physiologic principles to improve pulmonary gas exchange

- A. The physiologic principles that may be utilized to improve oxygenation, enhance carbon dioxide elimination, and establish ventilation at optimal FRC (and thereby with the least baro- and volutrauma) are listed in Fig. 4.2a–d.
- B. The clinically relevant interventional strategies are crucial to achieve optimal gas exchange.
- C. It is also valuable to be reminded that in a healthy newborn gas tensions are maintained in a narrow range by exquisitely sensitive feedback mechanisms of chemoreceptors and stretch receptors.
- D. Moreover, during fetal development the maternal physiology is significantly altered to maintain fetal normocapnia and neutral acid–base status.
- E. Thus, as clinicians assume control of the newborn’s ventilation with supportive technologies, the road map for optimal pulmonary gas exchange needs to be “quality controlled” from physiologic perspectives and with the least amount of baro- and volutrauma.

Chapter 5

Oxygen Therapy

Win Tin

I. Introduction

- A. *“The clinician must bear in mind that oxygen is a drug and must be used in accordance with well recognized pharmacologic principles; i.e., since it has certain toxic effects and is not completely harmless (as widely believed in clinical circles) it should be given only in the lowest dosage or concentration required by the particular patient.” [Julius Comroe, 1945].*
- B. Oxygen is the most commonly used therapy in neonatal intensive care units, and ocular oxygen toxicity in newborns (cicatrical retinopathy of prematurity, ROP) was first described more than 50 years ago.
- C. The ultimate aim of oxygen therapy is to achieve adequate tissue oxygenation, but without creating oxygen toxicity and oxidative stress.

II. Physiological considerations

- A. Tissue oxygenation depends upon:
 - 1. Fractional-inspired oxygen (FiO_2).
 - 2. Gas exchange mechanism within the lungs.
 - 3. Cardiac output.
 - 4. Oxygen carrying capacity of the blood. Approximately 97% of oxygen transported to the tissue is carried by hemoglobin and 3% is dissolved in plasma.
 - 5. Local tissue edema or ischemia.
- B. Fetal oxygen transport and postnatal changes:
 - 1. Fetal hemoglobin (HbF) has higher oxygen affinity and lower P_{50} (oxygen tension at which 50% of hemoglobin is saturated at standard pH and

W. Tin, FRCPCH (✉)
Department of Neonatal Medicine, The James Cook University Hospital,
Middlesbrough, UK TS4 3BW
e-mail: win.tin@tees.nhs.uk

temperature). This favors oxygen uptake from a placenta to a fetus as adequate transfer of oxygen is achieved at relatively low PaO_2 .

2. High oxygen affinity of HbF, however, has a disadvantage in oxygen delivery to the fetal tissue, but this is offset by the fact that the fetal oxygen–hemoglobin saturation curve is much steeper; therefore, adequate dissociation of oxygen from hemoglobin can occur with a relatively small decrease in oxygen tension at the tissue level.
3. The newborn infant needs more oxygen than the fetus (oxygen consumption of most animal species increases by 100–150% in the first few days of life); therefore, the P_{50} which is adequate for tissue oxygenation in a fetus is not enough in a newborn.
4. Changes in both oxygen affinity and oxygen carrying capacity occur postnatally, and in an infant born at term, P_{50} reaches adult levels by about 4–6 months of age.

C. Indices of oxygenation:

1. *Alveolar–arterial oxygen pressure difference (A–aDO₂)*. The difference in partial pressure of oxygen between alveolar and arterial levels correlates well with ventilation/perfusion (V/Q) mismatch. In a newborn who is breathing room air, this value can be as high as 40–50 torr, and may remain high (20–40 torr) for days. The increase in A–aDO₂ is generally caused by:
 - a. Block of oxygen diffusion at the alveolar-capillary level
 - b. V/Q mismatch in the lungs (from either increase in physiologic dead space or intrapulmonary shunting)
 - c. Fixed right-to-left shunt (intracardiac shunting)
2. *Oxygenation index (OI)*. This is most frequently used clinical and research metric because of its ease of calculation, and is felt to be a more sensitive indicator for severity of pulmonary illness as mean airway pressure ($\text{P}\bar{\text{a}}\text{w}$) is taken into its calculation

$$\text{OI} = \text{P}\bar{\text{a}}\text{w} \times \text{FiO}_2 / \text{PaO}_2 \times 100.$$

3. *Arterial-to-alveolar oxygen tension ratio (a/A ratio)*.
4. There is no significant difference in the performance of these indices in predicting death and adverse respiratory outcome.

D. PaO_2 and Oxygen saturation (SaO_2)

1. Several clinical studies have shown that fractional O₂ saturation above 92% can be associated with PaO_2 values of 80 mmHg (10.7 kPa) or even higher (Fig. 5.1).
2. Although PaO_2 and SaO_2 are directly related to each other, this correlation is influenced by several physiologic changes (quantity and quality of Hb, temperature, acid–base status, PaCO_2 , and concentration of 2–3 DPG).

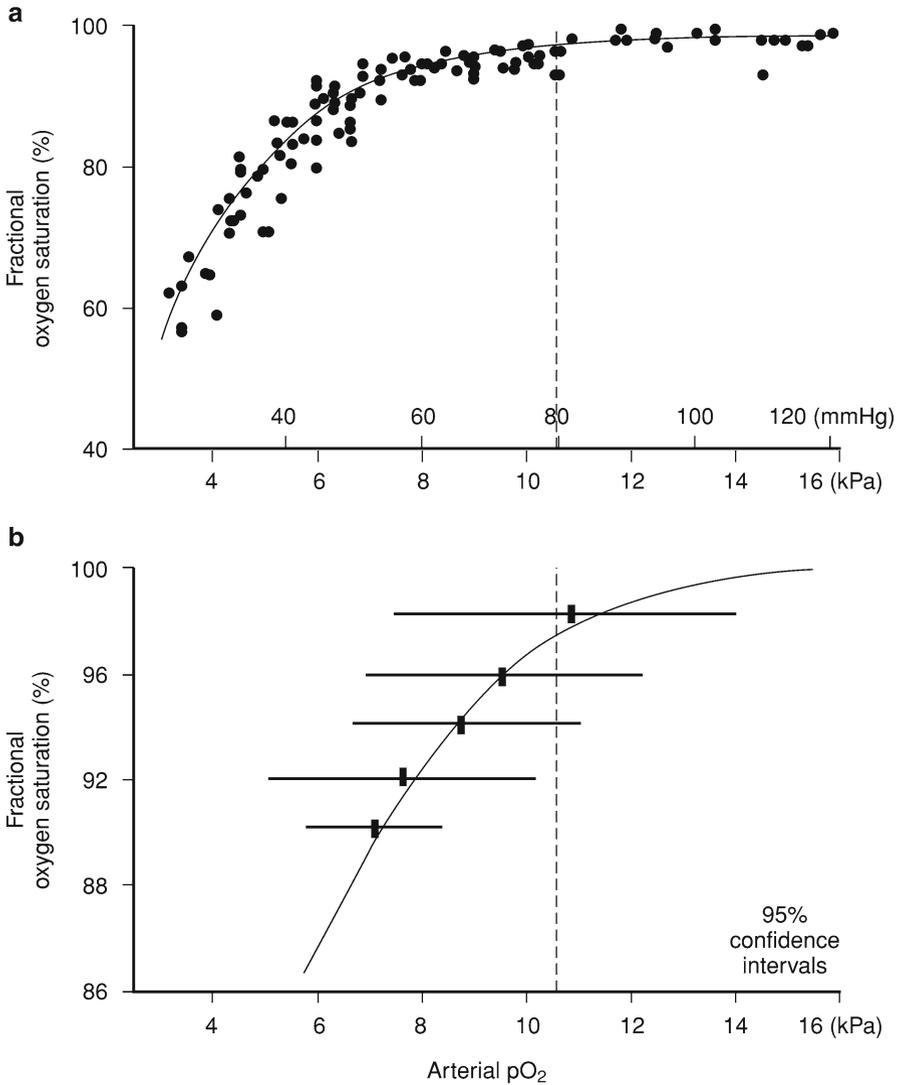


Fig. 5.1 Oxygen therapy and toxicity. The relation between fractional O₂ saturation measured with a pulse oximeter and arterial partial pressure (reproduced with permission from BMJ Books). The *dashed line* marks the TcO₂ above which there was an increased risk of ROP in the study reported by Flynn in 1992. The *bars* in (b) show the range within which 95% of all measures of partial pressure varied when oximeter read 90, 92, 94, 96, and 98% in the study reported by Brockway and Hay in 1998

III. Monitoring oxygen therapy (Chap. 17)

A. Continuous, noninvasive monitoring

1. Pulse oxygen saturation (Pulse oximetry, SpO_2): This is the most user friendly method and therefore most widely used technique for monitoring oxygen therapy, but it has limitations, mainly the failure to detect hyperoxia.
2. Transcutaneous PO_2 ($TcPO_2$): This is the preferred method by some clinicians, particularly for monitoring in the early life of newborn infants. The accuracy depends on skin thickness and perfusion status and sensor temperature. There is a risk of local skin burn in very premature infants.

B. Continuous, invasive monitoring (via umbilical arterial catheter)

1. Arterial oxygen tension (PaO_2)
2. Blood gas analysis

C. Intermittent monitoring

1. PaO_2 (via umbilical or peripheral arterial catheters)
2. Mixed central venous oxygen tension (PvO_2). This value, if taken from a catheter placed in the inferior vena cava, reflects the oxygen tension of the blood that has equilibrated with the tissues, and therefore can be a useful indicator of tissue oxygen delivery.

IV. Clinical evidence for monitoring oxygen therapy

- A. There is no clear evidence to date to suggest what the optimal SaO_2 or PaO_2 values are in premature infants (who receive supplemental oxygen therapy) in order to avoid potential oxygen toxicity while providing adequate oxygen delivery to tissues.
- B. Pulse oximetry is more widely used (and is often used solely) as continuous, noninvasive monitoring for oxygen therapy, yet there remains a wide variation in SaO_2 monitoring policies among neonatologists and NICUs.
- C. Several observational studies in the past have suggested that accepting lower arterial oxygen saturation (measured by pulse oximetry) in preterm infants during the neonatal period was associated with lower rates of severe ROP and other neonatal complications, including bronchopulmonary dysplasia.
- D. The STOP-ROP trial showed that keeping SaO_2 above 95% in very premature infants (mean gestational age 25.4 weeks) when they were found to have developed prethreshold ROP (mean postmenstrual age 35 weeks) slightly reduced the risk of the disease progressing to severe ROP needing retinal surgery, but the benefit was only seen in those without “plus disease.” However, this study also suggested that aiming to keep higher oxygen saturation was associated with significantly increased adverse pulmonary outcomes, without any benefit in growth or the eventual retinal outcome as assessed three months after the expected date of delivery.
- E. The BOOST trial also showed that aiming to keep high oxygen saturation in chronically oxygen-dependent babies, born before 30 weeks’ gestation was

not associated with the improvement in growth and development at 1 year, but was associated with increase in duration of oxygen therapy and the utilization of health care resources.

V. Emerging evidence from the “oxygen saturation targeting trials”

- A. Five masked randomized controlled trials (with a planned prospective meta-analysis) have been conducted recently to compare the clinical outcomes (primary outcome being death and severe disability) of targeting “low” oxygen saturation range of 85–89% vs. “high” range of 91–95% in preterm infants of less than 28 weeks’ gestation.
- B. Evidence available from some of these trials showed that targeting oxygen saturation range of 91–95%, compared to 85–89% reduces the risk of mortality but increases the risk of severe ROP.
- C. Final conclusions will be available when the information on the primary outcome of death and severe disability is available and the prospective meta-analysis is completed. However, clinicians should be aware that the current oxygen trials may not end the questions and controversies on “oxygen”—a powerful and the most commonly used “drug” in neonatal medicine.

Suggested Reading

- Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen saturation targets and outcomes in extremely preterm infants. *N Engl J Med.* 2003;349:959–67.
- Brockway J, Hay WW. Prediction of arterial partial pressure of oxygen with pulse oxygen saturation measurements. *J Pediatr.* 1998;133:63–6.
- Delivoria-Papadopoulos M, McGowan JE. Oxygen transport and delivery. In: Polin RA, Fox WW, Abman SH, editors. *Fetal and neonatal physiology.* Philadelphia: Saunders; 2004.
- Saugstad OD. Bronchopulmonary dysplasia – oxidative stress and antioxidants. *Semin Neonatol.* 2003;8:39–49.
- Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics.* 2004;113:394–6.
- Silverman WA. Retrolental fibroplasias: a modern parable. New York: Grune & Stratton; 1980.
- Smith LE. Pathogenesis of retinopathy of prematurity. *Semin Neonatol.* 2003;8:469–73.
- Stop ROP Investigators. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized controlled trial.1: primary outcomes. *Pediatrics.* 2000;105:295–310.
- SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362:1959–1969.
- Tin W, Gupta S. Optimal levels of oxygenation in preterm infants: impact on outcomes. In: Bancalari E, Polin R, editors. *Questions and controversies in neonatology series: pulmonary volume.* Philadelphia: Elsevier; 2008.
- Tin W, Gupta S. Optimum oxygen therapy in preterm babies. *Arch Dis Child.* 2007;92:F143–147.
- Tin W, Wariyar U. Giving small babies oxygen: 50 years of uncertainty. *Semin Neonatol.* 2002; 7:361–7.
- Weis CM, Cox CA, Fox WW. Oxygen therapy. In: Spitzer AR, editor. *Intensive care of the fetus and newborn.* St. Louis: Mosby; 1996.

Chapter 6

Oxygen Toxicity

Ola Didrik Saugstad

I. Oxygen toxicity in the newborn period

A. Historical aspects

1. Oxygen was discovered independently by Scheele and Priestly in 1772 and 1774, respectively. However, already in 1604 the Polish alchemist Michael Sendivogius had described oxygen as vital air.
2. Lavoisier coined the term oxygen in 1775. Only 5 years later oxygen was used to treat newborns. In 1928, Flagg published in the Journal of the American Medical Association (JAMA) a method to resuscitate newborns with oxygen and CO₂.
3. Already Priestly understood that oxygen might be toxic and during the nineteenth century more and more information was collected showing its toxic effects.
4. In the 1950s, oxygen was associated with the development of retrolental fibroplasia today called retinopathy of prematurity (ROP), and at the end of the 1960s oxygen toxicity was associated with the development of bronchopulmonary dysplasia (BPD).
5. Some years later, it was hypothesized oxygen might be toxic during resuscitation and in 2010 international guidelines were changed recommending starting resuscitation of term or late preterm infants with air instead of oxygen. Still the optimal FiO₂ for extremely low birth weight (ELBW) infants is not defined.

B. Evolutionary aspects

1. Life developed in an oxygen free and reducing atmosphere.

O.D. Saugstad, MD, PhD (✉)
Department of Pediatric Research, Oslo University Hospital, Rikshospitalet,
Sognsvannsveien 20, Oslo 0373, Norway
e-mail: odsaugstad@rr-research.no

2. The so-called Last Universal Common Ancestor was probably resistant to oxygen toxicity, and it is hypothesized that this was due to the fact that primitive organisms were forced through a “radiation bottleneck” making life resistant both to radiation injury and oxygen toxicity.
3. This prepared eukaryocytes for a life in a high oxygen atmosphere.

C. Basic mechanisms

1. In 1891, the Scottish chemist Sir James Dewar discovered that oxygen is magnetic. This is caused by spin of unpaired electrons in the outer electron orbit, and this makes it difficult for oxygen to form new chemical bonds.
2. In order to complete electron pairing oxygen can only receive single electrons with antiparallel spin. Accepting electrons stabilizes the oxygen molecule.
3. During oxidative phosphorylation in the mitochondria, single electrons escape and join with 1–2% of the total oxygen consumed by the cells to form superoxide radicals. By adding another 1, 2, or 3 electrons hydrogen peroxide, hydroxyl radicals, and finally water are formed.
4. Oxygen free radicals or reactive oxygen species (ROS) have the capability to oxidize unsaturated free fatty acids, proteins, and DNA. They are also important as signaling substances and therefore regulating physiologic processes such as circulatory aspects as well as growth and development. Therefore, it is important for the organism to control the redox status and oxidative stress tightly; even short deviations in oxidative stress indicators may trigger long-term effects.

D. Defense mechanisms

1. The body has a number of antioxidants both intracellular and extracellular. In fetal life, the intracellular antioxidant enzymes superoxide dismutases, catalases, and glutathione peroxidases are low and increase toward term.
2. Extracellular defense is not so low in the premature and after birth, for instance vitamin C is high. Another important antioxidant in this period of life is bilirubin and also uric acid.
3. The premature baby has less capacity to bind free iron, and thus these babies are more susceptible to damage through the Fenton reaction producing hydroxyl radicals.
4. DNA is protected against oxygen toxicity by a series of glycosylases. Base cutting repair is the most important cellular mechanism for repairing oxidative DNA injury. This repair is initiated by DNA glycosylases, which recognize and repair DNA base injuries. A number of glycosylases have been described as Neill 3, hMUTY, hOgg1, and others.

E. Control mechanisms

1. HIF-1 α is an important transcription factor which is activated in hypoxia and closed down by normoxia and hyperoxia. HIF-1 α transcribes a series of genes, such as vascular endothelial growth factor

(VEGF) and erythropoietin, which increases oxygen utilization and reduces oxygen consumption/demand.

2. A number of other transcription factors are involved in hyperoxia.
 - a. NF-erythroid 2-related factor (Nrf2) is activated by hyperoxia and activates antioxidant response element (ARE) and regulates detoxifying and antioxidant enzymes and increases expression of antioxidant enzymes. It is cytoprotective in type II cells of the lung and ameliorates O₂ induced lung injury in mice.
 - b. AP-1 controls genes regulating apoptosis, inflammation, and oxidative stress.
 - c. NF-κB activates genes regulating apoptosis, inflammation, and oxidative stress. It is activated by endotoxins and oxidative stress via toll-like receptors in the cell membrane.
 - d. p53 regulates expression of target genes related to cell cycle arrest, cell death, and DNA repair.
 - e. ccat/enhancer binding protein (CEBP) regulates cell proliferation and tissue development and is increased in the lung of rats exposed to hyperoxia.
 - f. STATs are polypeptides participating in signaling pathways and may be protective to hyperoxia by induction of heme-oxygenase which is a cytoprotective enzyme highly inducible following exposure to hyperoxia.

II. Potential risks of hyperoxia and oxygen toxicity

A. Brain

1. The neonatal brain is susceptible to hyperoxia because of a high content of unsaturated free fatty acids which are easily exposed to peroxidation, the presence of free iron, low antioxidant enzymes, and vulnerable oligodendrocytes. These brains are often also exposed to hyperoxia as well as inflammation which increase oxidative stress.
2. Pre- and immature oligodendrocytes are especially vulnerable to hyperoxia and oxidative stress.
3. This vulnerability is probably time dependent. The vulnerability of the brain to hyperoxia seems in rodents to be confined to a short window postpartum especially the first week of life. Whether such a vulnerable window exists in humans is not clear.
4. Microglia which peak in white matter in the 3rd trimester, when activated generate free radicals and secrete cytokines.

B. Retina

1. The transition from intra-to extrauterine life increases oxygen tension and decreases VEGF not only in the retina, but also in other tissues.
2. In the retina of the immature baby angiogenesis is halted, however after a few weeks, typically after 32 weeks' postconceptional age the retina

becomes hypoxic due to its increase in size without angiogenesis and consequently VEGF increases. This may lead to an uncontrolled vessel growth and development into the second stage of ROP.

3. In order for VEGF to be active, insulin like growth factor must reach a threshold level. Thus, the genesis of ROP is complex both dependent on hyperoxia and on a number of other nonhyperoxic factors related to growth.
4. Several studies, including one meta-analysis, strongly indicate that severe ROP can be significantly reduced by keeping the arterial oxygen saturation low and avoid fluctuations.

C. Lungs

1. Oxidative stress generally induces apoptosis in a relatively short period of time (hours).
2. Hyperoxia predominantly induces nonapoptotic cell death over a longer period of time (days).
3. Hyperoxia-induced lung injury is initially characterized by necrosis and swelling of capillary endothelial cells. Later, the epithelial cells are affected.
4. Hyperoxia-induced lung injury is also characterized by inflammation, destruction of the alveolar-capillary barrier, impaired gas exchange, and pulmonary edema.
5. Hyperoxia and ROS lead to increased release of chemo attractants and other proinflammatory cytokines promoting leukocyte recruitment to the lung. These activated leukocytes produce ROS, thus a vicious circle is established.
6. Hyperoxia activates caspases 3 and 9 as well as proinflammatory cytokines as IL-1, IL-6, IL-8, TGF β , TNF α , and VEGF.
7. Hyperoxia reduces protein synthesis. This seems to be mediated via mTOR pathways. Hyperoxia inhibits translation of mRNA.
8. A recent meta-analysis indicates that BPD can be reduced 20–25% by keeping arterial oxygen saturation low.

III. Clinical implications

B. Oxygenation in the delivery room

1. Term and late preterm infants. Recent international guidelines recommend starting resuscitation with air instead of supplemental oxygen. This is based on animal studies and ten clinical studies, including more than 2,000 babies resuscitated with either 21% or 100% oxygen. It seems that the use of 100% oxygen increases time to first breath approximately 30 seconds, reduces Apgar score, and heart rate at 90 s of life. More importantly is that resuscitation with air reduces relative risk of neonatal mortality approximately 30%. It is therefore recommended to start ventilation with air, and if possible have a blender so oxygen could be given in case the

baby does not respond adequately. A proper ventilation strategy to open the lungs is essential before oxygen is supplemented.

2. In babies with nonhealthy lungs (for instance after meconium aspiration) oxygen supplementation may be needed, and no clinical data exist regarding optimal FiO_2 for such babies. In the rare event of the need of chest compressions (<1/1,000 term or late preterm babies), it is not known which FiO_2 should be used.
3. If a pulse oximeter is available arterial oxygen saturations should aim at the 10th–50th percentile of the normal saturation limits recently published.
4. ELBW infants. Fewer data are available regarding how to oxygenate these babies in the delivery room. There are, however, data from smaller studies indicating that one should avoid starting with FiO_2 90–100%. Until more data are collected one advice, which is not evidence based, is to start ventilation with 21% or 30% oxygen and adjust FiO_2 to reach an arterial oxygen saturation between 10th and 50th percentile of the normal values recently published.

B. Oxygenation beyond the delivery room

1. Term babies should be weaned as quickly as possible, and this is often not difficult since their lungs are mature.
2. The optimal SpO_2 target of ELBW infants is not known. It is clear that especially severe ROP is reduced by keeping the saturation low and avoiding fluctuations. On the other hand, recent data indicate that a low saturation target between 85–89% increases mortality compared with a high target of 91–95%.

IV. Prevention of hyperoxia and hyperoxic injury

1. The best prevention of hyperoxic injury of the newborn is to avoid hyperoxia and inflammation, especially the combination of these.
2. Beta-carotene and vitamin A in one study was lower in preterm babies developing BPD. Postnatal vitamin A supplementation in the US multi-center trial reduced BPD (RR 0.89, 95% confidence interval 0.80–0.99, number needed to treat = 14–15).
3. Antioxidant enzymes, such as superoxide dismutase, as well as antioxidants such as vitamin E, have so far not been convincingly successful in preventing hyperoxic injury in newborn infants.
4. Early routine use of inhaled nitric oxide (iNO) in preterm infants with respiratory disease does not improve survival without BPD.
5. A number of different antioxidants such as allopurinol and erythropoietin have been tested with some protective effects. Nutrients, such as omega-3 fatty acids, especially docosahexaenoic acid, may have antioxidant properties in the newborn.
6. In the future, new and more powerful antioxidants may be developed giving clinical effects when administrated both pre- and postnatally.

Suggested Reading

- Bhandari V. Molecular mechanisms of hyperoxia-induced acute lung injury. *Front Biosci.* 2008;13:6653–61.
- Bhandari V. Hyperoxia-derived lung damage in preterm infants. *Semin Fetal Neonatal Med.* 2010;15:223–9.
- Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev.* 2010 Dec 8; (12):CD000509.
- Chen J, Smith LE. Retinopathy of prematurity. *Angiogenesis.* 2007;10:133–40.
- Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. *Pediatrics.* 2010;125:e1483–92.
- Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, Davis PG, Morley CJ. Defining the reference range for oxygen saturation for infants after birth. *Pediatrics.* 2010;125:e1340–7.
- Dennery PA. Oxidative stress in development: nature or nurture? *Free Radic Biol Med.* 2010;49:1147–51.
- Gerstner B, DeSilva TM, Genz K, Armstrong A, Brehmer F, Neve RL, Felderhoff-Mueser U, Volpe JJ, Rosenberg PA. Hyperoxia causes maturation-dependent cell death in the developing white matter. *J Neurosci.* 2008;28:1236–45.
- Haynes RL, Baud O, Li J, Kinney HC, Volpe JJ, Folkherth DR. Oxidative and nitrate injury in periventricular leukomalacia: a review. *Brain Pathol.* 2005;15:225–33.
- Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed.* 2008;93:F153–61.
- Lane N. *Oxygen: the molecule that made the world.* Oxford: Oxford University Press; 2002.
- Saugstad OD. Oxidative stress in the newborn—a 30-year perspective. *Biol Neonate.* 2005;88:228–36.
- Saugstad OD. Oxygen and oxidative stress in bronchopulmonary dysplasia. *J Perinat Med.* 2010;38:571–7.
- Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology.* 2011;100:1–8.
- Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, Stoll BJ, Lemons JA, Stevenson DK, Bauer CR, Korones SB, Fanaroff AA. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med.* 1999;340:1962–8.
- Vento M, Saugstad OD. Oxygen supplementation in the delivery room: updated information. *J Pediatr.* 2011;158(2 Suppl):e5–7.
- Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. *Int J Dev Neurosci.* 2011;29:423–40.
- Wright CJ, Dennery PA. Manipulation of gene expression by oxygen: a primer from bedside to bench. *Pediatr Res.* 2009;66:3–10.

Chapter 7

Pulmonary Mechanics

Emidio M. Sivieri and Vinod K. Bhutani

I. Introduction

Postnatal alterations in pulmonary mechanics, energetics, and functional residual capacity (FRC) describe the structural maturation of the preterm respiratory system. Surfactant deficiency among infants with very low gestational age is successfully ameliorated with prenatal steroids and/or surfactant replacement, but continues to be confounded by postnatal structural immaturity of airways, chest wall, and lung parenchyma. These, mechanical properties are encompassed by:

- A. The structural and physiologic characteristics of the neonatal respiratory system are unique and may act as impediments for normal respiration.
- B. These mechanical characteristics are the elastic and resistive properties of the respiratory system and the forces that cause airflow.
- C. The energy for ventilating the lungs is supplied by the active contraction of the respiratory muscles and these are required to overcome the elastic recoil of the lungs and the frictional resistance to airflow in the conducting airways.

II. Elastic properties

- A. The elastic properties of the lung parenchyma are dependent on the elasticity of pulmonary tissues, gas exchange spaces, smooth muscle, connective tissue, and the vascular tissue. Equally important as tissue elasticity is the recoil effect from surface tension forces at the alveolar liquid–air interface. The elastic properties of the airway depend on the smooth muscle, tissue

E.M. Sivieri, MS (✉)
Neonatal Pulmonary Function Laboratory, Pennsylvania Hospital,
800 Spruce Street, Philadelphia, PA 19107, USA
e-mail: sivierie@pahosp.com

V.K. Bhutani, MD
Department of Pediatrics, Stanford University, Lucile Packard Children's Hospital,
750 Welch Road, 3315, Palo Alto, CA 94305, USA

properties, and fibrocartilaginous structure, whereas the elastic properties of the thorax depend on the rib cage, intercostal muscle, the diaphragm, and tissues of the chest wall. These forces are interdependent, maintain a complex balance, and are influenced by the respiratory cycle and position of the body.

- B. Elasticity is the property of matter such that if a system is disturbed by stretching or expanding it, the system will tend to return to its original position when all external forces are removed. Like a spring, the tissues of the lungs and thorax stretch during inspiration, and when the force of contraction (respiratory muscular effort) is removed, the tissues return to their resting position. The resting position or lung volume is established by a balance of elastic forces. At rest, the elastic recoil forces of the lung tissues exactly equal those of the chest wall and diaphragm. This occurs at the end of every normal expiration, when the respiratory muscles are relaxed, and the volume remaining in the lungs is the FRC.
- C. The visceral pleura of the lung is separated from the parietal pleura of the chest wall by a thin film of fluid creating a potential space between the two structures. In a normal newborn at the end of expiration, the mean pressure in this space (i.e., the intrapleural pressure) is 3–6 cm H₂O below atmospheric pressure. This pressure results from the equal and opposite retractile forces of the lungs and chest wall and varies during the respiratory cycle, becoming more negative during active inspiration and more positive during expiration. During normal breathing, the pressure within the lungs is dependent upon the airway and tissue frictional resistive properties in response to airflow. Because there is no net movement of air at end-expiration and at end-inspiration, pressure throughout the lung at these times is in equilibrium with atmospheric air.
- D. Lung compliance
1. If pressure is sequentially decreased (made more subatmospheric) around the outside of an excised lung, the lung volume increases.
 2. When the pressure is removed from around the lung, it returns to its resting volume.
 3. This elastic behavior of the lungs is characterized by the pressure–volume curve (Fig. 21.12). Note that the pressure–volume curve during inspiration is different from that during expiration.
 4. This difference is typical of nonideal elastic systems and is called the hysteresis of the system.
 5. The ratio of change in lung volume to change in distending pressure defines the compliance of the lungs:

$$\text{Lung compliance} = \frac{\text{Change in lung volume}}{\text{Change in transpulmonary pressure}},$$

where transpulmonary pressure (P_{TP}) is the net driving pressure to expand the lungs only and is defined as the difference between alveolar pressure and intrapleural pressure. Intrapleural pressure cannot easily

- be measured directly, but it can be approximated by measuring the intraesophageal pressure.
6. By definition, lung compliance is a static characteristic obtained while the respiratory system is in a passive state and there is no airflow.
 - a. This can be achieved in infants by numerous, well-proven, static techniques.
 - b. Using special dynamic techniques, lung compliance can also be measured during uninterrupted spontaneous breathing or mechanical ventilation.
 - c. Compliance obtained in this manner is termed dynamic compliance.
 7. Although the pressure–volume relationship of the lung is not linear over the entire lung volume range, the compliance (of slope $\Delta V / \Delta P$) may be close to linear over the normal range of tidal volumes beginning at FRC (Fig. 7.1f). Thus, for a given change in pressure, tidal volume will increase in proportion to lung compliance, or $\Delta V = C / \Delta P$
 - a. As lung compliance is decreased, the lungs are stiffer and more difficult to expand.
 - b. When lung compliance is increased, the lung becomes easier to distend, and is thus more compliant.
 8. Lung compliance and pressure–volume relationships are determined by the interdependence of elastic tissue elements and alveolar surface tension. Tissue elasticity is dependent upon elastin and collagen content of the lung.
 9. A typical value for lung compliance in a young healthy newborn is 1.5–2.0 mL/cm H₂O/kg.
 - a. This value is dependent upon the size of the lung (mass of elastic tissue).
 - b. As may be expected, the compliance of the lung increases with development as the tissue mass of the lung increases.
 - c. When comparing values between different subjects, lung compliance should be normalized for lung volume by dividing by the FRC. This ratio is called the specific lung compliance.
 10. The surface-active substance (surfactant) lining the alveoli of the lung has a significant physiologic function.
 - a. Surfactant lowers surface tension inside the alveoli, thereby contributing to lung stability by reducing the pressure necessary to expand the alveoli.
 - b. Alveolar type II cells contain osmophilic lamellar bodies that are associated with the transformation of surfactant.
 - c. Impaired surface activity, as occurs in those premature infants with respiratory distress syndrome (RDS), typically results in lungs that are stiff (low compliance) and prone to collapse (atelectasis).

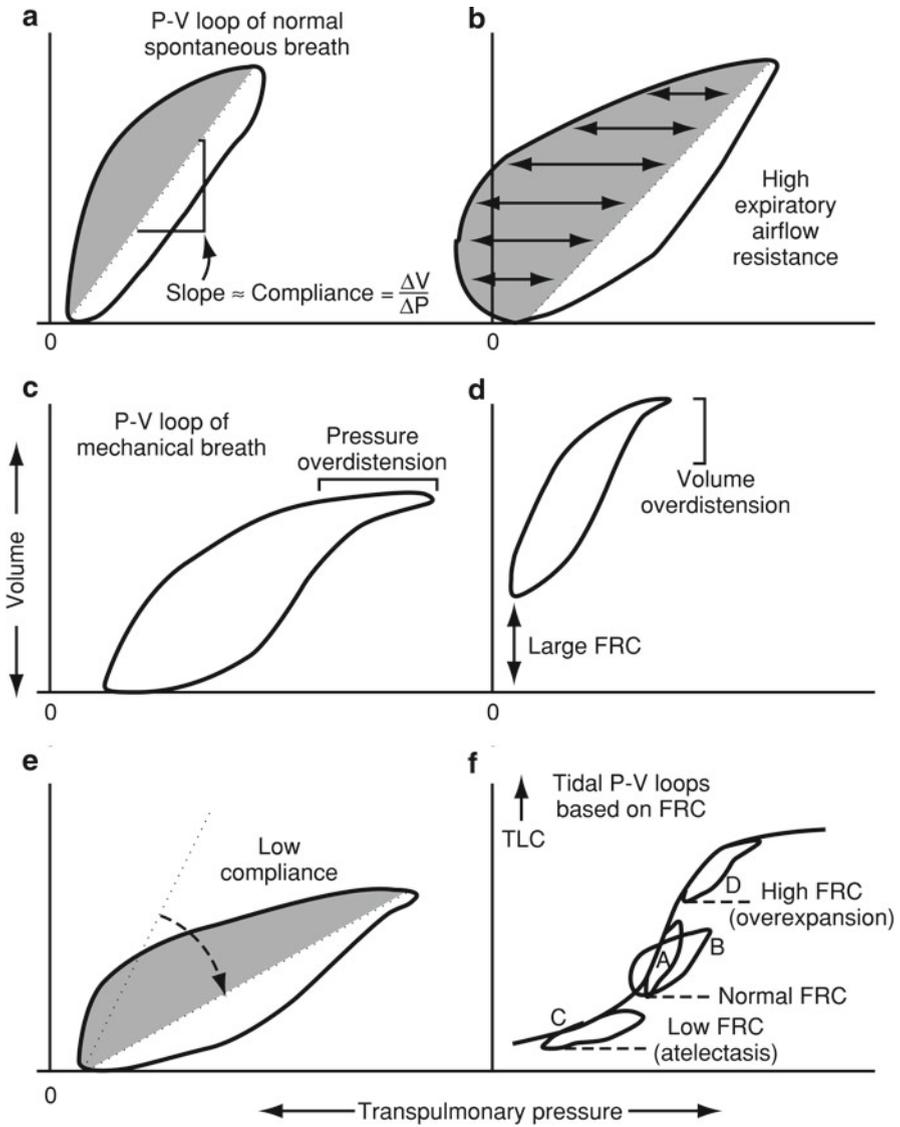


Fig. 7.1 Pressure–volume curves demonstrating elastic behavior of the lungs. (a) Normal spontaneous breath. (b) High expiratory airflow resistance. (c) Mechanical breath with pressure overdystension. (d). Mechanical breath with volume overdystension and large functional residual capacity. (e) Low compliance with clockwise shift of axis. (f) Tidal pressure–volume loops based on the functional residual capacity. (Modified from Bhutani VK, Sivieri EM. Physiological principles for bedside assessment of pulmonary graphics. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura; 1998. p. 70, with permission)

11. In bronchopulmonary dysplasia, the areas of fibrosis and scarring lead to a reduction in the lung compliance. In these conditions, the baby has to generate a higher driving pressure to achieve a similar tidal volume or else hypoventilation will occur.

E. Total respiratory system compliance

1. If the driving pressure is measured across the entire respiratory system (the transthoracic pressure), then for a given volume change we obtain the compliance of the combined lung and chest wall together:

$$\text{Total compliance} = \frac{\text{Change in lung volume}}{\text{Change in transthoracic pressure}},$$

where, in a passive respiratory system, transthoracic pressure is the differential between alveolar and atmospheric pressure.

2. In a newborn connected to a mechanical ventilator, the transthoracic pressure can be measured simply as the airway pressure applied at the mouth or endotracheal tube.

F. Chest wall compliance

1. Like the lung, the chest wall is elastic.
2. If air is introduced into the pleural cavity, the lungs will collapse inward and the chest wall will expand outward.

$$\text{Chest wall compliance} = \frac{\text{Volume change}}{\text{Change in intrathoracic pressure}},$$

where the intrathoracic pressure is the pressure differential across the chest wall to the atmosphere. Because it is difficult to measure chest wall pressure directly, chest wall compliance may be measured indirectly, where:

$$\text{Elastance of the respiratory system} = \text{Elastance of lungs} \\ + \text{Elastance of chest wall.}$$

Thus,

$$\frac{1}{\text{Total lung compliance}} = \frac{1}{\text{Lung compliance}} + \frac{1}{\text{Chest wall compliance}}.$$

3. As previously discussed, there is a balance of elastic recoil forces at rest (end of expiration) such that the lungs maintain a stable FRC (Fig. 7.2).
 - a. In the newborn, the chest wall compliance is higher than that of the adult.
 - b. The chest wall becomes more compliant at earlier stages of gestation.

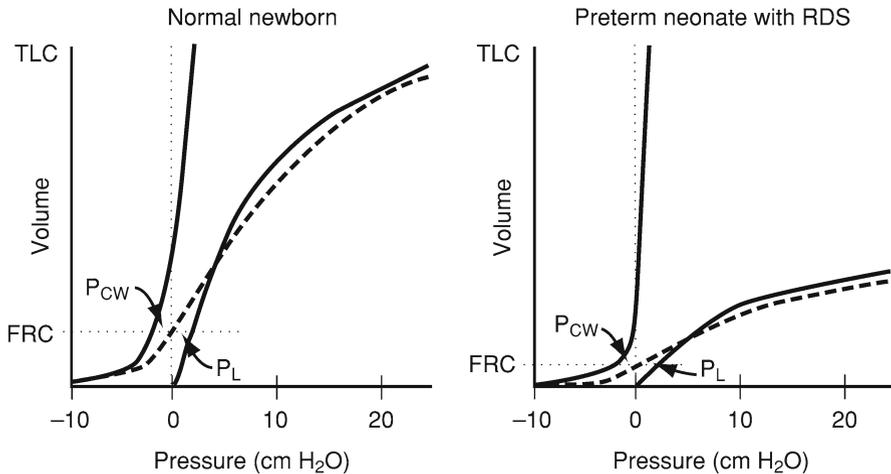


Fig. 7.2 Balance of elastic recoil at rest to maintain stable functional residual capacity. *Left.* Normal newborn; chest wall compliance is higher than that of the adult. *Right.* Preterm newborn with RDS. Chest wall is even more compliant and aggravated by disease state, FRC is lower. (Modified from Bhutani VK, Sivieri EM. Physiological principles for bedside assessment of pulmonary graphics. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura; 1998. p. 72, with permission)

- c. Even if the lungs have a normal elastic recoil and compliance, the FRC will be lowered because the chest wall would be unable to balance the elastic forces.
- d. The preterm newborn is therefore destined to have a lower FRC, and this state is aggravated if the FRC is lowered further because of disease states.

III. Resistive properties

- A. Nonelastic properties of the respiratory system characterize its resistance to motion.
- B. Since motion between two surfaces in contact usually involves friction or loss of energy, resistance to breathing occurs in any moving part of the respiratory system.
- C. These resistances would include frictional resistance to airflow, tissue resistance, and inertial forces.
 1. Lung resistance results predominantly (80%) from airway frictional resistance to airflow.
 2. Tissue resistance (19%) and inertia (1%) also influence lung resistance.
- D. Airflow through the airways requires a driving pressure generated by changes in alveolar pressure.

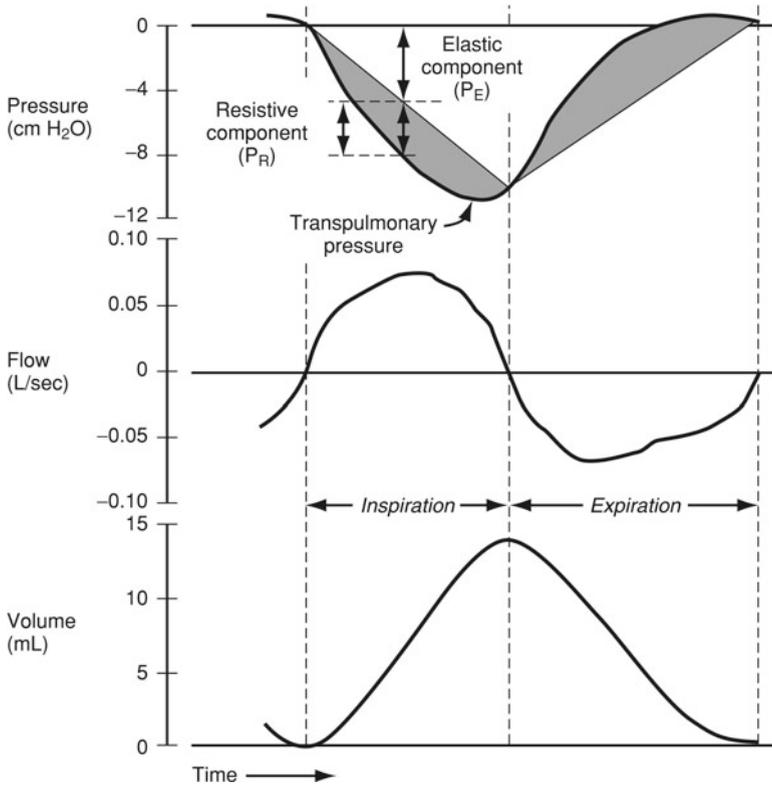


Fig. 7.3 The relative elastic and resistive components of transpulmonary pressure recorded from a typical single spontaneous breath. Pulmonary resistance is determined from simultaneous measures of the resistive component of pressure and the flow signal

- E. When alveolar pressure is less than atmospheric pressure (during spontaneous inspiration), air flows into the lung; when alveolar pressure is greater than atmospheric pressure, air flows out of the lung.
- F. By definition, resistance to airflow is equal to the resistive component of driving pressure (P_R) divided by the resulting airflow (\dot{V}), thus:

$$\text{Resistance} = \frac{P_R}{\dot{V}}$$

- G. When determining pulmonary resistance (tissue and airway), the resistive component of the measured transpulmonary pressure is used as the driving pressure (Fig. 7.3).
- H. To obtain airway resistance alone, the differential between alveolar pressure and atmospheric pressure is used as the driving pressure.

- I. Under normal tidal breathing conditions, there is a linear relationship between airflow and driving pressure.
1. The slope of the flow vs. pressure curve changes as the airways narrow, indicating that the patient with airway obstruction has a greater resistance to airflow.
 2. The resistance to airflow is greatly dependent on the size of the airway lumen.
 3. According to Poiseuille's law, the pressure (ΔP) required to achieve a given flow (\dot{V}) for a gas having viscosity η and flowing through a rigid and smooth cylindrical tube of length L and radius r is given as:

$$\Delta P = \frac{\dot{V} 8\eta L}{\pi r^4}.$$

Therefore, resistance to airflow is defined as:

$$\frac{\Delta P}{\dot{V}} = \frac{8\eta L}{\pi r^4}.$$

4. Thus, the resistance to airflow increases by a power of four with any decrease in airway diameter.
 5. Because the newborn airway lumen is approximately half that of the adult, the neonatal airway resistance is about 16-fold that of the adult. Normal airway resistance in a term newborn is approximately 20–40 cm H₂O/L/s (adults 1–2 cm H₂O/L/s).
- J. Nearly 80% of the total resistance to airflow occurs in large airways up to about the fourth to fifth generation of bronchial branching.
1. The patient usually has large airway disease when resistance to airflow is increased.
 2. Since the smaller airways contribute a small proportion of total airway resistance, they have been designated as the “silent zone” of the lung in which airway obstruction can occur without being readily detected.

IV. Inertial properties

Inertial forces are generally considered negligible for normal tidal breathing and when considering a linear model of respiration. However, with use of high airflow mechanical ventilation, high frequency ventilation, and in severe airway disease, inertial forces need to be considered.

V. Work of breathing

- A. True work of breathing may be expressed as the energy required by the respiratory muscles in moving a given tidal volume of air into and out of the lungs. For obvious reasons, this type of work is difficult to determine accurately,

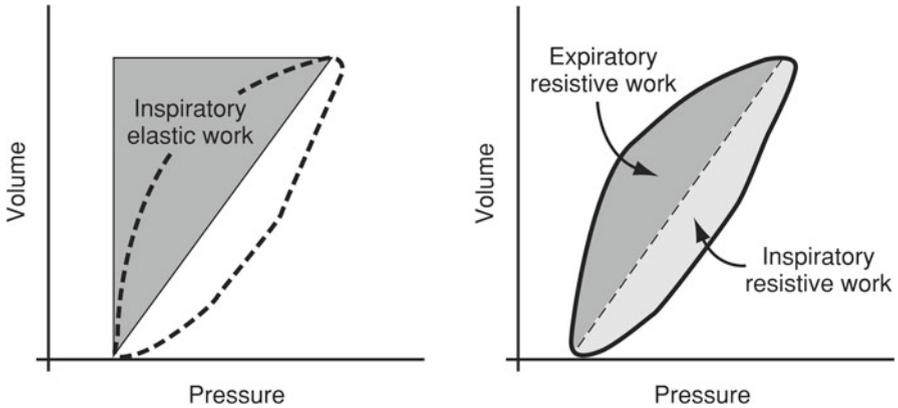


Fig. 7.4 Work of breathing is calculated as the area under the pressure versus volume curve (shaded areas)

whereas, the actual mechanical work done by or on the lungs is much easier to measure. The mechanical work expended in compressing or expanding a given volume is obtained from the integral product of the applied pressure and the resulting volume change or:

$$\text{Work} = \int PdV.$$

- B. This value is simply the area under the applied pressure vs. volume curve for any gas. Therefore, by integrating the transpulmonary pressure curve over volume, the pulmonary work of breathing is easily calculated (Fig. 7.4). This mechanical work can be partitioned into elastic and resistive components:
1. Elastic work is that portion needed to overcome elastic resistance to inflate the lungs. Under normal conditions, this work is stored as potential energy and is used in restoring the system to its resting volume.
 2. Resistive work is that portion needed to overcome airway and tissue frictional resistances. The hysteresis of the pressure–volume relationship represents the resistive work of breathing and can be further partitioned into inspiratory and expiratory components.
- C. Normally, the elastic energy stored during inspiration is sufficient to provide the work needed to overcome expiratory frictional resistance.
1. In babies with obstructive airway disease, the expiratory component of resistive work of breathing is increased (Fig. 7.1b).
 2. The units of work of breathing correspond to the units of pressure times volume ($\text{cm H}_2\text{O} \cdot \text{L}$), or equivalently, force times distance ($\text{kg} \cdot \text{m}$), and is usually expressed as the work per breath or respiratory cycle.

VI. Some reference values

- A. Calculated values of both elastic and resistive properties determined in adult and term newborns are listed in Table 7.1. These are compared to values obtained in infants with RDS and BPD.
- B. Table 7.2 lists values of neonatal pulmonary function parameters during the first month from several investigators collected over several decades of work in this area.

Table 7.1 Calculated respiratory parameters

	Units	Adult	Newborn	Newborn RDS	Newborn BPD
Pulmonary compliance	mL/cm H ₂ O/kg	2.5–3	2–2.5	<0.6	<1.0
Chest wall compliance	mL/cm H ₂ O	<1	>4	–	–
Pulmonary resistance	cm H ₂ O/L/s	1–2	20–40	>40	>150
Resistive work	g cm/kg	<10	20–30	30–40	>40

Table 7.2 Mean normal values of neonatal pulmonary function during the first month

Author	Study year	GA (weeks)	Age (days)	V _T (mL/kg)	FRC (mL/kg)	C _{DYN} (mL/cm H ₂ O)	R (cm H ₂ O/L/s)
Berglund/ Karlberg	1956	Term	7		27		
Cook et al.	1957	Term	1–6	5.3		5.2	29
Swyer et al.	1960	Term	1–11	6.7		4.9	26
Polgar	1961	Term	1–17		52.6	5.7	18.8
Strang/ McGrath	1962	Term	1–6		49.5		
Nelson et al.	1963	Preterm	1–16		38.7		
		Term	2–4		27		
Feather/Russell	1974	Term	1–3			3.7	42
Ronchetti et al.	1975	34	4–28		29.5		
Tausch et al.	1976	Term	4–6	7.2		3.7	
Adler/Wohl	1978	Term	2–5			3.5	
Mortola et al.	1984	Term	1–4	6.2		3.8	
Taussig et al.	1982	Term	1–9		31.4		
Migdal et al.	1987	34	1–28			2.4	
		Term	1–29			3.2	
Anday et al.	1987	28–30	2–3	5.9		2.0	50 exp
			5–7	6.6		2.3	70 exp
Gerhardt et al.	1987	31–36	3–30		16.7	2.2	87 exp
		Term	6–16		17.1	3.6	58 exp
Abbasi/Bhutani	1990	28–34	2–3	6.3		2.4	54
Sivieri et al.	1995	27–40	2–30		23.4		
		26–37	2–30		21.5 RDS		
		23–32	1–22		18.9 BPD		

GA gestational age, V_T tidal volume, FRC functional residual capacity, C_{DYN} dynamic lung compliance, R pulmonary resistance, exp expiratory, RDS infants with respiratory distress syndrome, BPD infants who developed bronchopulmonary dysplasia

Table 7.3 Pulmonary mechanics and energetics at age <3 days for infants with RDS who received surfactant replacement immediately after birth

Infants grouped by GA at birth	≤26 weeks (n=38)	27–28 weeks (n=50)	29–30 weeks (n=48)	≥31 weeks (n=63)
Tidal volume (mL/kg)	6.1±1.7	5.7±1.5	5.1±1.2	5.2±0.8
Pulmonary compliance (mL/cm H ₂ O/kg)	0.27±0.18	0.35±0.22	0.40±0.23	0.77±0.75
Pulmonary resistance (cm H ₂ O/L/s)	194±161	139±117	101±64	87±76
Flow resistive work (g-cm/kg)	38±29	28±17	21±14	15±1.2

Table 7.4 Predicted probability of BPD based on pulmonary mechanics and gestational age based on a predictive model for the study infants with RDS categorized by birth weight

Birth weight (g)	Gestational age (weeks)	Pulmonary compliance (mL/cm H ₂ O/kg)	Pulmonary resistance (cm H ₂ O/L/s)	Likelihood ratio for BPD	Percent predicted probability (%)
500–750	26±0.4	0.3±0.03	102±16	537±171	93±3
751–1,000	28±0.3	0.5±0.05	176±24	76±35	73±5
1,001–1,250	29±0.3	1.0±0.2	96±11	5.5±1.8	42±7
1,251–1,500	31±0.3	1.5±0.2	69±8	0.8±0.3	15±5
1,501–2,000	32±0.3	1.8±0.3	69±11	0.3±0.1	8±3

Predicted probability and likelihood ratio (LR) of BPD evaluated on the previously reported predictive model based on GA and pulmonary mechanics: $LR = \exp \{33.6 - 1.13GA - 0.93C_1/kg - 0.001R_1\}$

Table 7.5 Pulmonary mechanics and energetics at term PMA of surviving infants with RDS who received surfactant replacement immediately after birth

Surviving infants grouped by GA at birth	≤26 weeks (n=25)	27–28 weeks (n=35)	29–30 weeks (n=38)	≥31 weeks (n=59)
Term PMA (mean values) (weeks)	38.7	38.8	39.9	38.0
Tidal volume (mL)	13.3±4.1	14.3±4.2	15.2±4.4	14.4±4.7
Pulmonary compliance (mL/cm H ₂ O)	2.6±0.9	2.4±0.8	2.6±1.3	2.1±0.6
Pulmonary resistance (cm H ₂ O/L/s)	61±41	59±31	57±31	40±20
Flow-resistive work (g-cm/kg)	29±19	29±20	30±19	25±18

- C. Pulmonary mechanics and energetics at age <3 days for infants with RDS who received surfactant replacement immediately after birth (Table 7.3).
- D. Predicted probability of BPD based on pulmonary mechanics and gestational age based on a predictive model for the study infants with RDS categorized by birth weight (Table 7.4).
- E. Pulmonary mechanics and energetics at term PMA of surviving infants with RDS who received surfactant replacement immediately after birth (Table 7.5).

Suggested Reading

- Bancalari E. Pulmonary function testing and other diagnostic laboratory procedures in neonatal pulmonary care. In: Thibeault DW, Gary GA, editors. Neonatal pulmonary care. 2nd ed. East Norwalk, CT: Appleton-Century Crofts; 1986. p. 195–234.
- Bhutani VK, Sivieri EM. Physiological principles for bedside assessment of pulmonary graphics. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics. Principles and clinical applications. Armonk, NY: Futura; 1998. p. 57–79.
- Bhutani VK, Shaffer TH, Vidyasager D, editors. Neonatal pulmonary function testing: physiological, technical and clinical considerations. Ithaca, NY: Perinatology Press; 1988a.
- Bhutani VI, Sivieri EM, Abbasi S. Evaluation of pulmonary function in the neonate. In: Polin RA, Fox WW, editors. Fetal and neonatal physiology. 2nd ed. Philadelphia: Saunders; 1988b. p. 1143–64.
- Comroe JH, Forster RE, Dubois AB, et al. Clinical physiology and pulmonary function tests. 2nd ed. Year Book Medical Publishers: Chicago; 1971.
- Comroe JH. Physiology of respiration. 2nd ed. Year Book Medical Publishers: Chicago; 1974.
- Polgar G, Promadhat V. Pulmonary function testing in children. Philadelphia: Saunders; 1971.
- Rodarte JR, Rehder K. Dynamics of respiration. In: Geiger SR, editor. Handbook of Physiology, Section 3: The respiratory system, Macklem PT, Mead J (Volume Eds.), Volume III, Mechanical of breathing, Part I, Fishman AP (Section Ed.). Bethesda: American Physiological Society; 1986. p. 131–44.
- Stocks J, Sly PD, Tepper RS, Morgan WJ, editors. Infant respiratory function testing. New York: Wiley-Liss; 1996.
- West JB. Respiratory physiology: the essentials. Oxford: Blackwell; 1974.

Chapter 8

Basic Principles of Mechanical Ventilation

Waldemar A. Carlo, Namasivayam Ambalavanan,
and Robert L. Chatburn

- I. The ventilatory needs of a patient depend largely on the mechanical properties of the respiratory system and the type of abnormality in gas exchange.
- II. Pulmonary mechanics
 - A. The mechanical properties of the lungs is a determinant of the interaction between the ventilator and the infant.
 - B. A pressure gradient between the airway opening and alveoli drives the flow of gas.
 - C. The pressure gradient necessary for adequate ventilation is largely determined by the compliance and resistance (see below).
- III. Compliance
 - A. Compliance describes the elasticity or distensibility of the lungs or respiratory system (lungs plus the chest wall).
 - B. It is calculated as follows:

$$\text{Compliance} = \frac{\Delta\text{Volume}}{\Delta\text{Pressure}}.$$

W.A. Carlo, MD (✉) • N. Ambalavanan, MBBS, MD
Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham,
1700 6th Ave South, WIC 9380, Birmingham, AL 35249, USA
e-mail: wcarlo@peds.uab.edu; ambal@uab.edu

R.L. Chatburn, MHHS, RRT-NPS, FAARC
Cleveland Clinic, Respiratory Institute, 9500 Euclid Avenue,
Cleveland, OH 44195, USA
e-mail: CHATBUR@ccf.org

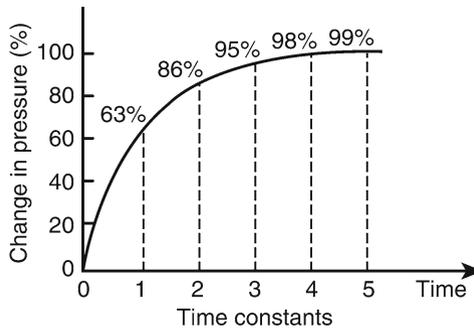


Fig. 8.1 A neonatal acid-base map. *CRA* compensated respiratory acidosis, *CMA* compensated metabolic acidosis, *RMA* mixed respiratory and metabolic acidosis (From Chatburn RL, Carlo WA: Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL [eds]: Neonatal Respiratory Care, 2nd ed. Chicago, Year Book Medical Publishers, 1988, p 58, with permission)

- C. Compliance in infants with normal lungs ranges from 3 to 5 mL/cm H₂O/kg.
- D. Compliance in infants with respiratory distress syndrome (RDS) is lower and often ranges from 0.1 to 1 mL/cm H₂O/kg.

IV. Resistance

- A. Resistance describes the ability of the gas conducting parts of the lungs or respiratory system (lungs plus chest wall) to resist airflow.
- B. It is calculated as follows:

$$\text{Resistance} = \frac{\Delta\text{Pressure}}{\Delta\text{Flow}}$$

- C. Resistance in infants with normal lungs ranges from 25 to 50 cm H₂O/L/s. Resistance is not markedly altered in infants with RDS or other acute pulmonary disorders, but can be increased to 100 cm H₂O/L/s or more by small endotracheal tubes.

V. Time constant

- A. The time constant is a measure of the time (expressed in seconds) necessary for the alveolar pressure (or volume) to reach 63% of a change in airway pressure (or volume) (Fig. 8.1).
- B. It is calculated as follows:

$$\text{Time constant} = \text{Compliance} \times \text{Resistance}.$$

For example, if an infant has lung compliance of 2 mL/cm H₂O (0.002 L/cm H₂O) and a resistance of 40 cm H₂O/L/s, time constant is calculated as follows:

$$\text{Time constant} = 0.002 \text{ L/cm H}_2\text{O} \times 40 \text{ cm H}_2\text{O/L/s} = 0.080 \text{ s}.$$

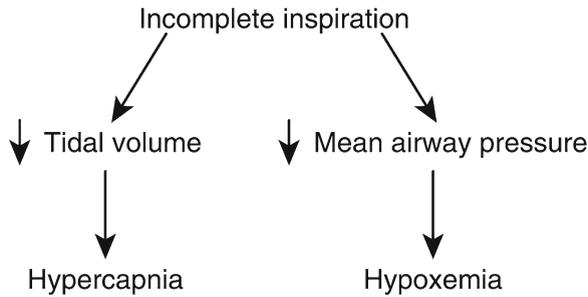


Fig. 8.2 Effect of incomplete inspiration on gas exchange (From Carlo WA, Greenough A, Chatburn RL: *Advances in mechanical ventilation*. In Boynton BR, Carlo WA, Jobe AH [eds]: *New Therapies for Neonatal Respiratory Failure: A Physiologic Approach*. Cambridge, UK, Cambridge University Press, 1994, p 137, with permission)

(Note that in the calculation of the time constant, compliance is not corrected for unit of weight).

- C. A duration of inspiration or expiration equivalent to 3–5 time constants is required for a relatively complete inspiration or expiration, respectively. Thus, in the infant described above, inspiratory and expiratory duration should be around 240–400 ms each (or 0.24–0.4 s).
- D. The time constant will be shorter if compliance is decreased (e.g., in patients with RDS) or if resistance is decreased. The time constant will be longer if compliance is high (e.g., big infants with normal lungs) or if resistance is high (e.g., infants with chronic lung disease).
- E. Patients with a short time constant ventilate well with short inspiratory and expiratory times and high ventilatory frequency, whereas patients with a long time constant require longer inspiratory and expiratory times and slower rates.
- F. If inspiratory time is too short (i.e., a duration shorter than approximately 3–5 time constants), there will be a decrease in tidal volume delivery and mean airway pressure (Fig. 8.2).
- G. If expiratory time is too short (i.e., a duration shorter than approximately 3–5 time constants), there will be gas trapping and inadvertent positive end expiratory pressure (PEEP) (Fig. 8.3).
- H. While the respiratory system is often modeled as being composed of a single compliance and a single resistance, it is known that the mechanical properties vary with changes in the lung volume, even within a breath. Furthermore, the mechanical characteristics of the respiratory system change somewhat between inspiration and expiration. In addition, lung disease can be heterogeneous, and thus, different areas of the lungs can have varying mechanical characteristics.

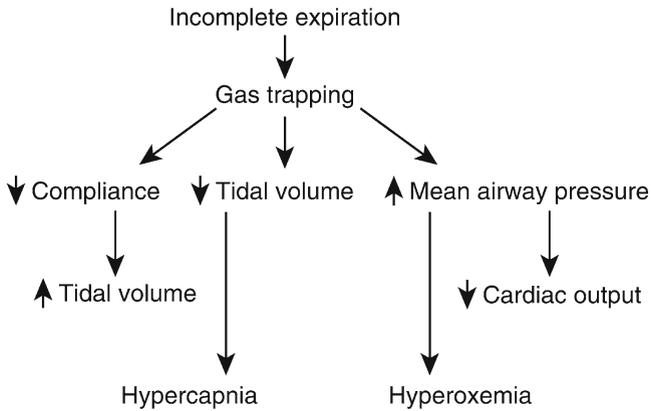


Fig. 8.3 Effect of incomplete expiration on gas exchange (From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH [eds]: New Therapies for Neonatal Respiratory Failure: A Physiologic Approach. Cambridge, UK, Cambridge University Press, 1994, p 137, with permission)

VI. Equation of motion

- A. The pressure necessary to drive the respiratory system is the sum of the elastic, resistive, and inertial components and can be calculated as follows:

$$P = \frac{1}{C}V + R\dot{V} + I\ddot{V},$$

where P is pressure, C is compliance, V is volume, R is resistance, \dot{V} is flow, \ddot{V} is the rate of change in flow, and I is inertia.

- B. Because the inertial component is small at physiologic flows, the last component ($I\ddot{V}$) can be neglected.
- C. The equation of motion can be used to derive estimates of compliance and resistance. For example, between points of $\dot{V} = 0$ (points of no flow) the pressure gradient results from compliance.

VII. Gas exchange

- A. Hypercapnia and/or hypoxemia occur during respiratory failure.
- B. Although impairment in CO_2 elimination and oxygen uptake and delivery may coexist, some conditions may affect gas exchange differentially.

VIII. Gas exchange during transition to extrauterine life

- A. Hemodynamic changes during transition to extrauterine life
1. Systemic vascular resistance increases
 2. Pulmonary vascular resistance decreases
 3. Pulmonary blood flow increases

B. Normal blood gas values in the perinatal period

	At birth	At 10 min of age
PaO ₂ (torr)	15–20	46–57
PaO ₂ (kPa)	2.0–2.67	6.0–7.6
PaCO ₂ (torr)	49–76	40–47
PaCO ₂ (kPa)	6.53–10.0	5.33–6.0

IX. Determinants of pulmonary gas exchange

- A. Composition and volume of alveolar gas
- B. Composition and volume of mixed venous blood
- C. Mechanisms of gas exchange

X. Composition of inspired and alveolar gases

- A. Partial pressure of oxygen in dry air

Partial pressure of O₂ = Fractional content × Total gas pressure.

If barometric pressure = 760 mm Hg, then

$$PO_2 = 0.21 \times (760 \text{ mmHg}) = PO_2 = 160 \text{ mmHg.}$$

- B. Partial pressure of oxygen in humidified air

Partial pressure O₂ = Fractional content ×

(Total gas pressure – Water vapor pressure),

$$PiO_2 = 0.21 \times (760 - 47 \text{ mmHg}) = PiO_2 = 149 \text{ mmHg.}$$

- C. Partial pressure of oxygen in humidified alveolar gas

Partial pressure of alveolar O₂ = PiO₂ – PACO₂ (FiO₂ + [1 – FiO₂]/R)

where PACO₂ is alveolar PCO₂ and R is the respiratory quotient. Because CO₂ diffuses very well through the alveoli, PACO₂ ≈ PaCO₂.

If barometric pressure = 760 mmHg and water vapor pressure is 47 mmHg, and FiO₂ = 1.00, then PiO₂ = 713.

If FiO₂ is 1.00, (FiO₂ + [1 – FiO₂]/R) = 1.0, then PAO₂ = 713 – 40 = 673 mmHg

If FiO₂ is 0.21, then PAO₂ = 149 – 40 (0.21 + 1 – 0.21/0.8) = 100 mmHg

XI. Composition of mixed venous blood

- A. Mixed venous PO₂ (PVO₂) depends on arterial O₂ content, cardiac output, and metabolic rate.

- B. Oxygen content of blood per 100 mL

Dissolved O₂ = 0.003 mL O₂ per torr of PaO₂

Hemoglobin bound O₂ = SaO₂ × 1.34/gm hemoglobin × hemoglobin concentration

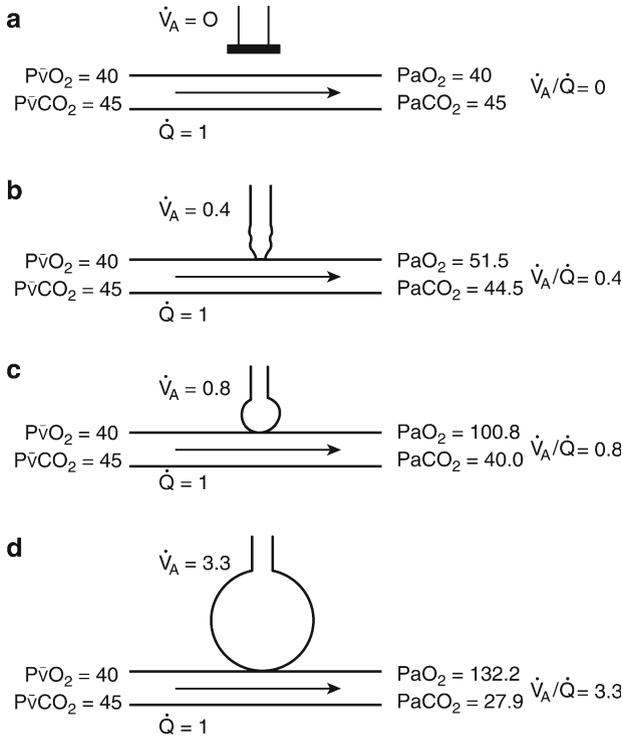


Fig. 8.4 Effects of various ventilation-perfusion ratios on blood gas tensions. (a) Direct venoarterial shunting ($VA/Q=0$). (b) Alveolus with a low VA/Q ratio. (c) Normal alveolus. (d) Underperfused alveolus with high VA/Q ratio (From Krauss AN: Ventilation-perfusion relationships in neonates. In Thibeault DW, Gregory GA [eds]: Neonatal Pulmonary Care, 2nd ed. Norwalk, CT, Appleton-Century-Crofts, 1986, p 127, with permission)

For example, 1 kg infant (blood volume ≈ 100 mL) with $PaO_2 = 100$ torr ($SaO_2 = 100\%$, or 1.0), and hemoglobin = 17 mg/dL

$$\begin{aligned} O_2 \text{ content} &= \text{hemoglobin bound } O_2 + \text{dissolved } O_2 \\ O_2 \text{ content} &= 1.00 \times 1.34 \times 17 + 0.003 \times 100 \\ O_2 \text{ content} &= 22.78 + 0.3 \text{ mL } O_2 \\ O_2 \text{ content} &= 23.08 \text{ mL } O_2 \end{aligned}$$

C. CO_2 content of blood

CO_2 is carried in three forms: (1) dissolved in plasma and red cells; (2) as bicarbonate; and (3) bound to hemoglobin.

XII. Hypoxemia

The pathophysiologic mechanisms responsible for hypoxemia are in order of relative importance in newborns: ventilation-perfusion mismatch, shunt, hypoventilation, and diffusion limitation (Figs. 8.4–8.6):

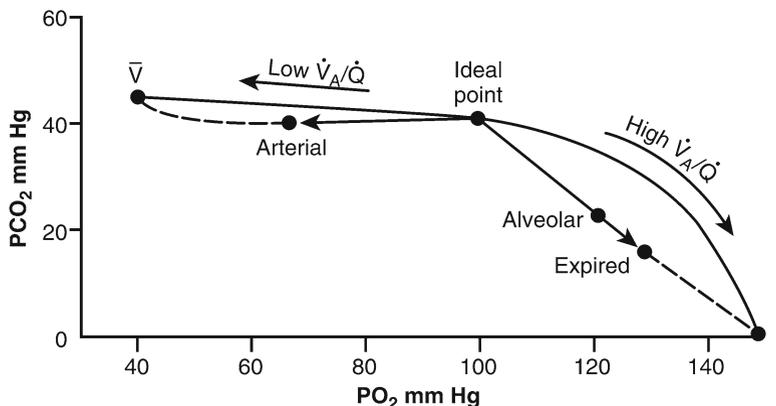


Fig. 8.5 O₂-CO₂ diagram showing the arterial, ideal, alveolar, and expired points. The curved line indicates the PO₂ and the PCO₂ of all lung units having different ventilation-perfusion ratios (From West JB: Gas exchange. In West JB [ed]: Pulmonary Pathophysiology: The Essentials, Baltimore, Williams & Wilkins, 1977, p 27, with permission)

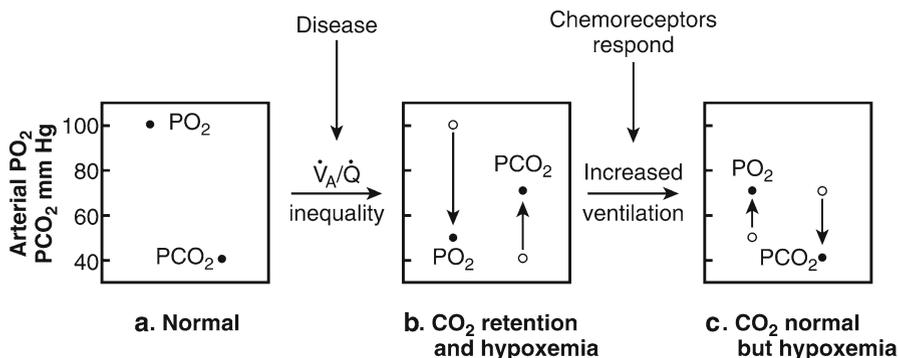


Fig. 8.6 PO₂ and PCO₂ in different stages of ventilation-perfusion inequality. Initially, there must be both a fall in oxygen and a rise in carbon dioxide tensions. However, when the ventilation to the alveoli is increased, the PCO₂ exchange increases (From West JB: Gas exchange. In West JB [ed]: Pulmonary Pathophysiology: The Essentials. Baltimore, Williams & Wilkins. 1977, p 30, with permission)

- A. Ventilation-perfusion (V/Q) mismatch. V/Q mismatch is an important cause of hypoxemia in newborns. Supplemental oxygen can largely overcome the hypoxemia resulting from V/Q mismatch.
- B. Shunt
 - Shunt is a common cause of hypoxemia in newborns. A shunt may be physiologic, intracardiac (e.g., PPHN, congenital cyanotic heart disease), or pulmonary (e.g., atelectasis). It can be thought of as a V/Q=0 and supplemental oxygen cannot reverse the hypoxemia.

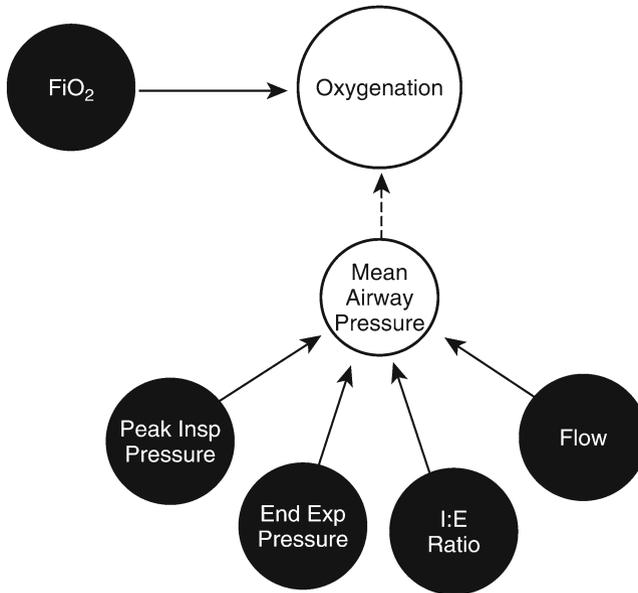


Fig. 8.7 Determinants of oxygenation during pressure-limited, time-cycled ventilation. *Shaded circles* represent ventilator-controlled variables. *Solid lines* represent the simple mathematical relationships that determine mean airway pressure and oxygenation, whereas the *dashed lines* represent relationships that cannot be quantified (From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH [eds]: New Therapies for Neonatal Respiratory Failure: A Physiologic Approach. Cambridge, UK, Cambridge University Press, 1994, p 134, with permission)

C. Hypoventilation

Hypoventilation results from a decrease in tidal volume or respiratory rate. During hypoventilation, the rate of oxygen uptake from the alveoli exceeds its replenishment. Thus, alveolar PO_2 falls and PaO_2 decreases. It can be thought of as low V/Q and supplemental oxygen can overcome the hypoxemia easily. Causes of hypoventilation include: depression of respiratory drive, weakness of the respiratory muscles, restrictive lung disease, and airway obstruction.

D. Diffusion limitation

Diffusion limitation is an uncommon cause of hypoxemia, even in the presence of lung disease. Diffusion limitation occurs when mixed venous blood does not equilibrate with alveolar gas. Supplemental oxygen can overcome hypoxemia secondary to diffusion limitation.

XIII. Oxygenation during assisted ventilation

- A. Oxygenation may be largely dependent upon lung volume, which in turn depends upon mean airway pressure (Fig. 8.7).
- B. During pressure-targeted ventilation, any of the following will increase mean airway pressure: increasing inspiratory flow, increasing peak inspiratory pressure (PIP), increasing the inspiratory:expiratory (I:E) ratio, or PEEP.

C. Mean airway pressure maybe calculated as follows:

$$\text{Mean airway pressure} = K (\text{PIP} - \text{PEEP}) \left[\frac{T_I}{T_I + T_E} \right] + \text{PEEP},$$

where K is a constant that depends upon the shape of the early inspiratory part of the airway pressure curve (K ranges from approximately 0.8–0.9 during pressure-limited ventilation); T_I is inspiratory time; T_E is expiratory time.

For the same change in mean airway pressure, increases in PIP and PEEP increase oxygenation more. A very high mean airway pressure transmitted to the intrathoracic structures may impair cardiac output and thus decrease oxygen transport despite an adequate PaO_2 .

XIV. Hypercapnia

- A. The pathophysiologic mechanisms responsible for hypercapnia are V/Q mismatch, shunt, hypoventilation, and increased physiologic dead space.
- B. The physiologic dead space results in part from areas of inefficient gas exchange because of low perfusion (wasted ventilation).
- C. Physiologic dead space includes ventilation to conducting airways and alveolar spaces not perfused (i.e., anatomical dead space).

XV. CO_2 elimination during assisted ventilation

- A. CO_2 diffuses easily into the alveoli and its elimination depends largely on the total amount of gas that comes into contact with the alveoli (alveolar ventilation). Minute alveolar ventilation is calculated from the product of the frequency (per minute) and the alveolar tidal volume (tidal volume minus dead space).

$$\text{Minute alveolar ventilation} = \text{Frequency} \times (\text{Tidal volume minus dead space}).$$

- B. On volume-targeted ventilators, the delivered volume is preset. On a pressure-targeted ventilator, the tidal volume depends upon the pressure gradient between the airway opening and the alveoli; this is PIP minus the positive end expiratory pressure (PEEP, also referred to as baseline pressure), or amplitude (ΔP).
- C. Depending upon the time constant of the respiratory system (and the ventilator), a very short inspiratory time (T_I) may reduce the tidal volume, and a very short expiratory time (T_E) may cause gas trapping and inadvertent PEEP, and consequently may also reduce tidal volume (see above).
- D. Figure 8.8 illustrates the relationships among ventilator controls, pulmonary mechanics, and minute ventilation. Ventilator controls are shown in shaded circles.

XVI. Blood gas analysis

A careful interpretation is essential for appropriate respiratory care (Table 8.1, Figs. 8.9 and 8.10, Chap. 19).

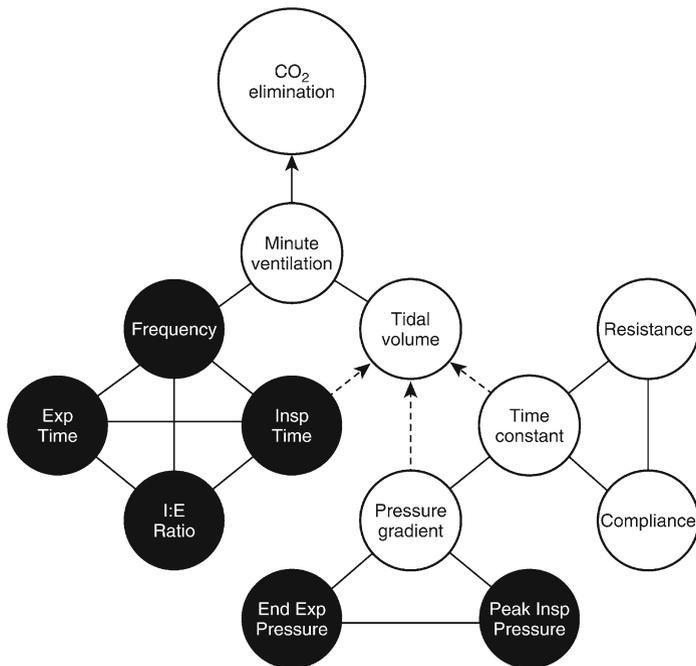


Fig. 8.8 Relationships among ventilator-controlled variables (*shaded circles*) and pulmonary mechanics (*unshaded circles*) that determine minute ventilation during time-cycled, Pressure-limited ventilation. Relationships between circles joined by *solid lines* are mathematically derived. The *dashed lines* represent relationships that cannot be precisely calculated without considering other variables such as pulmonary mechanics. Alveolar ventilation can be calculated from the product of tidal volume and frequency when dead space is subtracted from the former (From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH [eds]: New Therapies for Neonatal Respiratory Failure: A Physiologic Approach. Cambridge, UK, Cambridge University Press, 1994, p 133, with permission)

Table 8.1 Blood gas classifications

Classification	pH	PaCO ₂	HCO ₃ ⁻	BE
<i>Respiratory disorder</i>				
Uncompensated acidosis	↓	↑	N	N
Partly compensated acidosis	↓	↑	↑	↑
Compensated acidosis	N	↑	↑	↑
Uncompensated alkalosis	↑	↓	N	N
Partly compensated alkalosis	↑	↓	↓	↓
Compensated alkalosis	N	↓	↓	↓
<i>Metabolic disorder</i>				
Uncompensated acidosis	↓	N	↓	↓
Partly compensated acidosis	↓	↓	↓	↓
Uncompensated alkalosis	↑	N	↑	↑
Partly compensated alkalosis	↑	↑	↑	↑
Compensated alkalosis	N	↑	↑	↑

Arrows elevated or depressed values, *N* normal, *BE* base excess

From Carlo WA, Chatburn RL: Assessment of Neonatal Gas Exchange. In Carlo WA, Chatburn RL [eds.]: *Neonatal Respiratory Care*, 2nd Edition. Chicago, Year Book Medical Publishers, 1988, p. 51, with permission

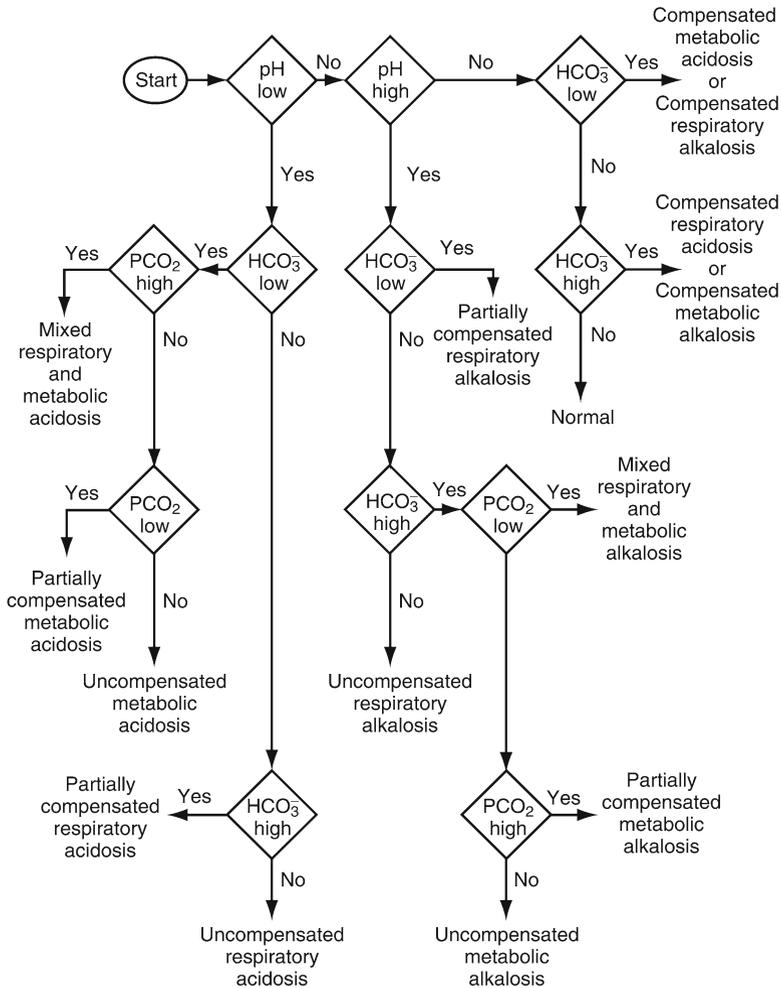


Fig. 8.9 A flow chart illustrating the algorithm through which a set of arterial blood gas values may be interpreted (From Chatburn RL, Carlo WA: Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL [eds]: Neonatal Respiratory Care, 2nd ed. Chicago, Year Book Medical Publishers, 1988, p 56, with permission)

A. Respiratory acidosis (low pH, high PaCO₂, normal HCO₃⁻)

1. From V/Q mismatch, shunt and/or hypoventilation
2. Secondary renal compensation
 - a. Reduction in bicarbonate excretion
 - b. Increased hydrogen ion excretion

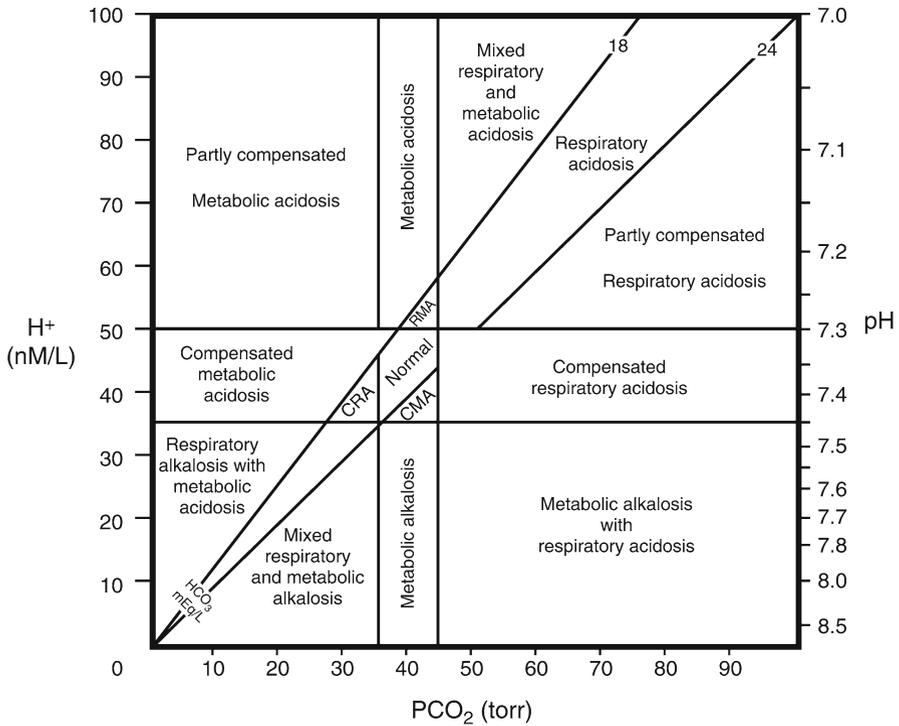


Fig. 8.10 A Neonatal acid-base map. *CRA* compensated respiratory acidosis, *CMA* compensated metabolic acidosis, *RMA* mixed respiratory and metabolic acidosis (From Chatburn RL, Carlo WA, Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL [eds]: Neonatal Respiratory Care, 2nd ed. Chicago, Year Book Medical Publishers, 1988, p 58, with permission)

- B. Respiratory alkalosis (high pH, low PaCO₂, normal HCO₃⁻)
1. From hyperventilation
 2. Secondary renal compensation
 - a. Increased bicarbonate excretion
 - b. Retention of chloride
 - c. Reduced excretion of acid salts and ammonia
- C. Metabolic acidosis (low pH, normal PaCO₂, low HCO₃⁻)
1. From increased acid production or impaired acid elimination
 2. Secondary pulmonary compensation: hyperventilation with decreased PaCO₂
- D. Metabolic alkalosis (high pH, normal PaCO₂, high HCO₃⁻)
1. From excessive NaHCO₃ administration, diuretic therapy, and loss of gastric secretions
 2. Secondary pulmonary compensation: hypoventilation

Suggested Reading

- Carlo WA, Chatburn RL. Assisted ventilation of the newborn. In: Carlo WA, Chatburn RL, editors. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers; 1988. p. 320–46.
- Carlo WA, Greenough A, Chatburn RL. Advances in conventional mechanical ventilation. In: Boynton BR, Carlo WA, Jobe AH, editors. New therapies for neonatal respiratory failure: a physiologic approach. Cambridge, England: Cambridge University Press; 1994. p. 131–51.
- Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1997.
- Greenough A, Milner AD, editors. Neonatal respiratory disorders. London: Arnold Publishers; 2003.
- Krauss AN. Ventilation-perfusion relationship in neonates. In: Thibeault DW, Gregory GA, editors. Neonatal pulmonary care. 2nd ed. Norwalk, CT: Appleton; 1986. p. 127.
- Mariani GL, Carlo WA. Ventilatory management in neonates. *Controversies in Neonatal Pulmonary Care*. 1998;25:33–48.
- Spitzer AR, Fox WW. Positive-pressure ventilation: pressure-limited and time-cycled ventilators. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 4th ed. Philadelphia, PA: WB Saunders Co; 2004. p. 167–86.
- West JB. Gas exchange. In: West JB, editor. Pulmonary pathophysiology—the essentials. 6th ed. Baltimore, MD: Williams & Wilkins; 2003.

Chapter 9

Classification of Mechanical Ventilation Devices

Waldemar A. Carlo, Namasivayam Ambalavanan, and Robert L. Chatburn

- I. Ventilators can be classified by the variables that are controlled (e.g., pressure or volume), as well as those that start (or trigger), sustain (or limit), and end (cycle) inspiration and those that maintain the expiratory support (or baseline pressure).
- II. *Control variables.* A ventilator can be classified as a pressure, volume, or flow controller (Fig. 9.1). Ventilators control more than one variable at different times.
 - A. Pressure controller
This type of ventilator controls either: (1) airway pressure, making it rise above the body surface pressure (i.e., positive pressure ventilator); or (2) body surface pressure, making it fall below the airway pressure (i.e., negative pressure ventilator).
 - B. Volume controller
This type of ventilator controls and measures the tidal volume generated by the ventilator despite changes in loads. In the past, the usefulness of this type of ventilator has been limited in newborns because the control variable was regulated near the ventilator and not near the patient, resulting in a tidal volume lower than the set one. Microprocessor and sensor technology has corrected this.
 - C. Flow controller
This type of ventilator controls the tidal volume but does not measure it directly. A ventilator is a flow controller if the gas delivery is limited by flow.

W.A. Carlo, MD (✉) • N. Ambalavanan, MBBS, MD
Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham,
1700 6th Ave South, WIC 9380, Birmingham, AL 35249, USA
e-mail: wcarlo@peds.uab.edu; ambal@uab.edu

R.L. Chatburn, MHHS, RRT-NPS, FAARC
Cleveland Clinic, Respiratory Institute, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: CHATBUR@ccf.org

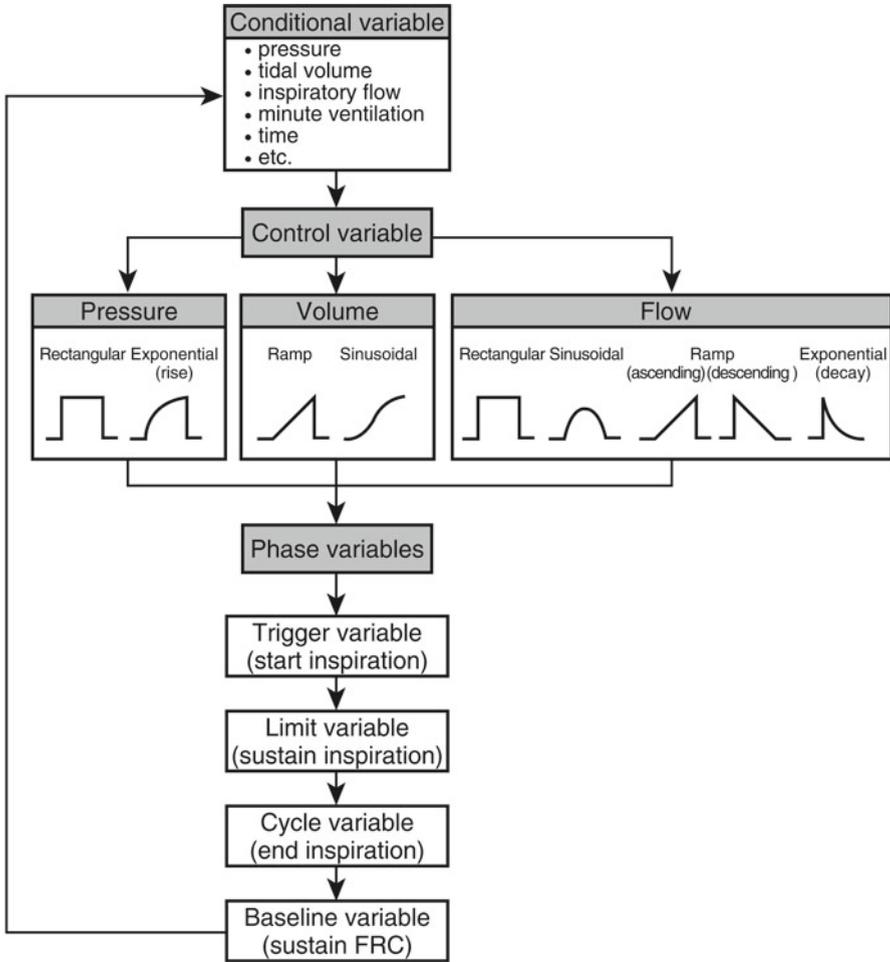


Fig. 9.1 Application of the equation of motion to the respiratory system. A common waveform for each control variable is shown. Pressure, volume, flow, and time are also used as a phase variables that determine the characteristics of each ventilatory cycle (e.g., trigger sensitivity, inspiratory time, baseline pressure). This emphasizes that each breath may have a different set of control and phase variables, depending on the mode of ventilation desired (From Chatburn RL. Classification of mechanical ventilator. In: Branson RD, Huess DR, Chatburn RL, editors. Respiratory care equipment. Philadelphia: JB Lippincott; 1995. p. 280, with permission)

D. Time controller

This type of ventilator controls the timing of the ventilatory cycle but not the pressure or volume. Most high-frequency ventilators are time controllers.

III. Phase variables

The ventilatory cycle has four phases: (1) the change from expiration to inspiration (trigger); (2) inspiratory limit; (3) the change from inspiration to expiration (cycle); and (4) expiration (baseline pressure) (Fig. 9.2).

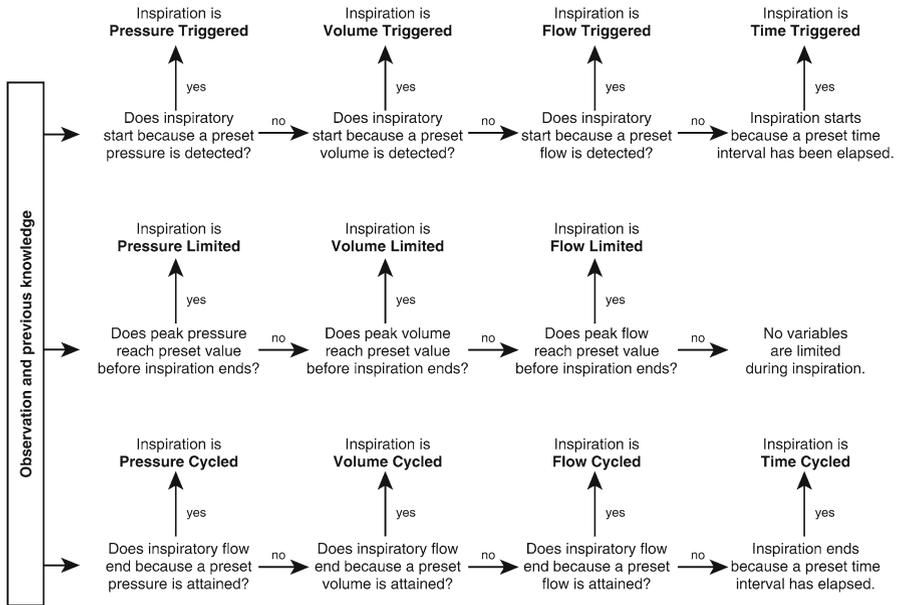


Fig. 9.2 Criteria for determining the phase variables during a ventilator-supported breath (From Chatburn RL. Classification of mechanical ventilators. In: Branson RD, Hues DR, Chatburn RL, editors. Respiratory care equipment. Philadelphia: JB Lippincott; 1995. p. 280, with permission)

A. Trigger

1. One or more variables in the equation of motion (i.e., pressure, volume, flow, and time) is/are measured by the ventilator and used to trigger (or start) inspiration.
2. Inspiration begins when one of these variables reaches a preset value.
3. The most common trigger variables are time (i.e., after a predefined time, the ventilator is triggered to start inspiration as in intermittent mandatory ventilation) and pressure (i.e., when an inspiratory effort is detected as a change in the end expiratory pressure, the ventilator is triggered to start inspiration as in patient-triggered ventilation). Flow-triggering involves less patient effort and is more commonly used in infant ventilators.

B. Limit

1. Pressure, volume, and flow increase during inspiration.
2. A limit variable restricts the inspiratory increase to a preset value but does not limit the duration.
3. Many neonatal ventilators are pressure-limited.

C. Cycle

1. The cycle variable is used to end inspiration.
2. Many neonatal ventilators, including high-frequency ventilators, are time-cycled.

Table 9.1 Ventilatory modes

Mode	Mandatory				Spontaneous			
	Control	Trigger ^a	Limit	Cycle	Control	Trigger	Limit	Cycle
Control	Flow ^b	Time	Volume Flow	Volume Time	NA ^c	NA	NA	NA
A/C or CMV	Flow	Pressure Volume Time	Volume Flow	Volume Time	NA	NA	NA	NA
IMV (continuous flow)	Pressure Flow	Time	Volume Flow	Volume Time	– ^d	–	–	–
SIMV (continuous flow)	Pressure Flow	Pressure Volume Flow Time	Pressure Volume Flow Time	Volume Time	–	–	–	–
SIMV (demand flow)	Pressure Flow	Pressure Volume Flow Time	Pressure Volume Flow Time	Volume Time	Pressure Flow	Pressure	Pressure	Pressure
PS	–	–	–	–	Pressure	Pressure	Pressure	Flow
PS+SIMV	Pressure Flow	Pressure Volume Flow Time	Pressure Volume Flow Time	Time	Pressure	Pressure Flow	Pressure	Flow
CAP or CPAP (continuous flow)	–	–	–	–	Pressure	–	Pressure	–
CAP or CPAP (demand flow)	–	–	–	–	Pressure	Pressure Flow	Pressure	–
PC	Pressure	Time	Pressure	Time	NA	NA	NA	–

From Carlo WA, Greenough A, Chatburn RL. Advances in conventional mechanical ventilation. New therapies for neonatal respiratory failure: a physiologic approach, Cambridge: Cambridge University Press; 1994. p. 144, with permission

A/C assist/control, CMV conventional mandatory ventilation, IMV intermittent mandatory ventilation, PS pressure support, SIMV synchronized mandatory ventilation, CAP constant airway pressure, CPAP continuous positive airway pressure, PC pressure control

^a Whether or not a breath is patient-triggered depends on the sensitivity setting and the magnitude of the patient’s inspiratory effort

^b For the purposes of this table, flow control is equivalent to volume control. Baseline PEEP is assumed to be available for all modes

^c NA, not applicable

^d Ventilator does not respond

3. Changes in airway flow may also be used to terminate the inspiratory phase and cycle into expiration.

D. Baseline (PEEP). The baseline variable maintains expiratory pressure and expiratory lung volume.

IV. *Ventilatory modes*. This classification of mechanical ventilation devices can be applied to the various ventilatory modes (Table 9.1).

Suggested Reading

- Carlo WA, Greenough A, Chatburn RL. Advances in conventional mechanical ventilation. In: Boynton BR, Carlo WA, Jobe AH, editors. *New therapies for neonatal respiratory failure: a physiologic approach*. Cambridge: Cambridge University Press; 1994. p. 131–51.
- Chatburn RL. Classification of mechanical ventilators. In: Branson RD, Hess DR, Chatburn RL, editors. *Respiratory care equipment*. Philadelphia: J. B. Lippincott Company; 1995. p. 264–93.
- Chatburn RL. Understanding mechanical ventilators. *Expert Rev Respir Med*. 2010;4:809–19.
- Chatburn RL, Mireles-Cabodevila E. Closed-loop control of mechanical ventilation: description and classification of targeting schemes. *Respir Care*. 2011;56:85–102.

Chapter 10

Ventilator Parameters

Waldemar A. Carlo, Namasivayam Ambalavanan, and Robert L. Chatburn

I. Peak inspiratory pressure (PIP)

A. Physiologic effects

1. PIP, in part, determines the pressure gradient between the onset and end of inspiration and thus affects the tidal volume and minute ventilation.
2. During volume ventilation, an increase in tidal volume corresponds to an increase in PIP during pressure ventilation. If tidal volume is not measured, initial PIP can be selected based on observation of the chest wall movement and magnitude of the breath sounds.

B. Gas exchange effects

1. An increase in PIP will increase tidal volume, increase CO₂ elimination, and decrease PaCO₂.
2. An increase in PIP will increase mean airway pressure and thus improve oxygenation.

C. Side effects

1. An elevated PIP may increase the risk of barotrauma, volutrauma, and bronchopulmonary dysplasia.

W.A. Carlo, MD (✉) • N. Ambalavanan, MBBS, MD
Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham,
1700 6th Ave South, WIC 9380, Birmingham, AL 35249, USA
e-mail: wcarlo@peds.uab.edu; ambal@uab.edu

R.L. Chatburn, MHHS, RRT-NPS, FAARC
Cleveland Clinic, Respiratory Institute, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: CHATBUR@ccf.org

2. There is increasing evidence that lung injury is primarily caused by large tidal volume delivery and lung overdistention.
3. It is important to adjust PIP based on lung compliance, and ventilate with relatively small tidal volumes (e.g., 4–6 mL/kg).

II. Positive end expiratory pressure (PEEP) (see Chap. 28)

A. Physiologic effects

1. PEEP in part determines lung volume during the expiratory phase, improves ventilation/perfusion mismatch, and prevents alveolar collapse.
2. PEEP contributes to the pressure gradient between the onset and end of inspiration, and thus, affects the tidal volume and minute ventilation.
3. At least, a minimum “physiologic” PEEP of 2–3 cm H₂O should be used in newborns.

B. Gas exchange effects

1. An increase in PEEP increases expiratory lung volume (functional residual capacity) during the expiratory phase, and thus, improves ventilation/perfusion matching and oxygenation in patients whose disease state reduces expiratory lung volume.
2. An increase in PEEP will increase mean airway pressure and thus improve oxygenation in patients with this type of disease.
3. An increase in PEEP will also reduce the pressure gradient during inspiration and thus reduce tidal volume, reduce CO₂ elimination, and increase PaCO₂.

C. Side effects

1. An elevated PEEP may overdistend the lungs and lead to decreased lung compliance, decreased tidal volume, less CO₂ elimination, and an increase in PaCO₂.
2. While use of low-to-moderate PEEP may improve lung volume, a very high PEEP may cause overdistention and impaired CO₂ elimination secondary to decreased compliance and gas trapping.
3. A very high PEEP may decrease cardiac output and oxygen transport.

III. Frequency (or rate)

- A. Physiologic effects. The ventilator frequency (or rate) in part determines minute ventilation and thus CO₂ elimination. Ventilation at high rates (≥ 60 /min) may facilitate synchronization of the ventilator with spontaneous breaths (“capturing the infant”). Spontaneous breathing rates are inversely related to gestational age and the time constant of the respiratory system. Thus, infants with smaller and less compliant lungs tend to breathe faster.
- B. Gas exchange effects. When very high frequencies are used, the problem of insufficient inspiratory time or insufficient expiratory time may occur (see below).

- C. Side effects. Use of very high ventilator frequencies may lead to insufficient inspiratory time and decreased tidal volume or insufficient expiratory time and gas trapping.

IV. Inspiratory time (T_I), expiratory time (T_E), and inspiratory to expiratory ratio (I:E ratio)

A. Physiologic effects

1. The effects of the T_I and T_E are strongly influenced by the relationship of those times to the inspiratory and expiratory time constants.
2. A T_I as long as 3–5 times constants allows relatively complete inspiration.
3. T_I of 0.2–0.5 s is usually adequate for newborns with respiratory distress syndrome.
4. Use of a longer T_I generally does not improve ventilation or gas exchange.
5. A very prolonged T_I may lead to patient-ventilator asynchrony.
6. A very short T_I will lead to decreased tidal volume.
7. Infants with a long time constant (e.g., chronic lung disease) may benefit from a longer T_I (up to approximately 0.6–0.8 s).

B. Gas exchange effects

1. Changes in T_I , T_E , and I:E ratio generally have modest effects on gas exchange.
2. A sufficient T_I is necessary for adequate tidal volume delivery and CO_2 elimination.
3. Use of relatively long T_I or high I:E ratio improves oxygenation slightly.

- C. Side effects. Very short T_I or T_E can lead to insufficient times and increase gas trapping, respectively, both of which can decrease tidal volume.

V. Inspired oxygen concentration (FiO_2)

A. Physiologic effects

1. Changes in FiO_2 alter alveolar oxygen pressure, and thus, oxygenation.
2. Because both FiO_2 and mean airway pressure determine oxygenation, the most effective and less adverse approach should be used to optimize oxygenation.
3. When FiO_2 is above 0.6–0.7, increases in mean airway pressure are generally warranted.
4. When FiO_2 is below 0.3–0.4, decreases in mean airway pressure are generally preferred.

- B. Gas exchange effects. FiO_2 directly determines alveolar PO_2 and thus PaO_2 .

- C. Side effects. A very high FiO_2 can damage the lung tissue, but the absolute level of FiO_2 that is toxic has not been determined.

Table 10.1 Desired blood gas goal and corresponding ventilator parameter changes

Desired goal	PIP	PEEP	Frequency	I:E ratio	Flow
Decrease PaCO ₂	↑	↓	↑	—	±↑
Increase PaCO ₂	↓	↑	↓	—	±↑
Decrease PaO ₂	↓	↓	—	↓	±↑
Increase PaO ₂	↑	↑	—	↑	±↑

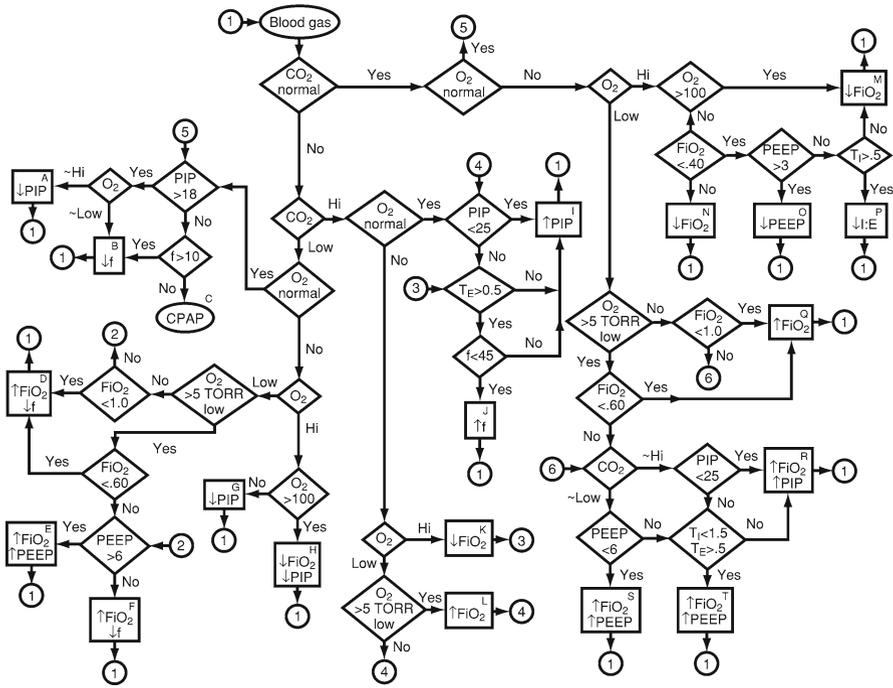


Fig. 10.1 Flow chart illustrating simplified version of algorithm used in this study. Symbols: 1, calls for decisions; O, type and direction of ventilator setting changes. Abbreviations: CO₂, arterial carbon dioxide tension (mm Hg); O₂, arterial oxygen tension (mm Hg); FiO₂, fraction of inspired oxygen; PIP, peak inspiratory pressure (cm H₂O); PEEP, positive end-expiratory pressure (cm H₂O); CPAP, continuous positive airway pressure (cm H₂O); I:E, ratio of inspiratory to expiratory time; f, ventilator frequency (breaths per minute); T_I, inspiratory time (s); T_E, expiratory time (s); HI, variable in decision symbol is above normal range; LOW, variable in decision symbol is below normal range; ~HI, variable in decision symbol is at high side of normal; ~LOW, variable in decision symbol is at low side of normal; ↑, increase; ↓, decrease; >, greater than; <, less than

Table 10.2 Abbreviations and symbols used in the flowchart in figure

CO_2	Arterial carbon dioxide tension (mmHg)
O_2	Arterial oxygen tension (mmHg)
FiO_2	Fraction of inspired oxygen
PIP	Peak inspiratory pressure (cm H_2O)
Paw	Mean airway pressure (cm H_2O)
PEEP	Positive end-expiratory pressure (cm H_2O)
CPAP	Continuous positive airway pressure without mechanical ventilation (cm H_2O)
I:E	Ratio of inspiratory to expiratory time
f	Ventilator frequency (breaths/min). Unless otherwise specified, a change in frequency should be accompanied by a change in I:E to maintain the same T_I so that tidal volume remains constant
T_I	Inspiratory time (s)
T_E	Expiratory time (s)
HI	The variable in the decision symbol is above normal range
LOW	The variable in the decision symbol is below normal range
$\approx\text{HI}$	The variable in the decision symbol is at the high end of normal
$\approx\text{LOW}$	The variable in the decision symbol is at the low end of normal
\uparrow	Increase
\downarrow	Decrease
$>$	Greater than
$<$	Less than
Torr	Unit of pressure; 1 Torr—1 mmHg

From Carlo WA, Chatburn RL. Assisted ventilation of the newborn. In: Carlo WA, Chatburn RL, editors. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers; 1988. p. 339, with permission

VI. Flow

- A. Flow is the time rate of volume delivery.
- B. Changes in flow rate have not been well studied in infants, but they probably impact arterial blood gases minimally as long as a sufficient flow is used (which is generally the case with most ventilators). Suboptimal flow may result in rheotrauma (damage to the airway and lungs brought about by inappropriate flow).
 1. Inadequate flow may contribute to air hunger, asynchrony, and increased work of breathing.
 2. Excessive flow may contribute to turbulence, inefficient gas exchange, hyperinflation, and inadvertent PEEP.

VII. In summary, depending on the desired change in blood gases, the following ventilator parameter changes can be performed (Table 10.1).

VIII. Suggested management algorithm for RDS (Fig. 10.1, Table 10.2, Chap. 61).

Suggested Reading

- Chatburn RL, Volsko TA. Documentation issues for mechanical ventilation in pressure-control modes. *Respir Care*. 2011;55:1705–1716.
- Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1997.
- Greenough A. Respiratory Support. In: Greenough A, Robertson NRC, Milner AD, editors. Neonatal respiratory disorders. New York: Oxford University Press; 1996. p. 115–51.
- Mariani GL, Carlo WA. Ventilatory management in neonates. *Controversies in neonatal pulmonary care*. 1998;25:33–48.
- Spitzer AR, Fox WW. Positive-pressure ventilation: pressure-limited and time-cycled ventilators. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 3rd ed. Philadelphia: W.B. Saunders Co.; 1996. p. 167–86.

Chapter 11

Respiratory Gas Conditioning and Humidification

Andreas Schulze

I. Introduction

- A. Inadequate humidification and warming of respiratory gas may lead to adverse effects within minutes to hours in infants with an artificial airway through various mechanisms.
 - 1. Impaired mucociliary clearance with subsequent retention of inspissated secretions, inhaled particles, and microorganisms. Associated risks are airway clogging, atelectasis, and air leak syndromes.
 - 2. Inflammatory and necrotic injury to the bronchial epithelium.
 - 3. Heat loss.
- B. Humidifier malfunction may also impose risks.
 - 1. Flushing of contaminated condensate into the airways with subsequent pneumonia.
 - 2. Thermal injury to airways.
 - 3. Overhydration.
 - 4. Airway occlusion [“artificial noses,” also called heat and moisture exchangers (HMEs)].

II. Physiology: structure and function of the airway lining

- A. Three layers cover the luminal surface of most of the upper respiratory tract and the entire tracheobronchial tree as far as the respiratory bronchioles. These layers constitute the mucociliary clearance function.

A. Schulze, MD, PhD (✉)
Division of Neonatology, Dr. von Hauner Children’s Hospital, Munich, Germany
Department of Pediatrics, Klinikum Grosshadern, Ludwig Maximilian University,
Marchioninstr. 15, 81377 Munich, Germany
e-mail: andreas.schulze@med.uni-muenchen.de

1. A basal cellular layer of mainly ciliated epithelial cells. A variety of other cell types in this layer may each be concerned with a specific function. Serous cells, brush cells, and Clara cells produce and reabsorb aqueous fluid; goblet cells and submucosal mucous glands secrete mucus globules.
2. An aqueous (sol) layer.
3. A viscoelastic gel (mucus) layer at the luminal surface of the airway. Neighboring cilia beat in a coordinated fashion so that waves of aligned cilia move through the airway-lining fluid, propelling the mucus and entrapped particles in a cephalad direction. Dry inspired gas may dehydrate the mucus, decrease the depth of the aqueous layer, and change the viscosity gradient across the layers, all of which impair the function of the mucociliary elevator.

B. The respiratory tract functions as a counter current HME.

1. The inspired air gains heat and water vapor from the upper airway lining, which is partly recovered when the expired gas loses heat, and water condenses on the airway surface. This recovery occurs because the upper airway temperature remains lower than core body temperature during expiration under physiologic circumstances. Breathing is associated with a net loss of heat and water when the expired air temperature is higher than the ambient temperature. The greater the difference in temperature between the inspired and expired gases, the greater the losses. They must be replenished by the airway epithelium, which in turn is supplied by the bronchial circulation. It is unclear under which circumstances the capacity of the airway lining to humidify cold and dry gas becomes overcharged. This capacity is likely different in health than in disease.
2. The level at which the inspired air reaches core body temperature and full saturation with water vapor is called the isothermic saturation boundary. It is located at the level of the main bronchi during normal quiet breathing. Its position will move distally when frigid dry gas is inhaled, when minute ventilation is high, or when the upper airway is by-passed (e.g., use of a tracheostomy tube). Overall, however, under normal physiologic circumstances, only a small segment of the airway surface is exposed to a temperature below core body temperature and to less than full saturation.
3. Damage to the airway epithelial cells and their luminal coverage deprives the system of its function as an HME. Loss of this function may in turn induce structural damage in a vicious cycle that leads to penetration of the injury into the periphery of the bronchial tree.

III. Basic physics of humidity and heat

A. Air can accommodate water in two different ways.

1. Nebulized water (aerosol) is a dispersion of droplets of water in air. They are visible because they scatter light (clouds) and may carry infectious agents. Deposition occurs along the tracheobronchial tree by impaction and sedimentation. The smaller the particles, the better they penetrate into more peripheral areas of the lung.

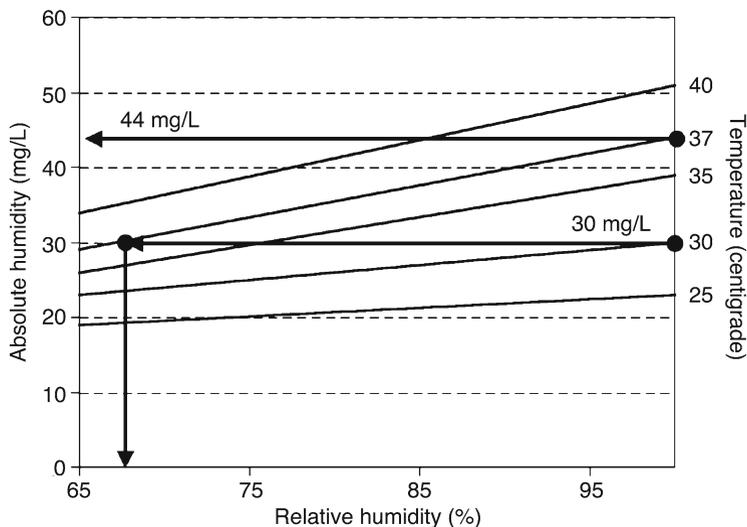


Fig. 11.1 Relationship between absolute humidity, relative humidity, and temperature of gases. The relative humidity depends on the absolute water content and the temperature of the gas. At 37.0°C and 100% relative humidity, the respiratory gas has 44 mg/L absolute water content. If the gas is saturated (100% relative humidity) at 30.0°C, its water content will be only 30 mg/L. When the gas is then warmed to 37.0°C, its relative humidity will fall to below 70%

2. Vaporized water is a molecular (i.e., gaseous) distribution of water in air. It is invisible and unable to carry infectious agents. The gaseous partial pressure of water vapor is 47 mmHg when air is fully saturated (100% relative humidity) at 37°C. This corresponds to 44 mg of water per liter of gas (absolute humidity). The term absolute humidity (AH) is defined as the amount of water vapor (mg) per gas volume (mL) at a given temperature.
 3. Relative humidity (RH) is the actual amount of water (mg) in a given gas volume relative to the amount of water content (mg) in this same gas volume at the same temperature at full saturation.
 4. There is a fixed relationship between AH, RH, and temperature (Fig. 11.1).
- B. Air can accommodate heat in two distinct variants. The total heat content determines the capacity of inspired gas to cool or overheat the airway.
1. The air temperature represents sensible heat. Increasing the air temperature alone without adding water vapor adds very little to the total energy content of the gas. Therefore, if the respiratory gas leaves the humidifier chamber fully saturated at 37°C and is subsequently dry-heated to 40°C within the inspiratory limb of the ventilator circuit, it does not entail the risk of overheating or thermal injury to the airway.
 2. The water vapor mass reflects the latent heat content. Changes in humidity represent major changes in total energy content compared to changes in air temperature alone. Therefore, vaporization consumes much energy,

and thus vaporization of water from the airway lining fluid for humidification of dry inspiratory gas has a strong capacity to cool the airway, even if warm gas enters the airway. Conversely, rainout (condensation of water vapor) generates energy. If it occurs inside the inspiratory limb of the ventilator circuit, the tubing may feel “nice and warm” even though the gas loses the required energy (and water vapor) content.

IV. Inspired gas conditioning devices and procedures

Medical-grade compressed gases from cylinders or central supply systems have virtually negligible water content. It is rational to deliver the inspiratory gas at or close to core body temperature and close to full saturation with water vapor to infants with an artificial airway (nasal or pharyngeal prongs or cannula, endotracheal tube, or tracheostomy tube).

A. Heated humidifiers.

1. The respiratory gas is warmed inside the humidification chamber to a set target temperature, and water vapor is added from the heated water reservoir.
2. Heated-wire inspiratory circuit tubing is then used to maintain or slightly raise the gas temperature so as to prevent rainout before the gas reaches the infant. Heated humidifiers are safe and effective respiratory gas conditioning devices for short-term and long-term application in infants. However, their technology is complex, and device malfunction is not always immediately obvious. Consideration should be given to basic principles of operation common to all types of heated humidifiers.
 - a. The target respiratory gas condition is a temperature close to core temperature with nearly full water vapor saturation. To achieve this target, the gas must be loaded with nearly 44 mg of water/L.
 - b. Knowing the circuit flow rate of the ventilator, the minimum water consumption rate of the humidifier chamber to meet this target can easily be estimated and can be used to check the function of the humidifier (Fig. 11.2).
 - c. Rainout in the inspiratory limb of the ventilator does not prove that there is proper humidification. Major circuit condensation usually indicates a moisture loss that leads to underhumidification of the respiratory gas. This may occur if the maximum heating capacity of the heated circuit wire cannot meet requirements under specific conditions such as drafts around the tubing (air-conditioned rooms), low room temperatures, or a large outer surface area of small diameter tubing (particularly if corrugated).
 - d. Rainout should also be avoided for other reasons: condensate is easily contaminated, may be flushed down the endotracheal tube with risks of airway obstruction and nosocomial pneumonia, and may disturb the function of the ventilator (particularly autocycling in patient-triggered ventilators). Binding the inspiratory and expiratory limbs of the tubing closely may obviate the problem.

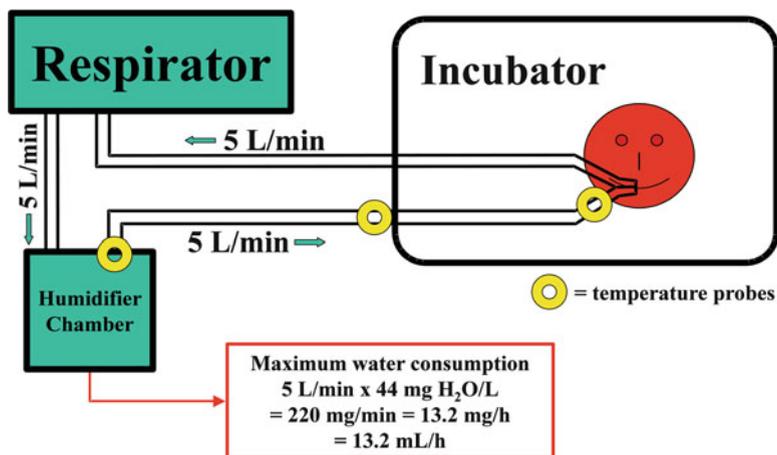


Fig. 11.2 Position of three temperature probes of a heated-wire humidification system for infants. The user sets the target temperature to be reached at the endotracheal tube adaptor. This temperature is commonly set at or slightly above 37.0°C. The temperature inside the humidifier chamber must be high enough to vaporize an amount of water near the absolute water content of gas saturated at 37°C (44 mg/L). The water consumption rate of a humidifier chamber required to reach a target respiratory gas humidity can be calculated from the circuit flow rate. Observation of this water consumption rate can be employed as a simple test of the efficiency of a humidifier

3. The temperature probe close to the patient connection serves to monitor the respiratory gas temperature. It is commonly part of a servo-control aimed at maintaining the set gas temperature at the wye adapter by controlling the heated-wire power output.
 - a. If the temperature probe is in the presence of a heated field (incubator or radiant warmer), it may register a temperature higher than the actual respiratory gas temperature as a result of radiation or convection from the warmer environment. This may cause the servo-control to decrease the heating output of the ventilator circuit and may lead to loss of gas temperature and rainout.
 - b. Insulating the temperature probe by a light reflective patch or other material can improve the performance of the system.
 - c. Another way to alleviate this problem is to place the temperature probe just outside the heated field and use an unheated extension adapter tubing to carry the gas through the heated field to the infant. The extension tube does not need to incorporate heated wires because its temperature is maintained by the heated field.
 - d. If cooler incubator temperatures are employed, as for older preterm infants, rainout will occur in the unheated segment, particularly at low circuit gas flow rates. A circuit should then be used that is equipped with a heated wire along the entire length of its inspiratory limb.

- e. Another suitable type of circuit is one with two temperature probes, one outside the heated field and another one close to the wye adapter. These circuits can perform well over a range of incubator temperatures above and below the target respiratory gas temperature, because the heated-wire servo-control can be programmed to select the lower of the two recorded temperatures to drive the power output.

B. Artificial noses.

1. Working principle: HMEs recover part of the heat and moisture contained in the expired air. A sponge material of low thermal conductivity inside the clear plastic housing of these devices absorbs heat and condenses water vapor during expiration for subsequent release during inspiration.
2. Different brands may vary widely in performance characteristics. Device performance has improved, and further advances can be expected to facilitate neonatal applications.
 - a. Some HMEs are additionally coated with bacteriostatic substances and equipped with bacterial or viral filters.
 - b. Hygroscopic condenser humidifiers (HCH) use hygroscopic compounds, such as CaCl_2 , MgCl_2 , and LiCl to increase the water retention capacity.
3. Application.
 - a. These devices are appropriate for short-term conventional and high-frequency mechanical ventilation in infants, such as during transport or surgical procedures.
 - b. The safety and effectiveness of HME/HCH for long-term mechanical ventilation is controversial in adults and has not been established in infants.
 - c. HMEs/HCHs must not be used in conjunction with heated humidifiers, nebulizers, or metered dose inhalers. This may cause a hazardous increase in device resistance and/or leaching of the hygroscopic coating.
4. Advantages of HMEs/HCHs.
 - a. Simplification of the ventilator circuit
 - b. Passive operation without requirement of external energy and water sources
 - c. No ventilator circuit condensate
 - d. Low risk of circuit contamination
 - e. Low expense
5. Potential risks and drawbacks of HMEs/HCHs.
 - a. Depending upon the actual water load, these devices add a variable resistance and dead space to the circuit.

- b. A risk of airway occlusion from clogging with secretions or from a dislodgement of internal components has been reported for infants, even during short-term application.
 - c. An expiratory air leak will impair the barrier effect of any HMEs/HCH against moisture loss.
 6. Measures of effectiveness of HMEs/HCHs.
 - a. Performance is not reliably reflected by indirect clinical measures, such as the occurrence of nosocomial pneumonia, number of endotracheal tube occlusions, or frequency of suctioning.
 - b. Visual evaluation of the amount of moisture in the adapter segment between the endotracheal tube and the HME/HCH was found to closely correlate with objective measurements of the delivered humidity.
- C. Aerosol application for respiratory gas conditioning. Water or normal saline nebulization offer no significant benefits for inspiratory gas conditioning compared to the use of heated humidifiers. It may entail a risk of overhumidification.
 1. With appropriate use of heated humidifiers, the isothermic saturation boundary is close to the tip of the endotracheal tube. Downstream of this, aerosol particles cannot be eliminated through evaporation and exhalation. They will therefore become a water burden to the mucosa.
 - a. The surplus water needs to be absorbed by the airway epithelium in order to maintain an appropriate periciliary fluid depth.
 - b. An increase in depth of the airway lining fluid's aqueous layer may make it impossible for the cilia to reach the mucous layer and thus impair mucus transport.
 - c. Furthermore, if the aerosol deposition rate exceeds absorption capacity, this may lead to increased airway resistance and possibly narrowing or occlusion of small airways.
 - d. Severe systemic overhydration subsequent to ultrasound aerosol therapy has been described in the term newborn and in adults.
 2. If an aerosol stream meets the airway proximal to the isothermic saturation boundary, the particulate water can theoretically contribute to the gas conditioning process by evaporation before and after deposition. The droplets, however, contain sensible heat only, and the mucosa needs to supply most of the latent heat for vaporization. This will cool the airway.
- D. Irrigation of the airway.
 1. It is a common clinical practice to instill small amounts (0.1–0.5 mL/kg) of water, normal saline solution, or diluted sodium bicarbonate periodically into the endotracheal tube prior to suctioning procedures in the belief that this provides moisture and loosens tenacious secretions.
 2. The safety and efficacy of this practice has not been established.

V. Inspiratory gas conditioning and the nosocomial infection risk

- A. There is no evidence that appropriate warming and humidifying of respiratory gases increase the risk of nosocomial pneumonia in infants with an artificial airway.
- B. The incidence of nosocomial pneumonia in adults was not increased when ventilator circuits were changed less frequently than every 24 h or even between patients only.
- C. The optimal rate of ventilator circuit changes for infants is unknown. Changing a ventilator circuit may disrupt ventilation in a potentially dangerous way, and medical personnel may become a vector for cross-contamination between patients. Weekly circuit changes or no circuit changes at all except between patients appears to be a rational (though unproven) approach.

Suggested Reading

- Kelly M, Gillies D, Todd DA, Lockwood C. Heated humidification versus heat and moisture exchangers for ventilated adults and children. *Cochrane Database Syst Rev.* 2010;CD004711.
- Kollef MH, Shapiro SD, Boyd V, et al. A randomized clinical trial comparing an extended-use hygroscopic condenser humidifier with heated-water humidification in mechanically ventilated patients. *Chest.* 1998;113:759.
- Lellouche F, Taillé S, Lefrançois F, Deye N, Maggiore SM, Jouve P, et al.; and Groupe de travail sur les Respirateurs de l'AP-HP. Humidification performance of 48 passive airway humidifiers: comparison with manufacturer data. *Chest.* 2009;135:276.
- Nakagawa NK, Macchione M, Petrolino HM, et al. Effects of a heat and moisture exchanger and a heated humidifier on respiratory mucus in patients undergoing mechanical ventilation. *Crit Care Med.* 2000;28:312.
- Ricard JD, Le Miere E, Markowicz P, et al. Efficiency and safety of mechanical ventilation with a heat and moisture exchanger changed only once a week. *Am J Respir Crit Care Med.* 2000;161:104.
- Schiffmann H, Rathgeber J, Singer D, et al. Airway humidification in mechanically ventilated neonates and infants: a comparative study of a heat and moisture exchanger vs. a heated humidifier using a new fast-response capacitive humidity sensor. *Crit Care Med.* 1997;25:1755.
- Schulze A. Respiratory gas conditioning in infants with an artificial airway. *Semin Neonatol.* 2002;7:369.
- Shelly MP, Lloyd GM, Park GR. A review of the mechanisms and methods of humidification of inspired gases. *Intensive Care Med.* 1988;14:1.
- Siempos II, Vardakas KZ, Kopterides P, Falagas ME. Impact of passive humidification on clinical outcomes of mechanically ventilated patients: a meta-analysis of randomized controlled trials. *Crit Care Med.* 2007;35:2843.
- Williams R, Rankin N, Smith T, et al. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. *Crit Care Med.* 1996;24:1920.
- Williams RB. The effects of excessive humidity. *Respir Care Clin N Am.* 1998;4:215.

Part III
Procedures and Techniques

Chapter 12

Clinical Examination

Avroy A. Fanaroff and Jonathan M. Fanaroff

I. Normal physical findings

A. Respiratory rate 40–60/min.

1. Irregular with pauses ≤ 5 s in REM sleep
2. Regular in non-REM sleep, rate 5–10 breaths/min slower than in REM sleep or when awake
3. Comfortable (no dyspnea)
4. No chest retractions (subcostal or intercostal)
5. No flaring of nostrils
6. No grunting

B. Pulse rate 120–160 beats/min (but may go as low as 80 during sleep).

1. Sinus arrhythmia rare in the newborn.
2. Pulses easy to feel.
 - a. Femoral pulses may be decreased in the first 48 h.
 - b. Femoral pulses may be impalpable, reduced or delayed with coarctation of the aorta. In any infant with suspected heart disease, blood pressure should be measured in all four limbs. A difference of >15 mmHg between the upper (higher) and lower extremities is significant.
 - c. Bounding pulses are characteristic of a patent ductus arteriosus.

A.A. Fanaroff, MD, FRCPE, FRCPCH, FAAP (✉)
Department of Pediatrics, Rainbow Babies and Children's Hospital,
11100 Euclid Avenue, Cleveland, OH 44106, USA
e-mail: aaf2@case.edu

J.M. Fanaroff, MD, JD
Division of Neonatology, Department of Pediatrics, Rainbow Babies & Children's Hospital,
11100 Euclid Avenue, Cleveland, OH 44106, USA

3. Interpreting the heart rate is best done in conjunction with the respiratory rate and oxygen saturation.
 - a. Episodes of desaturation are mostly transient or from movement artifact, but if more severe and prolonged will be accompanied by bradycardia.
 - b. An increase in heart rate may be observed with movement/crying, respiratory distress, anemia, hypovolemia, fever, infection pain, fluid overload, arrhythmia.
 - c. Slowing of the heart is seen with hypoxia, hypothermia, seizures, heart block, and rarely increased intracranial pressure.
 - d. Monitor artifacts may also produce bradycardia. The clinical diagnosis of neonatal sepsis is preceded by abnormal heart rate characteristics of transient decelerations and reduced variability.
- C. First and second heart sounds are often single; S_2 splits by 48 h in 75% of infants.
- D. Murmurs common in first few days (1–2% of normal infants).
- E. Blood pressure (see below).

II. Clinical examination of cardiorespiratory system

- A. The four classic components should be followed.
 1. Observation.
 2. Palpation.
 3. Percussion.
 4. Auscultation. Murmurs are common in healthy newborns. Their source may be pulmonary branch stenosis, patent ductus arteriosus, tricuspid regurgitation, or other congenital cardiac lesions.
- B. In the newborn, careful visual as well as auditory observation is important.
- C. Cardinal signs of respiratory distress.
 1. Intercostal, subcostal, and substernal *retractions* (use of accessory muscles)
 2. Nasal *flaring* (decreases airway resistance)
 3. Expiratory *grunting* (increases positive end expiratory pressure)
 4. *Tachypnea* $>60/\text{min}$
 5. *Cyanosis*
 - a. Peripheral cyanosis (extremities) is common in normal infants.
 - b. Central cyanosis (lips and tongue) signifies >5 g/dL of desaturated hemoglobin and is significant (pulse oximeter $<90\%$).
 - c. The commonest causes of cyanosis are heart disease, pulmonary disease and methemoglobinemia. The underlying cause of cyanosis must be determined. If cyanosis is relieved by oxygen administration, the most likely cause is pulmonary disease.

III. Observation

A. Respiratory rate

1. Rates >60 breaths/min are abnormal.
2. Very fast rates may have a better prognosis as they occur in more mature babies with a good respiratory pump able to sustain the tachypnea.
3. Slow irregular rates <30 breaths/min with or without gasping are ominous as are apneic periods in term infants.
4. Remember that tachypnea is a very nonspecific finding and can be caused by:
 - a. Pulmonary disease
 - b. Cardiac disease
 - c. Sepsis
 - d. Anemia
 - e. Metabolic acidemia of any cause
 - f. Fever
 - g. CNS pathology
 - h. Stress (e.g., after feeding or crying)

IV. Dyspnea

- A. Distortion of the chest by the powerful attempts of the muscles of respiration to expand noncompliant lungs is one of the most significant findings in parenchymal lung disease.
- B. With anemia, acidemia, cyanotic heart disease, or fever, there is often tachycardia without dyspnea (“comfortable tachypnea”).
- C. Preterm babies (<1.5 kg) in non-REM sleep when muscle tone is low show mild intercostal and subcostal retractions.
- D. Other features of dyspnea include:
 1. Flaring of the alae nasi. By enlarging the nostrils, there is a reduction in nasal resistance enhancing air flow.
 2. “See-saw” respiration; abdominal expansion (from diaphragmatic contraction) at the same time as sternal retractions.
 3. Intercostal and subcostal retractions.
 4. Retractions (suprasternal, intercostals, and subcostal) result from the compliant rib cage being drawn in on inspiration by the diaphragm as the infant attempts to generate high intrathoracic pressures to ventilate poorly compliant lungs.

V. Interaction with positive pressure ventilation

- A. In the early stages of severe lung disease, especially respiratory distress syndrome (RDS), the baby may breathe out of phase with the ventilator. This compromises oxygenation and increases the risk of air leaks. Synchronization of the ventilator to the baby’s own respiratory effort has been shown to decrease time on the ventilator and assists weaning.

- B. In both situations, it is important to be aware of the ventilator rate as well as the baby's spontaneous ventilation rate (total respiratory rate).
- C. If the baby's condition has deteriorated rapidly, is the chest moving at all with the ventilator? If it is not, it may suggest a blocked or dislodged endotracheal tube. Always consider a pneumothorax in an infant whose condition has deteriorated rapidly.

VI. Apnea and gasping

When counting the respiratory rate note if there are any pauses lasting more than 20 s, or if there are any gasping respirations (both very abnormal), as opposed to normal sighs (deep inspirations against the normal background respiratory pattern).

VII. General appearance

A. Does the baby look ill or well? Multiple factors to assess are as follows:

1. Color (pallor, cyanosis, plethora)
2. Level of activity and overall tone
3. Cry
4. Eye opening
5. Posture
6. Edema
7. Perfusion
8. Dysmorphic features

B. Edema—leaky capillaries in ill babies lead to subcutaneous edema as well as pulmonary edema

C. Perfusion

1. Pallor (capillary refill time >3 s)
2. Nonspecific illness
3. Anemia
4. Hypotension
5. Shock (septic or other)
6. Visible veins in skin (especially in preterm)
 - a. Hypercapnia
 - b. Nonspecific severe illness with shock (e.g., extensive hemorrhage)

D. Cyanosis

1. Assessed from lips, mucous membranes (acrocyanosis is peripheral cyanosis of hands and feet; it is common and rarely significant).
May be difficult to see in nonwhite races (even in mucosa).
2. Cyanosis results from >5.0 g/dL desaturated hemoglobin.
 - a. Seen in normally oxygenated polycythemic babies
 - b. Difficult to detect in very anemic babies

3. In an oxygen enriched environment, oxygen may be absorbed through the skin making the baby look pink although central cyanosis may be present.

E. Saturation (see Chaps. 17 and 18):

1. Because clinical signs of hypoxemia are unreliable, if in doubt initially check oxygen saturation (SpO_2) by oximetry (quick and easy) and if necessary confirm hypoxemia by arterial blood gas analysis.
2. An arterial oxygen tension of 60–90 torr results in a saturation of 94–98% and changes of 1–2% usually reflect a PaO_2 change of 6–12 torr. Below 40 torr, the saturation falls below 90%.
3. Saturations above 95% are normal in term babies.
4. Note that SpO_2 does not correct for abnormal hemoglobin as in methemoglobinemia—baby is blue but saturation is high.

VIII. Clubbing (rarely seen in newborns)

IX. Venous pressure

- A. Observe venous pulsation in the neck for evidence of congestive heart failure.
- B. Prominent pulsation in the neck may be observed with vein of Galen arteriovenous malformation.
- C. Auscultation of the head will reveal a bruit.

X. Other systems

A. Abdomen

1. Distention

- a. Large amount of gas in stomach after positive pressure ventilation, especially with mask and bag
- b. Enlarged liver from heart failure, hepatitis, or metabolic disorder; normal liver is 1–2 cm below the costal margin
- c. Liver may be pushed down by hyperinflated chest or tension pneumothorax
- d. Enlarged spleen, kidneys, or other abdominal mass
- e. Retention of urine secondary to drugs, CNS disease

2. Scaphoid abdomen strongly suggests congenital diaphragmatic hernia

B. Central nervous system

1. Seizures.
2. Tense fontanel when the newborn is not crying suggests increased intracranial pressure.
3. Abnormal tone.
4. Abnormal level of consciousness (e.g., irritability, lethargy, coma).

XI. Auditory observations

- A. Listen to the baby. If he/she is crying vigorously, he/she is unlikely to be seriously ill.
- B. Three important auditory clues:
 - 1. Grunting—a pathognomonic feature of neonatal lung disease—expiration against a partially closed glottis traps alveolar air and maintains FRC.
 - 2. Stridor, usually inspiratory.
 - a. Upper airway problems (e.g., laryngomalacia is the commonest)
 - b. Glottic and subglottic injury or postintubation edema
 - c. Local trauma following over-vigorous laryngeal instrumentation
 - d. Congenital subglottic stenosis
 - e. Vascular rings, hemangiomas, hamartomas (rare)
 - 3. “Rattle”—the bubbling of gas through secretions in the oropharynx. Often an ominous sign in a baby with severe CNS injury as well as lung disease.
 - 4. Excessive drooling with choking and cyanosis suggests esophageal atresia (diagnose by placing an orogastric tube and obtaining chest radiograph; if present, tube will end in esophageal pouch; a stomach bubble indicates a fistula).

XII. Palpation

- A. Not usually of great help. The following may be noted:
 - 1. Mediastinal shift (trachea, apical beat) with air leak, diaphragmatic hernia, collapse (consolidation).
 - 2. Tense abdomen (tension pneumothorax or pneumoperitoneum).
 - 3. Subcutaneous emphysema following air leaks.
 - 4. Pulses.
 - a. Should be checked in all four limbs if there is any suspicion of cardiac disease and documented by blood pressure measurements.
 - b. Bounding pulses are a feature of an increased cardiac output often with a left-to-right shunt. In the preterm infant, this may be the first sign of a PDA.
 - 5. Cardiac precordial activity.
 - 6. Thrills are very rare in the neonatal period; if present, always significant.

XIII. Percussion

- A. Increased resonance may be seen with a pneumothorax and occasionally with severe pulmonary interstitial emphysema (PIE).
- B. Decreased resonance accompanies pleural effusions.
- C. Decreased resonance with marked collapse/consolidation.
 - 1. Pneumonia
 - 2. Endotracheal tube in one bronchus

D. Decreased resonance with congenital diaphragmatic hernia.

XIV. Auscultation

- A. Always use the small neonatal stethoscope. It can be difficult to apply to the chest of a preterm newborn in a way that excludes extraneous noise, and trial and error will identify whether the bell or diaphragm is best in a given situation. Use whichever gives the best acoustic seal.
- B. Another problem is that babies, particularly preterm ones, wiggle when the stethoscope is placed on the chest making cardiac examination difficult. The trick is to hold the prewarmed stethoscope in the same place and after 10–15 s the baby habituates to the stimulus and lies still.
- C. Breath sounds are widely conducted through the upper torso of the newborn, and the smaller the baby, the greater the conduction. Even with the neonatal stethoscope head it is difficult to be certain about where air is going. Two common (and very serious) auscultation mistakes are the following:
 - 1. Failing to realize during mechanical ventilation that air is going in and out of the stomach rather than the lungs.
 - 2. Failing to realize that only one lung is being ventilated (particularly if there is some mediastinal shift).

XV. Air entry

- A. The breath sounds in newborns with normal lungs can be heard in both inspiration and expiration, being slightly louder and longer in inspiration. In other words, part of the expiratory phase, which is physiologically longer, is silent.
- B. A general reduction in air entry is heard with:
 - 1. Any severe lung disease (e.g., RDS)
 - 2. Occluded endotracheal tube
- C. Unilateral decrease in air entry—any unilateral lung disease, which will usually require a chest radiograph for further evaluation.
 - 1. Pneumonia
 - 2. Air leak
 - 3. Pleural Effusion
 - 4. Misplaced endotracheal tube/spontaneous extubation

XVI. Other sounds

- A. There should be no rales or crepitations (discontinuous sounds) and no rhonchi (continuous sounds). The other common sound heard on auscultating the chest of a preterm baby is condensed water bubbling in the ventilator circuit or endotracheal tube. Clearly, it is impossible to do a successful clinical examination under these circumstances. The tubing should be transiently disconnected from the ventilator circuit and emptied.

B. Crepitations occur in the following:

1. Pneumonia
2. Aspiration
3. Heart failure (PDA and other)
4. Massive pulmonary hemorrhage
5. Bronchopulmonary dysplasia (BPD)
6. Meconium aspiration (stickier and louder)

C. Rhonchi occur with:

1. Retained secretions during mechanical ventilation
2. Meconium aspiration
3. BPD

D. None of these findings is specific. They indicate a lung disease that requires further evaluation, initially by radiography.

E. Bowel sounds in the chest are a specific finding of congenital diaphragmatic hernia.

XVII. Cardiac auscultation

A. Heart sounds—the ready availability of echocardiography has blunted the need for sophisticated auscultatory diagnostic skills for the newborn. The following, however, should always be noted:

1. S_1 and S_2 are usually single in the first 24–48 h, with splitting of S_2 being present in 75% of babies by 48 h.
2. A gallop rhythm (S_3 and S_4) is always abnormal, usually indicating heart failure.

B. Innocent murmurs are very common in the first 24–48 h, with the following characteristics:

1. Grade 1–2/6 mid-systolic at the left sternal edge
2. No ejection clicks
3. Occur in babies with normal pulses (especially femoral; document by blood pressure measurements)
4. Occur in babies with an otherwise normal clinical examination

C. Significant murmurs are more likely to be heard >48 h of age; their features include:

1. Pansystolic \pm diastolic \pm thrills
2. Grade 3/6 or more and harsh
3. Best heard at upper left sternal edge (e.g., PDA)
4. Abnormal S_2 (not splitting) \pm gallop rhythm
5. Early or mid-systolic click
6. Decreased femoral pulses with murmur heard at back
7. Other signs of illness (heart failure, shock, and cyanosis)

- D. Any baby with these features needs urgent evaluation (radiography, electrocardiography, and echocardiography). The absence of murmurs or auscultatory abnormality in the first 48–72 h does not exclude serious or even fatal heart disease.

XVIII. Transillumination (Chap. 22)

- A. A bright light source applied to the chest wall can be a very useful and effective way of detecting a collection of intrapleural air, typically a pneumothorax, but large cysts, severe PIE, or marked lobar emphysema may also transilluminate. To be effective, the light source has to be very bright (ideally a fiberoptic source), the room around the baby needs to be very dark, and some experience is required to differentiate the normal 0.5–0.1 cm halo of light around the probe from increased transillumination from a small collection of air. In cases where the whole hemithorax lights up, the diagnosis is easy.
- B. The technique is more useful in smaller babies in whom the light is transmitted into the pleural cavity much more easily than with term babies with a thick layer of subcutaneous fat.

XIX. Blood pressure

- A. The readily available automatic blood pressure recording devices now mean that this is a routine part of the assessment of all newborns.
- B. Attention to the following details is important:
 - 1. Baby quiet and not recently crying.
 - 2. Cuff covers 75% of the distance between the axilla and the elbow.
 - 3. Bladder virtually encircles the arm.
 - 4. A similar cuff size if appropriate for the upper arm and the calf.
- C. In ill preterm babies, the oscillometric device may overestimate the true blood pressure, and if there is any doubt about systolic pressure accuracy, direct measurement from an indwelling arterial catheter may be indicated.
- D. In summary, in the newborn the circulation is assessed by:
 - 1. Blood pressure measurement. Normative values are available for term infants, but there is less reliable data for extremely low birth weight infants (Fig. 12.1). BP may correlate poorly with systemic blood flow and circulating volume. Cerebral blood flow is critical.
 - 2. Heart rate. Tachycardia from hypovolemia is common, and bradycardia is a late sign of shock.
 - 3. Temperature gap (between abdomen and toes) $>2^{\circ}\text{C}$ may suggest shock. Also caused by a cold environment and infection without shock.

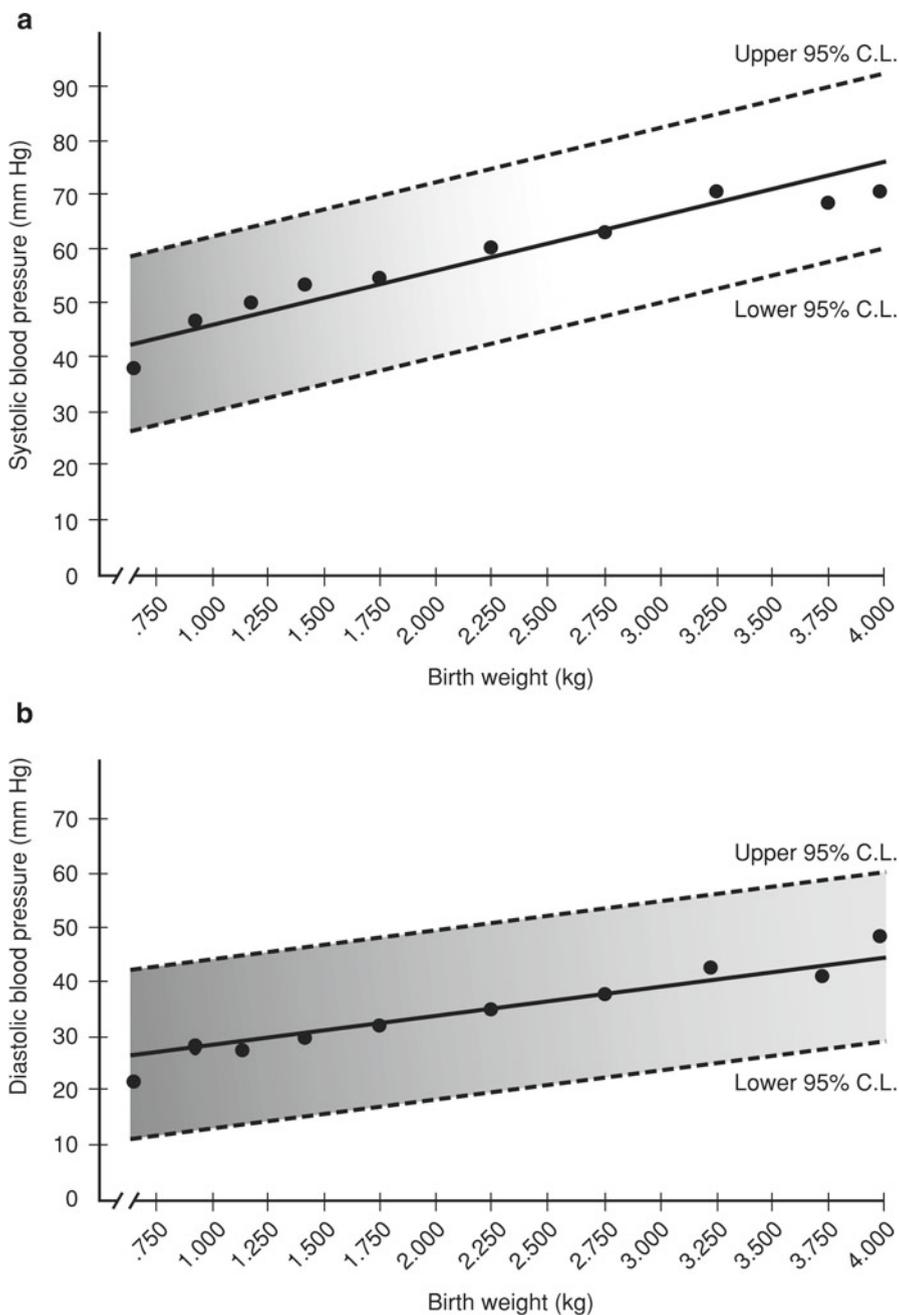


Fig. 12.1 Linear regression of mean (a) and diastolic (b) blood pressure on birth weight in 329 infants admitted to the NICU on day 1 of life is plotted. C.L., Confidence limits (From Zubrow AB, Hulman S, Kushner H, et al: Determination of blood pressure in infants admitted to neonatal intensive care units. A prospective multicenter study. *J Perinatol* 1995; 15:470–479. Copyright, the Nature Publishing Group, reprinted with permission)

4. Capillary refill time >3 s is abnormal.
5. Acid–base status (increased lactate with circulating insufficiency).
6. Echocardiographic evaluation of cardiac function.
7. Urine output (after the first 24 h).

Suggested Reading

- Arlettaz R, Archer N, Wilkinson AR. Natural history of innocent heart murmurs in newborn babies: controlled echocardiographic study. *Arch Dis Child Fetal Neonatal Ed.* 1998;78:F166–70.
- Barrington K. Neonatal screening for life threatening congenital heart disease. *BMJ.* 2009;338:a2663.
- Frommelt MA. Differential diagnosis and approach to a heart murmur in term infants. *Pediatr Clin North Am.* 2004;51:1023–32.
- Greenough A, Greenall F. Observation of spontaneous respiratory interaction with artificial ventilation. *Arch Dis Child.* 1988;63:168–71.
- Yi MS, Kimball TR, Tsevat J, Mrus JM, Kotagal UR. Evaluation of heart murmurs in children: cost-effectiveness and practical implications. *J Pediatr.* 2002;141:504–11.

Chapter 13

Neonatal Resuscitation

Janet M. Rennie

- I. Anticipating resuscitation. “*Time* is of the utmost importance. *Delay* is damaging to the infant. *Act* promptly, accurately and gently” (Virginia Apgar). Some form of resuscitation is required in about 5–10% of all deliveries; about 2 per 1,000 require intubation. A person with sole responsibility for the baby and who is trained in the skills of basic resuscitation should be present at all deliveries, but an individual with advanced resuscitation skills should be present at the following types of deliveries (the list is not exhaustive). A person with more experience should be called if there has been prolonged fetal bradycardia, or the delivery is of a preterm baby of marginal viability.
 - A. Preterm delivery
 - B. Multiple deliveries
 - C. Vaginal breech delivery
 - D. Instrumental delivery
 - E. Fetal compromise
- II. Normal postnatal transition. Most babies establish independent breathing and circulation quickly after birth, crying lustily and becoming pink within a few minutes. During this period of time, the baby normally:
 - A. Clears lung liquid from the trachea and alveoli
 - B. Establishes a functional residual volume with the aid of surfactant
 - C. Reduces pulmonary vascular resistance
 - D. Increases pulmonary blood flow, and reverses intra- and extra-cardiac shunts (foramen ovale and ductus arteriosus)
- III. Equipment needed for resuscitation
 - A. A warm, well-lit area in which resuscitation can take place.

J.M. Rennie, MA, MD, FRCP, FRCPCH, FRCOG (✉)
Institute of Women’s Health, University College London Hospitals,
2 North, 250 Euston Rd, London NW1 2PQ, UK
e-mail: jmr@janetrennie.com

- B. A heater.
 - C. Towels, gloves, hat for baby. Food grade plastic wrap for very preterm babies.
 - D. Immediate access to a telephone or intercom.
 - E. An assured oxygen supply and blender, with a suitable pressure valve to limit the pressure.
 - F. A supply of medical gases.
 - G. A suction device with a range of catheter sizes.
 - H. Laryngoscopes with back-up bulbs and batteries, assorted blades.
 - I. Endotracheal tubes varying from 2.5 mm to 4.5 mm with stylets.
 - J. A mask resuscitation system with masks of various sizes.
 - K. All systems capable of providing respiratory support should have protective “pop-off devices.” However, in case high pressures are needed on an individual basis, the resuscitator should be able to override such a device or revert to an alternative system.
 - L. Equipment for placing a peripheral and/or umbilical venous catheter.
 - M. Scissors.
 - N. Stethoscope.
 - O. A timing device.
 - P. Fluids and resuscitative drugs (naloxone, epinephrine, dextrose, saline).
- IV. Assessing the infant after birth
- A. Start the clock.
 - B. Receive the baby, remove any wet wraps, and dry the baby with a warm towel unless very preterm, in which case place into plastic bag.
 - C. Place the infant on the resuscitation surface, cover with a warm towel, and make an assessment of breathing, heart rate, and color.
 - D. Babies fall into one of three categories at this point:
 - 1. Pink, breathing spontaneously and regular, heart rate >100 ; active tone
 - 2. Cyanotic, breathing irregularly, with a heart rate >100 ; some tone
 - 3. Pale, floppy, not breathing, heart rate <100
- V. The Apgar score (Table 13.1). The Apgar score can be helpful in categorizing infants at this stage. A score of less than 3 means that advanced resuscitation is required immediately and is an indication to call for help.
- VI. Initiating resuscitation
- A. Babies who are pink, breathing and have a good heart rate should be returned to their mothers as soon as possible, without any further intervention.
 - B. If the baby falls into one of the other two categories above where respiration is not established, resuscitation should be started.
 - C. Babies who are blue but with a good heart rate usually respond to simple resuscitation.
 - D. Babies who are white, floppy, and not breathing will most likely need full resuscitation with intubation and chest compression following the “A, B, C, D” approach outlined below.
 - E. Optimally, two people should be dedicated to the resuscitation of a baby in this situation. Call for help immediately if you are single-handed in this situation.

Table 13.1 The Apgar score

	Score	0	1	2
A	Appearance	Pale or blue	Body pink but extremities blue	Pink
P	Pulse rate	Absent	<100	>100
G	Grimace	Nil	Some	Cry
A	Activity (muscle tone)	Limp	Some flexion	Well flexed
R	Respiratory effort	Absent	Hypoventilation	Good

VII. The “A, B, C, D” of resuscitation (Fig. 13.1)

A. Airway

1. Make sure the airway is clear.
2. Position the baby supine with the jaw drawn forward.
3. Gently suction the mouth, then the nose if secretions are present. Many babies will resuscitate themselves once the airway is clear.
4. Do not insert the suction catheter too far into the oropharynx or it may induce a vagal response with bradycardia and apnea.
5. Do not suction for more than 5 s at a time.
6. Suctioning is particularly important for depressed babies born through meconium, but is not required for those who remain vigorous.

B. Breathing

1. If resuscitation does not commence rapidly, try gentle stimulation—rubbing the soles of the feet, drying the body with the towel.
2. If respirations do not commence within 20 s or remain irregular the baby will require artificial lung inflation.
3. Choose a face mask that fits over the baby’s mouth and nose but does not overhang the chin or cover the eyes. Masks with cushioned rims are preferable because it is easier to make a tight seal.
4. Hold the mask over the face making a tight seal.
5. Begin to inflate the lungs with the T piece (easier and better, can give sustained inflation) or self-inflating bag.
6. Never, ever, connect a baby directly to the “wall” oxygen supply, which is at a dangerously high pressure. Hospital gas supplies must be passed through a pressure reducing system before being delivered to babies via a T piece or bag and mask. Babies have died from air leak caused by high pressure gas delivered this way.
7. Ventilate at 30–40 breaths per minute, giving the first few breaths a sustained (1–2 s) inflation time (“rescue breaths”).
 - a. The first few breaths need to overcome surface tension.
 - b. The pressure given should be enough to move the chest wall (about 20 cm H₂O, although the first few breaths may need to be 30–40 cm H₂O).

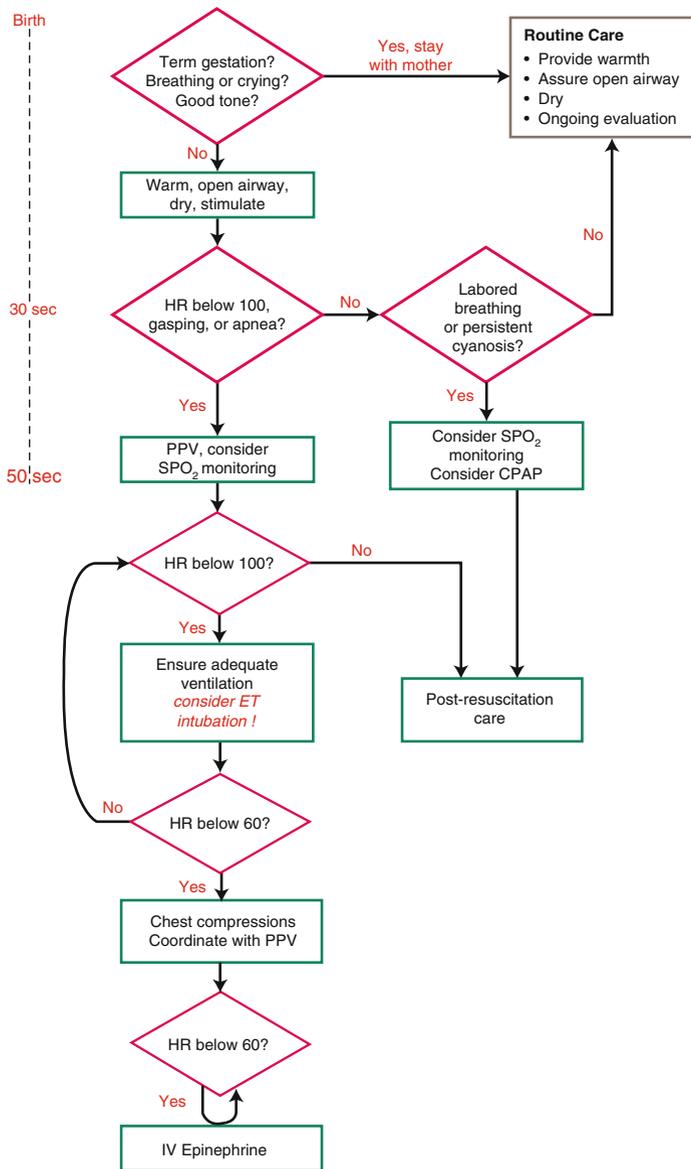


Fig. 13.1 The ILCOR algorithm

- c. Watch to see that the chest moves and listen to the heart rate, which should rapidly rise.
- d. If the heart rate remains low, or falls in spite of adequate ventilation, the baby will need intubation and external chest compression.
- e. In an emergency, oral intubation is generally preferred. Take care to use the correct tube size and to insert it to the appropriate depth (Chap. 14).
- f. Use capnography to confirm ETT placement.

C. Circulation

1. Chest compressions should be administered if the heart rate is less than 60 bpm for more than 30 s despite adequate assisted ventilation.
2. A baby who needs chest compressions should be intubated.
3. The recommended method for external chest compression in babies is to encircle the chest with both hands at the level of the lower third of the sternum, and to compress the sternum with the thumbs.
4. Aim to compress the chest by about a third of the antero-posterior diameter, at a rate of about 100 per minute.
5. Chest compressions should be sufficiently deep to generate a palpable pulse.
6. Coordinate chest compression with ventilation; inflate the lungs after every third compression (a ratio of 3:1).

D. Drugs. Used rarely, if there no response after intubation and effective ventilation and chest compressions. If the baby remains white, not breathing, and with a heart rate of 60 or less, drugs can sometimes achieve a “jump start” of the system. The ideal route is via the umbilicus. Intraosseous access can be used if IV access cannot be quickly achieved.

1. Epinephrine 0.1–0.3 mL/kg 1:10,000 by IV (preferred route) or ET tube (use higher dose).
2. Dextrose 2 mL/kg, 10% solution.
3. Naloxone is of use if the mother was given opiate analgesia less than 6 h before delivery. Use 100 mcg/kg. The dose may need to be repeated. *Do not* give if history or suspicion of maternal drug abuse, as it may initiate immediate neonatal withdrawal syndrome.
4. Calcium—there is no evidence that calcium is useful in resuscitation.

VIII. Monitoring the response to resuscitation

- A. Resuscitation does not end with the baby achieving a good heart rate and spontaneous breathing.
- B. Observations should continue and a decision made as to whether it is safe for the baby to remain with the mother or whether he/she should be admitted to the nursery for observation.
- C. Any baby who has required resuscitation should have early glucose screening until stable.

- IX. Reasons for failure to respond to resuscitation
- A. There is a leak in the system delivering oxygen or air to the baby, or the source may not be connected
 - B. The endotracheal tube is in the esophagus
 - C. Hemorrhagic shock—consider blood transfusion
 - D. Sepsis, including pneumonia
 - E. Pneumothorax
 - F. Pleural effusion
 - G. Pulmonary hypoplasia—may respond to high ventilatory pressures
 - H. Laryngeal abnormality; choanal atresia; Pierre Robin sequence
 - I. Congenital diaphragmatic hernia
 - J. Congenital heart disease
 - K. Spinal cord injury
- X. Ceasing resuscitation (see also Chaps. 81 and 82)
- A. This decision should only be made by a senior physician.
 - B. If there has been no spontaneous cardiac output after more than 10 min of adequate resuscitation, further attempts should be stopped.
 - C. If the baby has a cardiac output but is not making respiratory effort, artificial ventilation should continue while further information is sought.
- XI. Documentation. Good records are vital (see Chap. 83)
- A. Condition at birth, color/tone/respiration
 - B. Time to first gasp, time to regular respiration, and cry
 - C. Heart rate at the start and at intervals: time when heart rate rose above 100 bpm
 - D. Apgar scores at 5-min intervals to supplement the above (but not to replace these observations)
 - E. Time commencing bag and mask ventilation, and duration
 - F. Time at tracheal intubation, duration of intubation, length of ETT at the lips or nares
 - G. Umbilical cord pH; specify whether arterial or venous (include other blood gas parameters, if available)
 - H. Drugs given, dose, route, and time
 - I. Names and designations of personnel; times of their arrival
 - J. Reasons for any delay
 - K. Information given to the parents
- XII. Controversies in resuscitation
- A. Concern has been expressed regarding the possibility that resuscitation with 100% oxygen could cause damage from free radical release and cerebral vasoconstriction (Chap. 6). Trials have been conducted comparing resuscitation with room air and 100% oxygen. Meta-analysis of these studies showed significantly reduced mortality in the infants who were initially resuscitated in air. ILCOR recommendations now state term infants

- should be initially resuscitated with air, with oxygen considered for infants who fail to respond to effective ventilation and the use of oxygen guided by pulse oximetry.
- B. Resuscitation of extremely preterm babies can be contentious (Chap. 81). This is a job for an experienced neonatologist, who should meet the parents *beforehand* if at all possible. Occasionally, it is considered appropriate to offer comfort care only to a baby of very low gestation who is not vigorous at birth. The reported success rate of full CPR in the delivery room when applied to this group varies, with some units claiming good results and others reporting a gloomy prognosis.
 - C. Cooling. Therapeutic hypothermia is now standard care in term and late-preterm asphyxiated babies who meet the criteria of a low Apgar score and early encephalopathy. Passive cooling can be started in the delivery suite, while awaiting confirmation of eligibility, although care should be taken not to over-cool. Therapeutic hypothermia is defined as a temperature of 33.5°C, and most hospitals continue cooling for 72 h in eligible babies.
 - D. Babies who are born through meconium-stained fluid, but who are vigorous, do not require aggressive suctioning of the oropharynx or tracheal intubation. Babies who are depressed at birth should have their airways cleared of meconium before commencing active resuscitation (Chap. 63).
 - E. Sodium bicarbonate. Once a standard resuscitative drug, its use has also become very controversial and has been eliminated from the Neonatal Resuscitation Program in the USA. If used, do so with extreme caution. Ventilation must be established and effective, use only a 4.2% concentration, give slowly, and assure that it is not being injected directly into the liver. Remember, it is a sodium salt, and hypernatremia may ensue.

Suggested Reading

- The American Academy of Pediatrics Neonatal Resuscitation Program http://www.aap.org/nrp/intl/intl_abroad.html.
- Perlman JM, Wyllie J, Kattwinkel J, et al. Neonatal resuscitation: 2010 International Consensus on cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation*. 2010;122:S516–38.
- Richmond S, Wyllie J. European Resuscitation Council guidelines for resuscitation 2010. Section 7, Resuscitation of babies at birth. *Resuscitation*. 2010;81:1389–99.
- Richmond S, Wyllie J. Neonatal Life Support Guidelines 2010. <http://www.resus.org.uk/pages/nls.pdf>.
- The International Liaison Committee on Resuscitation. The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: neonatal resuscitation. *Pediatrics*. 2006;117:978–88.

Chapter 14

Laryngoscopy and Endotracheal Intubation

Karen Wiseman and Steven M. Donn

I. Indications for intubation

- A. Need for prolonged positive pressure ventilation for respiratory failure.
- B. Inability to provide effective bag and mask ventilation.
- C. Need for administration of surfactant.
- D. Apnea, either central, or obstructive.
- E. Airway maintenance.
 - 1. Anatomic anomalies of the airway, such as choanal atresia, micrognathia, laryngomalacia, laryngeal web, or vocal cord paralysis
 - 2. Compressive lesions on the airway, such as cystic hygroma or hemangioma
 - 3. Airway protection in cases of congenital neuromuscular disorders or other neurologic injury
- F. Congenital diaphragmatic hernia. Avoidance of mask ventilation and delivery of air into the gastrointestinal tract is critical, and immediate intubation should be performed.

K. Wiseman, MD

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital, University of Michigan Health System, 1500 East Medical Center Drive, Room F5790, Ann Arbor, MI 48109, USA

S.M. Donn, MD, FAAP (✉)

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital, F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5254, USA

e-mail: smdonnmd@med.umich.edu

II. Endotracheal tube diameter

A. Size of tube (internal diameter, mm):

Up to 1,000 g	2.5
1,001–2,000 g	3.0
2,001–3,000 g	3.5
>3,000 g	3.5–4.0

B. Tube length in centimeters measured at lip for orotracheal intubation:

Up to 1,000 g	7
1,001–2,000 g	8
2,001–3,000 g	9
>3,000 g	10

C. Tube length in centimeters for nasal intubation:

750 g	7
1,000 g	7.5
1,500 g	8.5
2,000 g	9.5
3,000 g	10.5
4,000 g	12

III. Use of premedication

- A. Anesthesia or analgesia should be provided except in emergency situations.
 B. Can help attenuate the adverse physiologic effects of intubation. When practical, premedication prior to intubation in the newborn offers the following potential advantages:

1. Increased hemodynamic stability
2. Faster intubation
3. Less hypoxemia
4. Less rise in intracranial pressure

C. Premedication regimens (see Chaps. 52 and 54).

1. Pain relief (e.g., morphine)
2. Sedation (e.g., midazolam)
3. Paralytic agent (e.g., succinylcholine, atracurium, rocuronium). Muscle relaxants should only be used with experienced neonatologists present. Do not paralyze the baby unless you are confident the airway can be maintained and adequate manual ventilation provided.
4. Adjunctive or reversal agents
 - a. Atropine: can be given prior to anesthesia to reduce secretions and prevent bradycardia and hypotension. Intravenous bolus will produce an effect in 30 s that will last for up to 12 h.
 - b. Neostigmine: reverses the effects of nondepolarizing muscle relaxants.

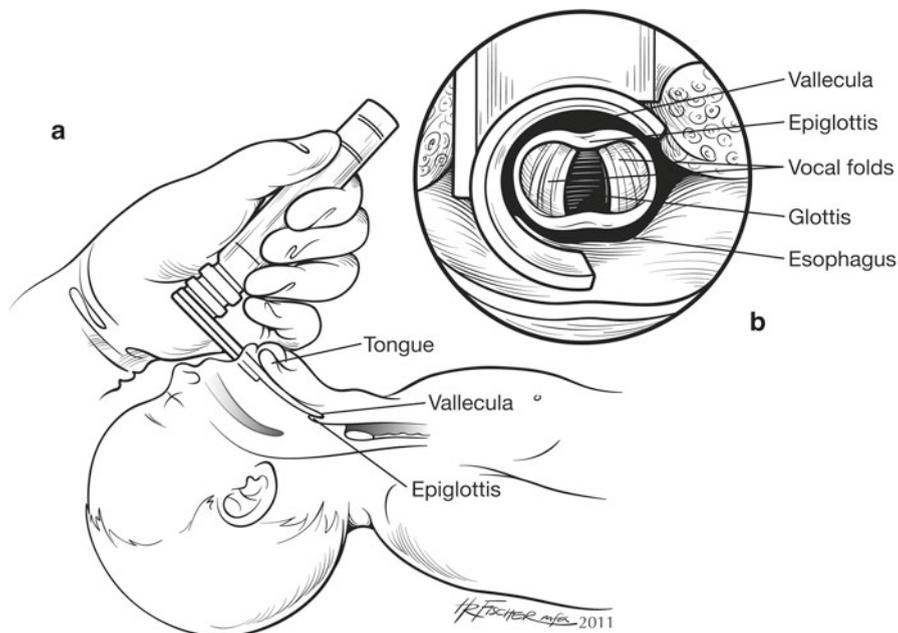


Fig. 14.1 Demonstration of technique of laryngoscopy and visualization of the airway (a) Correct positioning of patient and laryngoscope. (b) View of airway seen through properly placed laryngoscope blade

IV. Laryngoscopy and oral intubation (Fig. 14.1)

- A. Place all the equipment you need close by and prepare a means of securing the tracheal tube once it is in place.
- B. Position the baby on a firm flat surface. Place a small roll or blanket under the baby's shoulders so as to lift the shoulders (not the head) about 1.5 in. (3 cm) off the surface. Extend the baby's neck *slightly* beyond the neutral position.
- C. Open the baby's mouth with the index finger of your right hand. Holding the laryngoscope in your left hand, insert the blade carefully into the right side of the baby's mouth while looking along the blade.
- D. Move the laryngoscope into the center by pushing the tongue over to the left side of the mouth.
- E. Position yourself so you can see comfortably along the laryngoscope blade. If the blade is pushed in too far, all you will see is the esophagus; you must then withdraw the blade slightly to allow the larynx to drop into view from above. Alternatively, if the blade is not in far enough, you may see little except the tongue and the roof of the mouth: you must advance the blade gently until you can see the epiglottis.
- F. Once you have found the epiglottis, place the tip of the blade at the base where it meets the tongue (the vallecula). Lift the laryngoscope gently upward. This will open the mouth further and gently compress the tongue and will bring the larynx into view from behind the epiglottis. Slight external

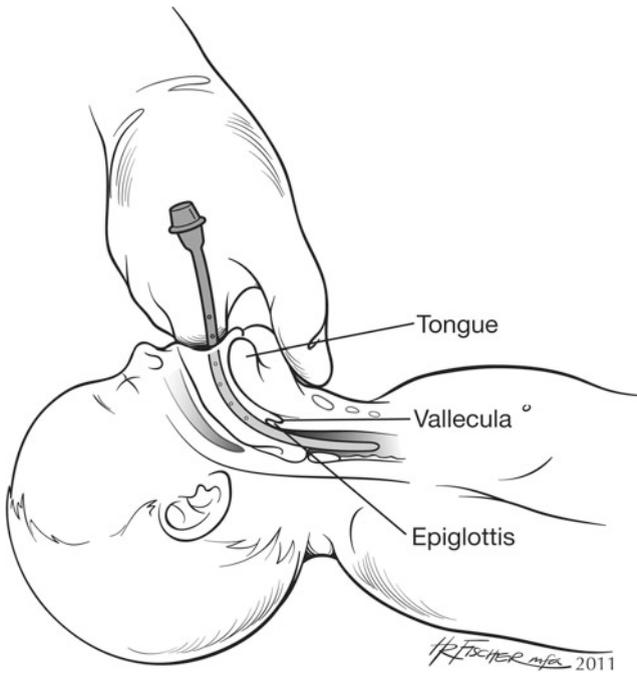


Fig. 14.2 Demonstration of technique of manual intubation

- downward pressure on the cricoid should bring the larynx into the center of the field of view. Do not lever the end of the laryngoscope blade forward by pressing backward on the baby's upper jaw, as this may damage the alveolar ridge and developing teeth.
- G. Bring the endotracheal tube (ETT) in from the right hand corner of the mouth and keep the curve of the tube horizontal so as not to obscure the view of the larynx. Visualize the vocal cords through the groove in the laryngoscope blade. If necessary, wait for the cords to relax. Insert the tube 1–2 cm through the cords. Several commercially available tubes have markings to indicate, where the ETT should align with the vocal cords.
 - H. Tape the tube in place immediately while it is still optimally positioned. Most tubes are marked in centimeters from the tip; make a note of the length at the upper lip.
 - I. Inflate the lung using a controlled inflation device. Watch the chest to check that it is moving appropriately and listen at the mouth to check that there is no significant leak around the ETT.
 - J. Placement of a gastric tube (e.g., nasogastric or orogastric tube) is recommended to decompress the stomach.
- V. Oral intubation without a laryngoscope (Fig. 14.2). Oral intubation using a finger rather than a laryngoscope is possible. Skilled practitioners can place a tube in a baby with normal anatomy in 3–5 s.

- A. Insert the index finger of the nondominant hand into the baby's mouth, with the palmar surface sliding along the tongue. Use the little finger if the baby is small.
 - B. Slide the finger along the tongue until it meets the epiglottis. This feels like a small band running across the root of the tongue.
 - C. Slide the finger a little further until its tip lies behind and superior to the larynx and the nail touches the posterior pharyngeal wall.
 - D. Using your dominant hand, slide the tube into the mouth between your finger and the tongue until the tip lies in the midline at the root of the distal phalanx of your finger.
 - E. At this point, place the thumb of your nondominant hand on the baby's neck just below the cricoid cartilage in order to grasp the larynx between the thumb on the outside and the fingertip on the inside.
 - F. While the thumb and finger steady the larynx, the dominant hand advances the tube a short distance, about 1–2 cm.
 - G. A slight give can sometimes be felt as the tube passes into the larynx *but no force is needed for insertion*.
 - H. When the tube is in the trachea, the laryngeal cartilages can be felt to encircle it. If it has passed into the esophagus, it can be felt between the finger and the larynx.
- VI. Nasotracheal intubation. Nasal intubation is not normally used for emergency intubation but many neonatologists prefer this route. Nasal intubation is most commonly an elective procedure in an orally intubated baby.
- A. Get the baby well oxygenated in preparation for the procedure.
 - B. Use of premedication (see Section "Use of Pre-medication", above).
 - C. Position the baby supine with the shoulders supported on a small towel roll (see above) with the neck *slightly* extended beyond the neutral position.
 - D. Take a small feeding tube, narrow enough to fit inside the intended ETT, remove the flared end and lubricate the other end. Lift up the tip of the nose and pass the tube into one nostril, directing it toward the back of the mouth until it has passed through the nose into the nasopharynx. Remember that the nasal passages follow the line of the palate and not the line of the nasal bone.
 - E. Choose an appropriately sized tube, cut it to an appropriate length (see chart above) and attach the appropriate connector.
 - F. Lubricate the end of the tracheal tube, thread it over the feeding tube, and insert it through the nostril and into the nasopharynx.
 - G. Remove the feeding tube.
 - H. Loosen the attachments of the oral tube and have an assistant prepare to remove it when requested.
 - I. Visualize the larynx with the oral tube in place using a laryngoscope. Identify the nasal tube within the nasopharynx.
 - J. Ask an assistant to remove the oral tube. Grasp the nasal tube with a small pair of Magill or crocodile forceps and position the end of the tube into the laryngeal opening.

- K. It may not be possible to advance the tip of the nasal tube directly into the larynx because the nasal tube, approaching from the nasopharynx rather than the oropharynx, is likely to be at an angle to the line of the trachea. Gently flexing the neck while advancing the tube into the nose may suffice to correct this. Alternatively, take hold of the tube connector at the nose and gently twist it clockwise 120° while maintaining some forward pressure and the tube will slip gently through the vocal cords.
- L. Fix the tube in place and continue ventilation.

VII. Confirming tube position

A. Clinically.

1. Equality of breath sounds.
2. Absence of phonation.
3. Good chest excursions, symmetrical.
4. Appropriate physiologic responses (HR, RR, SaO₂).

B. Radiologic.

1. Should always be obtained for initial intubation.
2. Obtain with head and neck in *neutral* position.
3. Optimal position is midway between glottis and carina.

C. Capnography may also be helpful.

1. Disposable end-tidal CO₂ detectors are now available to confirm that the tube is in the trachea.
2. The color changes from purple to yellow in the presence of exhaled CO₂.
3. False negative results may occur with reduced pulmonary blood flow (e.g., after cardiopulmonary resuscitation, cardiac anomalies) or with severe airway obstruction.

VIII. Replacing the endotracheal tube

- A. Despite meticulous postextubation care, use of methylxanthines, and a trial of CPAP, about 20–25% of babies require re-intubation. The immediate goal is to re-intubate and provide assisted ventilation in order to stabilize their cardio-pulmonary status.
- B. The following factors, singularly or in combination should alert the caregiver that a trial of extubation is failing.
 1. Clinical manifestation of respiratory muscle fatigue, such as progressive respiratory distress (increased work of breathing), or apnea.
 2. Cardiovascular collapse.
 3. Increasing base deficit and developing respiratory or metabolic acidosis.
 4. Increasing FiO₂ requirement to achieve reasonable PaO₂ or SpO₂.

C. Suggested protocol for re-intubation.

1. Stabilization with pre-oxygenation and bag and mask ventilation.
2. Select optimal size (and length) of the ETT.
3. Use of premedication (see Section “Use of Pre-medication”).
4. Insert ETT by previously described techniques.
5. Before fixation determine for correct placement by assessing air entry, chest wall movement, and improvement in oxygenation saturation and heart rate. If in doubt, obtain a chest radiograph.

D. Changing an indwelling tube.

1. Prepare new ETT and adjunctive equipment (e.g., tape, stylet, adhesives).
2. Remove tape and adhesive from existing ETT, but stabilize tube position manually while doing so.
3. Visualize the glottis by direct laryngoscopy.
4. Hold new tube in the right hand.
5. Ask assistant to remove old ETT and quickly insert new ETT to desired depth.
6. Secure new ETT when successful placement is confirmed clinically.
7. A radiograph is necessary only if there is a question of suitable placement.

Suggested Reading

- Donn SM, Blane CE. Endotracheal tube movement in the preterm infant: oral versus nasal intubation. *Ann Otol Rhinol Laryngol.* 1985;94:18–20.
- Donn SM, Engmann C. Neonatal resuscitation: special procedures. In: Donn SM, editor. *The Michigan Manual – A guide to neonatal intensive care.* 3rd ed. Philadelphia, PA: Hanley & Belfus; 2003. p. 33–4.
- Donn SM, Kuhns LR. Mechanism of endotracheal tube movement with change of head position in the neonate. *Pediatr Radiol.* 1980;9:37–40.
- Hancock PJ, Peterson G. Finger intubation of the trachea in newborns. *Pediatrics.* 1992 Feb;89(2):325–7.
- Sarkar S, Schumacher RE, Baumgart S, Donn SM. Are newborns receiving premedication before elective intubation? *J Perinatol.* 2006;26(5):286–9.
- Woody NC, Woody HB. Direct digital intubation for neonatal resuscitation. *J Pediatr.* 1968;73:47–5.

Chapter 15

Vascular Access

Steven M. Donn

I. Umbilical artery catheterization (UAC)

A. Indications

1. Monitoring arterial blood gases
 - a. $FiO_2 \geq 0.4$
 - b. Unreliable capillary samples
 - c. Continuous monitoring
2. Need for invasive blood pressure monitoring

B. Procedure

1. *Elective* procedure
2. Use sterile technique
3. Catheterize vessel after cutdown technique using 3.5 F (<1,500 g) or 5 F catheter
4. Preferred position of tip
 - a. High (T_7-T_{10})
 - b. Low (L_3-L_4)
5. Confirm position radiographically
6. Secure with tape bridge and (optional) sutures

C. Complications

1. Blood loss
2. Infection

S.M. Donn, MD, FAAP (✉)

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital, F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

3. Thrombo-embolic events
 - a. Digit necrosis
 - b. NEC
 - c. Renal artery thrombosis
 - d. Spinal cord injury (rare, but reported)
4. Vasospasm
5. Vessel perforation
6. Air embolus
7. Hypertension (renal artery thrombosis)

D. Removal

1. When $\text{FiO}_2 < 0.4$ and decreasing
2. When noninvasive blood pressure monitoring is adequate
3. At first signs of complications

E. Comments

1. Confirm position. A malpositioned umbilical artery catheterization (UAC) can have life-threatening consequences.
2. Remember that samples obtained from the UAC are postductal.
3. Never infuse pressor agents through a UAC.
4. When removing, withdraw last 5 cm *very* slowly, no faster than 1 cm/min. Watch for pulsations to stop.
5. Controversy still exists regarding infusion of TPN and certain medications through a UAC.
6. Inadequate line clearing prior to sampling may result in spurious laboratory results.

II. Umbilical vein catheterization

A. Indications

1. Emergent need for vascular access (i.e., resuscitation)
2. Need for central venous line
 - a. Pressure monitoring
 - b. TPN or hypertonic glucose administration
 - c. Frequent blood sampling in unstable patient without other access
3. Exchange transfusion

B. Procedure

1. Sterile technique should be used.
2. Direct cutdown approach.
3. Use umbilical catheter (5.0 F; 8.0 F for exchange transfusion in term infant); do not use feeding tube except as last resort.

4. Preferred positions.
 - a. Low: Insert 4–6 cm to achieve blood return if using for resuscitation or exchange transfusion.
 - b. High: Tip should be above diaphragm and below right atrium in the vena cava for indwelling use.
5. Confirm position radiographically.
6. Secure with tape and (optional) sutures.

C. Complications

1. Blood loss
2. Infection
3. Vessel perforation. Commercially available exchange transfusion kits contain catheters with side holes to decrease resistance. These should not be left in situ, as they may injure the intima.
4. Thrombo-embolic events
5. Air embolus
6. Liver necrosis (see below)
7. NEC (may be more related to procedures such as exchange transfusion than to catheter itself)

D. Removal

1. When no longer needed or when other central venous access is achieved
2. At first signs of complications
3. When procedure is completed
4. May be pulled directly

E. Comments

1. Avoid infusion or injection of hypertonic solutions (e.g., sodium bicarbonate) unless catheter tip is above diaphragm. This may cause hepatic necrosis.
2. CVP monitoring may provide useful trend data regarding intravascular fluid status and hemodynamics.
3. Recent trend in increased long-term use in ELBW infants.
4. Inadequate line clearing prior to sampling may result in spurious laboratory results.

III. Peripheral artery catheterization

- A. Indications generally same as for UAC when umbilical access is unavailable or cannot be achieved
- B. Procedure
 1. Preferred sites.
 - a. Radial artery
 - b. Posterior tibial artery

2. Assess for adequate collateral circulation (i.e., Allen's test).
3. Prepare site thoroughly using antiseptic solution.
4. Cannulate vessel percutaneously. Transillumination may be helpful in locating vessel.
5. Secure catheter with tape.
6. Check for blood return, pulse waveform, and adequacy of distal circulation.

C. Complications

1. Infection
2. Blood loss
3. Thrombo-embolic events
4. Vasospasm, ischemic injury

D. Removal

1. At first signs of complications
2. When no longer indicated

E. Comments

1. Transillumination may be very helpful in locating vessel.
2. Keep patency by infusing continuously, but slowly. Use low tonicity fluid (e.g., 0.45% sodium chloride). Many centers prefer use of low-dose heparin (0.5–1.0 U/mL) to decrease risk of clotting.
3. Brachial artery should not be cannulated (inadequate collateral circulation) and femoral artery should be used only as a last resort.
4. Cerebral infarction has been reported following superficial temporal artery cannulation and thus this vessel is also not used. However, it is not clear whether this was causally related or just an association.

IV. Peripheral intravenous catheters

A. Indications

1. To provide partial or total fluids and/or nutrition when gastrointestinal nutrition is not possible.
2. Used when central access is unnecessary or unattainable.

B. Procedure

1. Visualize, palpate, and/or use transillumination to select vessel for cannulation. Suggested order of preference for vessels to cannulate:
 - a. Dorsal venous plexus of back of hand
 - b. Median antebrachial, accessory, or cephalic veins of forearm
 - c. Dorsal venous plexus of foot
 - d. Basilic or cubital veins of antecubital fossa
 - e. Small saphenous or great saphenous veins of ankle
 - f. Supratrochlear, superficial temporal, or posterior auricular veins of scalp

2. Apply tourniquet if placing in extremity.
3. Clean area with antiseptic.
4. Attach syringe to cannula and fill with saline, then detach syringe.
5. Hold needle parallel to vessel, in the direction of blood flow.
6. Introduce needle into skin a few millimeters distal to the point of entry into the vessel. Introduce needle into the vessel until blood flashback appears in the cannula.
7. Remove stylet and advance needle into vessel.
8. Remove tourniquet.
9. Infuse a small amount of saline to assure patency then attach IV tubing.

C. Special considerations

1. Placement should not be near area of skin loss or infection, or across joints, if possible, because of problems with joint immobilization.
2. Care should be taken to assure that vessel is actually a vein and not an artery.
 - a. Note color of blood obtained from vessel and if pulsations are present.
 - b. Look for blanching of skin over vessel when fluid is infused suggesting arterial spasm.
 - c. When attempting scalp vein cannulation, shave area of head where IV is to be placed. Avoid sites beyond hairline.

D. Complications

1. Phlebitis
2. Infection
3. Hematoma
4. Embolization of formed clot with vigorous flushing
5. Air embolus
6. Infiltration of subcutaneous tissue with IV fluid. Infiltration may cause:
 - a. Superficial blistering
 - b. Sloughing of deep layers of skin that may require skin grafting
 - c. Subcutaneous tissue calcification from infiltration of calcium-containing IV solutions

Suggested Reading

Donn SM. Vascular catheters. In: Donn SM, editor. *The Michigan Manual of neonatal intensive care*. 3rd ed. Philadelphia, PA: Hanley & Belfus; 2003. p. 46–9.

Feick HJ, Donn SM. Vascular access and blood sampling. In: Donn SM, Faix RG, editors. *Neonatal emergencies*. Mt, Kisco, NY: Futura; 1991. p. 31–50.

Workman EL, Donn SM. Intravascular catheters. In: Donn SM, Fisher CW, editors. *Risk management techniques in perinatal and neonatal practice*. Armonk, NY: Futura; 1996. p. 531–49.

Chapter 16

Tracheostomy

Steven M. Donn

I. Description. Creation of an artificial airway through the trachea for the purposes of establishing either airway patency below an obstruction or an airway for prolonged ventilatory support.

II. Indications

A. Emergent

1. Upper airway malformations
2. Upper airway obstructions

B. Elective

1. Prolonged ventilatory support
 - a. Broncho pulmonary dysplasia
 - b. Neurologic or neuromuscular dysfunction
2. Subglottic stenosis following endotracheal intubation
3. Neurologic or neuromuscular impairment

III. Preparation

- A. Rare need for emergent tracheostomy because of obstructive lesion which precludes performing endotracheal intubation first.
- B. Baby should be intubated.
- C. Should generally be performed in operating room because of availability of:
 1. General anesthesia
 2. Optimal lighting

S.M. Donn, MD, FAAP (✉)

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA

e-mail: smdonnmd@med.umich.edu

3. Available suction
4. Proper exposure
5. All necessary personnel and equipment

IV. Technique

- A. Baby placed supine with head and neck maximally extended. Use towel roll or sandbag.
- B. Cricoid cartilage is identified by palpation of tracheal rings.
- C. Short (1.0 cm) transverse skin incision made over second tracheal ring.
- D. Incision dilated with hemostat.
- E. Incision deepened by needle point cautery.
- F. Maintain meticulous hemostasis.
- G. Strap muscles separated by fine hemostat.
- H. Trachea exposed by dividing isthmus of thyroid gland by cautery, if necessary.
- I. Longitudinal incision made in trachea (by cautery) through second and third tracheal rings. Do not excise tracheal cartilage, which would lead to loss of tracheal support and stricture formation.
- J. Place silk ties on each side to facilitate placement of tracheostomy tube and postoperative replacement.
- K. Withdraw endotracheal tube until it is visualized just proximal to incision.
- L. Insert tracheostomy tube. Choose a size that requires minimal pressure to insert; avoid metal tubes. Remove endotracheal tube.
- M. Assess proper fit by manual ventilation through tracheostomy tube. If leak is large, replace with bigger tube.
- N. Secure tube with tapes around neck. These should be padded and can be tightened during neck flexion.
- O. Trachea may be irrigated with 2.0 mL saline and suctioned.
- P. Auscultate chest; obtain radiograph.

V. Postoperative care

- A. Minimize movement of head and neck for 3–5 days to establish stoma. Sedation and analgesia strongly recommended. Occasionally, skeletal muscle relaxants are required.
- B. Frequent suctioning and humidification required until stoma established.
- C. Caretakers must know how to replace tube if it becomes dislodged or occluded.
- D. Removal should be accomplished in intensive care unit setting.

VI. Ex utero intrapartum treatment (EXIT) procedure

- A. Performed in selected centers to manage various forms of fetal airway obstruction
 1. Neck masses
 2. Congenital high airway obstruction syndrome (CHAOS)

3. Intrathoracic masses
4. Unilateral pulmonary agenesis and diaphragmatic hernia

B. Procedure

1. Requires multidiscipline team
 - a. Obstetrics
 - b. Neonatology
 - c. Pediatric surgery
 - d. Pediatric anesthesiology
 - e. Radiology
 - f. Nursing
2. Tocolytic (e.g., indomethacin) given to mother
3. Maternal rapid sequence intubation after anesthesia
4. Maintain uterine relaxation and maternal blood pressure
 - a. Inhalational agents
 - b. Terbutaline or intravenous nitroglycerine
5. Fetal anesthesia with pancuronium and fentanyl
6. Maternal laparotomy
7. Ultrasound to map placental borders
8. Hysterotomy
9. Exposure of fetal head
10. Attempt intubation
11. Clamp and cut cord, deliver infant
12. EXIT to ECMO has also been successfully reported

Suggested Reading

- Coran AG, Behrendt DM, Weintraub WH, et al. Surgery of the neonate. Boston: Little, Brown; 1978. p. 31–5.
- Coran AG. Tracheostomy. In: Donn SM, Faix RG, editors. Neonatal emergencies. Mount Kisco, NY: Futura; 1991. p. 247–51.
- Hirose S, Harrison MR. The ex utero intrapartum treatment (EXIT) procedure. *Semin Neonatol.* 2003;8:207–21.

Part IV
Monitoring the Ventilated Patient

Chapter 17

Continuous Monitoring Techniques

Christian F. Poets

I. Pulse oximetry (SpO₂)

A. Principle of operation

1. The ratio of the absorbances of red and infrared light sent through a tissue correlates with the proportion of oxygenated to deoxygenated hemoglobin in the tissue.
2. First-generation oximeters determined the arterial component within this absorbance only by identifying the peaks and troughs in the absorbance over time, thereby obtaining a “pulse-added” absorbance that is independent of the absorbance characteristics of the nonpulsating parts of the tissue.
3. Current instruments use additional techniques. For example, they scan through all red-to-infrared ratios found in the tissue, determine the intensity of these, and choose the right-most peak of these intensities, which will correspond to the absorbance by the arterial blood in the tissue. Some also use frequency analysis, time domain analysis, and adaptive filtering to establish a noise reference in the detected physiologic signal, thereby improving the ability to separate signal from noise.
4. All instruments have built-in algorithms to associate their measured light absorbances with empirically determined arterial oxygen saturation (SaO₂) values.

B. Factors influencing measurements

1. Probe placement. The light receiving diode must be placed exactly opposite the emitting diode; both must be shielded against ambient light and not be applied with too much pressure. Light by-passing the tissue can

C.F. Poets, MD (✉)
Department of Neonatology, Tuebingen University Hospital,
Calwerstr. 7, 72076 Tuebingen, Germany
e-mail: Christian-F.Poets@med.uni-tuebingen.de

cause both falsely high and falsely low values. The sensor site must be checked every 6–8 h. Highly flexible sensors (usually disposable) provide better skin contact and thus a better signal-to-noise ratio.

2. Peripheral perfusion. Most oximeters require a pulse pressure above 20 mmHg or a systolic blood pressure above 30 mmHg to operate reliably; performance at low perfusion is substantially better with current (next-generation) instruments.
3. Response times depend on the averaging time used. Longer averaging times may reduce alarm rates but will increase response time and will hide the true severity of short-lived hypoxemic episodes.
4. Movement artifact. This is the most frequent cause of false alarms. It has been reduced with next-generation instruments, but potentially at the expense of an unreliable detection of true alarms. It may be identified from the analysis of the pulse waveform signal or via a signal quality indicator displayed by some instruments.
5. Other hemoglobins and pigments. Methemoglobin (MetHb) will cause pulse oximetry (SpO_2) readings to tend toward 85%, independent of SaO_2 . Carboxyhemoglobin (COHb) will cause overestimation of SaO_2 by 1% for each percent COHb in the blood. Fetal hemoglobin (HbF) and bilirubin do not affect pulse oximeters, but may lead to an underestimation of SaO_2 by co-oximeters. In patients with dark skin, SpO_2 values may be falsely high, particularly during hypoxemia.
6. Algorithms. These may vary between brands and even between different software versions from the same manufacturer. Also, some instruments subtract a priori the typical levels of COHb, MetHb, etc. in healthy nonsmoking adults from their measurements and will thus display SpO_2 values that are 2–3% lower than those displayed by other instruments.

C. Detection of hypoxemia and hyperoxemia

1. In the absence of movement, pulse oximeters have a high sensitivity for the detection of hypoxemia.
2. Because of the shape of the O_2 -hemoglobin dissociation curve, they are less well suited for detecting hyperoxemia (e.g., a $\text{PaO}_2 > 80$ Torr). The upper alarm setting at which hyperoxemia can be reliably avoided with different instruments ranges from 88 to 95%, although it is at the upper end of this range with most next-generation instruments.

II. Transcutaneous partial pressure of oxygen (TcPO_2) monitoring

A. Principle of operation

Electrodes consist of a platinum cathode and a silver reference anode, encased in an electrolyte solution and separated from the skin by an O_2 -permeable membrane. Electrodes are heated to improve oxygen diffusion and to arterialize the capillary blood. Oxygen is reduced at the cathode, generating an electric current proportional to the O_2 -concentration in the capillary bed underneath the sensor. Sensors require a 10–15 min. warm-up period after application and have to be recalibrated every 4–8 h.

B. Factors influencing measurements

1. Sensor temperature. Good agreement with PaO_2 only at 44°C , but then frequent (every 2–4 h) repositioning necessary. At lower sensor temperatures, increasing PaO_2 – TcPO_2 -difference with increasing PaO_2 .
2. Probe placement. TcPO_2 will under-read PaO_2 if sensor is placed on bony surface, if pressure is applied on sensor, or if too much contact gel is used. With patent ductus arteriosus and right-to-left shunting, TcPO_2 will be higher on upper than on lower half of thorax.
3. Peripheral perfusion. TcPO_2 depends on skin perfusion. If the latter is reduced (e.g., hypotension, anemia, severe acidosis, hypothermia, or marked skin edema), TcPO_2 will be falsely low. If under-reading of PaO_2 occurs, check the patient for these conditions.
4. Skin thickness. Close agreement with PaO_2 occurs only in neonates; beyond 8 weeks of age, TcPO_2 will only be 80% of PaO_2 .
5. Response times. In vivo response time to a sudden fall in PaO_2 is 16–20 s.

C. Detection of hypoxemia and hyperoxemia: sensitivity to these conditions (at 44°C sensor temperature) is approximately 85%.

III. Transcutaneous partial pressure of carbon dioxide (TcPCO_2) monitoring

A. Principle of operation

1. The TcPCO_2 sensor consists of a pH-sensing glass electrode and a silver–silver chloride reference electrode, covered by a hydrophobic CO_2 -permeable membrane from which they are separated by a sodium bicarbonate–electrolyte solution. As CO_2 diffuses across the membrane, there is a pH change of the electrolyte solution ($\text{CO}_2 + \text{H}_2\text{O} + \text{HCO}_3^- + \text{H}^+$), which is sensed by the glass electrode.
2. All instruments have built-in correction factors since their uncorrected measurements will be 50% higher than arterial PCO_2 . They must also be calibrated at regular intervals and require a 10–15 min. equilibration time following resiting.

B. Factors influencing measurements

1. Sensor temperature. Optimal sensor temperature is 42°C , but if sensors are used in combination with a TcPCO_2 sensor, a sensor temperature of 44°C can be used without jeopardizing the precision of the TcPCO_2 measurement.
2. Sensor placement and skin thickness. TcPCO_2 measurements are relatively independent of sensor site or skin thickness, but TcPCO_2 may be falsely high if pressure is applied onto the sensor.
3. Peripheral perfusion. TcPCO_2 may be falsely high in severe shock. Precision may already be affected if PaCO_2 is >45 torr and/or arterial pH is <7.30 , but there is no systematic over- or underestimation of PaCO_2 under these conditions.

4. Response times. A 90% response time to a sudden change in PaCO_2 is between 30 and 50 s.

C. Detection of hypocarbia and hypercarbia: sensitivity to both hypocarbia and hypercarbia is 80–90%.

IV. End-tidal carbon dioxide (ETCO_2) monitoring (capnometry)

A. Principle of operation: an infrared beam is directed through a gas sample and the amount of light absorbed by the CO_2 molecules in the sample is measured; this is proportional to the CO_2 concentration in the sample.

B. Factors influencing measurements

1. Gas sampling technique.

- a. With mainstream capnometers, the CO_2 analyzer is built into an adapter, which is placed in the breathing circuit. Advantage: fast response time (10 ms), therefore reliable even at high respiratory rates. Disadvantage: 1–10 mL extra deadspace; risk of tube kinking.
- b. Sidestream capnometers aspirate the expired air via a sample flow. Advantages: no extra deadspace; can be used in nonintubated patients. Disadvantages: risk of dilution of expired gas by entrainment of ambient air at the sampling tube-patient interface, longer response time, falsely low values at high respiratory rates (>60/min).

2. Influence of V/Q mismatch. ETCO_2 will only approximate PaCO_2 if:

- a. CO_2 equilibrium is achieved between end-capillary blood and alveolar gas.
- b. ETCO_2 approximates the average alveolar CO_2 during a respiratory cycle.
- c. Ventilation/perfusion relationships are uniform within the lung.

3. These conditions are rarely achieved in patients with respiratory disorders.

4. The reliability of an ETCO_2 measurement can be assessed from the expiratory signal: this must have a steep rise, a clear end-expiratory plateau, and no detectable CO_2 during inspiration.

V. Chest wall movements

A. Impedance plethysmography. Changes in the ratio of air-to-fluid in the thorax, occurring during the respiratory cycle, create changes in transthoracic impedance. This cannot be used to quantify respiration and may be heavily influenced by cardiac and movement artifacts.

B. Inductance plethysmography. Changes in the volume of the thoracic and abdominal compartment create changes in inductance, which is registered via abdominal and thoracic bands. The sum of these changes is proportional to tidal volume, and several methods have been developed to calibrate the systems so that tidal volume can be quantified. This, however, only works as long as the patient does not shift position.

- C. Strain gauges (usually mercury in silicon rubber) sense respiratory efforts by measuring changes in electrical resistance in response to stretching. These measurements, however, are not reproducible enough to quantify tidal volume.
- D. Pressure capsules detect movements of an infant's diaphragm by means of an air-filled capsule that is taped to the abdomen and connected to a pressure transducer via a narrow air-filled tube. The outward movement of the abdomen during inspiration compresses the capsule to produce a positive pressure pulse that is interpreted as a breath. The technique is predominantly used in apnea monitors and triggering devices for infant ventilators and is not suitable for quantifying tidal volume.

VI. Electrocardiography (ECG)

The ECG records electrical depolarization of the myocardium. During continuous monitoring, only heart rate can be determined with sufficient precision; any analysis of P and T waves, axis, rhythm, or QT-times requires a printout and/or a 12-lead ECG.

Suggested Reading

- Poets CF. Monitoring in the NICU. In: Mathew OP, editor. *Respiratory control and its disorders in the newborn*. New York: Marcel Dekker; 2003. p. 217–36.
- Poets CF, Bassler D. Providing stability in oxygenation for preterm infants: is transcutaneous oxygen monitoring really better than pulse oximetry? *Arch Dis Child Fetal Neonatal Ed*. 2008;93:F330–31.
- Poets CF, Southall DP. Non-invasive monitoring of oxygenation in infants and children: practical considerations and areas of concern. *Pediatrics*. 1994;93:737–46.
- Raju TN, Stevenson DK, Higgins RD, Stark AR. Safe and effective devices and instruments for use in the neonatal intensive care units: NICHD Workshop summary. *Biomed Instrument Technol*. 2009;43:308–18.

Chapter 18

Pulse Oximetry

Win Tin and Samir Gupta

I. Introduction

- A. Noninvasive monitoring of oxygenation has become a standard procedure in neonatology.
- B. Pulse oximetry (SpO_2) is based on using the pulsatile variations in optical density of tissues in the red and infrared wavelengths to compute arterial oxygen saturation without the need for calibration.
- C. The method was invented in 1972 by Takuo Aoyagi, and its clinical usage was first reported in 1975 by Susumu Nakajima, a surgeon, and his associates.

II. Advantages of SpO_2

- A. Saturation is a basic physiologic determinant of tissue oxygen delivery.
- B. Noninvasive, and provides immediate and continuous readouts.
- C. No warm-up or equilibration time is needed.
- D. Can detect rapid or transient changes in oxygen saturation.
- E. Skin burns from oximeter probe are very rare compared to transcutaneous monitoring.
- F. Minimal effect of motion, light, perfusion, and temperature with the advent of “Signal Extraction Technology.”
- G. Substantially lower maintenance.

III. Disadvantages

- A. Failure to detect hyperoxia at functional saturation of more than 94% and thus slow weaning of oxygen as high PaO_2 is not recognized.

W. Tin, FRCPCH (✉)

Department of Neonatal Medicine, The James Cook University Hospital,
Middlesbrough, UK TS4 3BW
e-mail: win.tin@stees.nhs.uk

S. Gupta, DM, MRCP, MD, FRCPCH, FRCPI

Department of Neonatal Paediatrics, University Hospital of North Tees,
Stockton-on-Tees, Cleveland, UK TS19 8PE

- B. Not reliable in cases of severe hypotension or marked edema.
- C. May provoke unnecessary evaluation of transient clinically insignificant desaturation episodes.

IV. Terminology in SpO₂

A. Functional and fractional saturation

1. Functional saturation. Any forms of hemoglobin in the sample which do not bind oxygen in a reversible way are not included in calculating functional hemoglobin saturation. Pulse oximeter can measure functional saturation from only two forms of hemoglobin, oxyhemoglobin (HbO₂) and deoxyhemoglobin (Hb), which is calculated by:

$$\text{Functional saturation} = \frac{\text{HbO}_2}{\text{HbO}_2 + \text{Hb}} \cdot 100.$$

2. Fractional saturation. The fractional saturation is defined as ratio of the amount of hemoglobin saturated with oxygen to all other forms of hemoglobin, including dyshemoglobinemia (CoHb and Met Hb). The co-oximeters used in blood gas laboratories measure fractional saturation as they use many wavelengths of light and are thus able to measure all types of hemoglobin present in blood.

$$\text{Fractional saturation} = \frac{\text{HbO}_2}{\text{HbO}_2 + \text{Hb} + \text{CoHb} + \text{MetH}} \cdot 100.$$

3. Pulse oximeters can measure only functional saturation. Some instruments display fractional saturation measurements which are derived by subtracting 2% from the functional saturation. It is important to be aware of what the instrument is reading.

B. Bias and precision

Normal level of dyshemoglobin is <2%. The mean of the difference (error) between oxygen saturation and oxyhemoglobin (SpO₂ and HbO₂) measured by a co-oximeter is called “*Bias*” and the standard deviation of this is called “*Precision*.”

V. Practical considerations

- A. Oxyhemoglobin dissociation curve and SpO₂ (see Chap. 5).
- B. Presence of abnormal hemoglobins (dyshemoglobin).
 1. Carboxyhemoglobin—SpO₂ is overestimated in the presence of COHb (e.g., neonatal jaundice).
 2. Methemoglobin—SpO₂ decreases in proportion to the percentage of MetHb present.

C. Reduced perfusion states.

1. Hypothermia: does not cause problem if the temperature is $>30^{\circ}\text{C}$
2. Hypovolemia: loss of signal (but the presence of signal does not indicate adequate perfusion)

D. Anemia: does not cause problem as long as Hb is >5 g/dL.

E. Effect of dyes.

1. Bilirubin: has no influence except if there is acute hemolysis (COHb).
2. Meconium staining of skin can cause falsely low SpO_2 readings.

F. Venous pulsations (e.g., tricuspid regurgitation) may cause falsely low SpO_2 readings.

G. Abnormal absorption spectrum of hemoglobin (e.g., Hb Köln) may affect the reliability of SpO_2 but is extremely rare.

VI. Technical considerations

A. Calibration and accuracy

1. Quality of signal: before interpreting an SpO_2 reading, the quality of signal received by probe should be confirmed by a good plethysmographic waveform and/or heart rate similar to that on ECG monitor.
2. Differing software among brands. There are small differences between the measurements obtained with different brands of pulse oximeters.
3. Inaccuracy increases when saturation is $<75\text{--}80\%$: The bias and precision between SpO_2 and HbO_2 measured by co-oximetry:
 - a. 0.5% and 2.5%, respectively, when SpO_2 is $>90\%$
 - b. 1.9% and 2.7%, respectively, when SpO_2 is $80\text{--}90\%$
 - c. 5.8% and 4.8%, respectively, when SpO_2 is $<80\%$
4. Use of longer signal averaging time reduces the detection of brief periodic desaturation events and those of greater severity. It can also interpret a cluster of shorter events as a single, prolonged episode, and thus, potentially overestimate the frequency of long events.

B. Delay of response

1. Response time is faster if probe is centrally placed, 50–60% earlier detection by sensors placed centrally (ear, cheek, tongue) than by sensors placed peripherally (finger, toe).
2. Depends on averaging time. The shortest averaging time would minimize the delay, although this usually increases sensitivity to motion.
3. Response time is shorter if the sensor is first applied on the baby and then connected to the pulse oximeter.

C. Motion artifact—The performance of pulse oximeters is affected by motion. To overcome this several brands of pulse oximeters are now equipped with new algorithms that cancel noise signal that is common to both wave lengths.

D. Interference from other light sources

1. Fluctuating light sources: shielding the probe with cloth or opaque material can overcome the problem of light interference.
2. Incorrectly placed probe (optical shunt or penumbra effect). Part of the light is transmitted without any tissue absorption. This is particularly so if too large a probe is used.

E. Electrical or magnetic interference

1. When using SpO₂ in MRI suite, care should be taken to use specially designed equipment in order to avoid interference with SpO₂ or even burns (ferrous metals).
2. Electrocautery can also cause failure of pulse oximetry.

VII. Rules for the optimal use of pulse oximetry

- A. Verify probe integrity before use.
- B. Avoid mixing probes and monitors of different brands.
- C. Check the quality of the signal received by the probe (good waveform or true heart rate).
- D. Maintain probe positioning under direct visual control.
- E. Consider physiologic limitations of SpO₂ and interpret it accordingly.
- F. In case of doubt, check the patient.
- G. Remember that high SpO₂ may indicate significant hyperoxemia.
- H. Application of sensor:
 1. Right hand during resuscitation.
 2. Left/right foot during routine postnatal check.

Suggested Reading

- Ahmed SJ, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics*. 2010;125(1):e115–21.
- Hay Jr WW, Rodden DJ, Collins SM, et al. Reliability of conventional and new pulse oximetry in neonatal patients. *J Perinatol*. 2002;22:360–6.
- Morgan C, Newell SJ, Ducker DA, et al. Continuous neonatal blood gas monitoring using a multi-parameter intra arterial sensor. *Arch Dis Child*. 1999;80:F93–8.
- Moyle JTB, Hahn CEW, Adams AP, editors. Principles and practice series: pulse oximetry. London: BMJ; 1998.
- O'Donnell CP, Kamlin CO, Davis PG, et al. Obtaining pulse oximetry data in neonates: a randomised crossover study of sensor application techniques. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(1):F84–5.
- Poets CF, Southhall DP. Noninvasive monitoring of oxygenation in infants and children: practical considerations and areas of concern. *Pediatrics*. 1994;3:737–46.
- Richardson DK, Eichenwald EC. Blood gas monitoring and pulmonary function tests. In: Cloherty JP, Stark AR, editors. *Manual of Neonatal Care*. New York: Lippincott-Raven; 1998. p. 354–5.
- Veyckemans F. Equipment, Monitoring and environmental conditions. In: Bissonnette B, Dalens BJ, editors. *Pediatric anesthesia – principles and practice*. New York: McGraw-Hill; 2002. p. 442–5.

Chapter 19

Interpretation of Blood Gases

David J. Durand

I. Physiology of gas exchange

A. Oxygenation. The movement of O_2 from the alveolus into the blood is dependent upon the matching of ventilation and perfusion. Ventilation/perfusion matching is abnormal if:

1. Pulmonary blood flows past unventilated alveoli, causing an intrapulmonary right-to-left shunt. In newborns, this is typically caused by atelectasis. The treatment for atelectasis is positive pressure, which opens previously unventilated alveoli and decreases intrapulmonary shunting.
2. Blood flows right-to-left through the foramen ovale or patent ductus arteriosus, causing an extrapulmonary right-to-left shunt. This sort of extrapulmonary shunt is typically caused by elevated pulmonary vascular resistance (pulmonary hypertension), and can be treated by decreasing pulmonary vascular resistance (e.g., with inhaled nitric oxide).

B. Ventilation. Ventilation is the removal of CO_2 from the blood.

1. During spontaneous breathing or conventional mechanical ventilation, the movement of CO_2 from the blood into the alveolus is dependent upon the amount of gas that flows past the alveoli, or alveolar ventilation. Alveolar ventilation is the product of alveolar volume and respiratory rate. Thus, any change in ventilatory strategy, which results in an increase in alveolar volume and/or respiratory frequency, will increase ventilation and decrease $PaCO_2$.
2. During high frequency ventilation, gas exchange between the alveolus and the upper airway is predominantly a consequence of mixing, rather

D.J. Durand, MD (✉)

Division of Neonatology, Department of Neonatology,

Children's Hospital & Research Center Oakland, 747 52nd St., Oakland, CA 94609, USA

e-mail: ddurand@mail.cho.org

than bulk flow. Because of this, CO_2 removal during high-frequency ventilation is proportional to (frequency) \times (volume of the high frequency “breaths”)².

C. Acid–base status

1. The pH of arterial blood is determined primarily by:
 - a. PaCO_2
 - b. Lactic acid, produced by anaerobic metabolism
 - c. Buffering capacity, particularly the amount of bicarbonate in the blood
2. Respiratory acidosis occurs when an increase in PaCO_2 causes a decrease in pH. Respiratory alkalosis occurs when a decrease in PaCO_2 causes an increase in pH.
3. Metabolic acidosis occurs when there is either an excess of lactic acid, or a deficiency in the buffering capacity of the blood, causing a decrease in pH. It is reflected in an increased base deficit, also termed a decreased base excess.
4. If PaCO_2 remains persistently elevated, the pH will gradually return to normal as a result of a gradual increase in bicarbonate in the blood, termed a compensatory metabolic alkalosis. Conversely, a patient with a persistently low PaCO_2 will gradually develop a compensatory metabolic acidosis.
5. In patients with intact respiratory drive, a persistent metabolic acidosis will result in hyperventilation, termed a compensatory respiratory alkalosis.
6. Most extremely low birth weight infants have immature renal tubular function in the first week of life and spill bicarbonate in the urine, leading to a metabolic acidosis. Administration of extra base in the intravenous fluids will prevent and/or correct this metabolic acidosis.
7. If an infant has severe hypoxemia and/or decreased tissue perfusion, anaerobic metabolism causes the accumulation of lactic acid, and results in a metabolic acidosis. *This should be treated by improving the underlying problem, rather than by administering additional base (bicarbonate).* Lactic acid can be directly measured by most blood gas machines, and is a useful tool for tracking the development and resolution of impaired perfusion (e.g., in patients with septic or cardiogenic shock).

II. Oxygen content of blood

A. Oxygen is carried in the blood in two ways.

1. Bound to hemoglobin. The amount of O_2 that is carried in the blood bound to hemoglobin is dependent upon both the hemoglobin concentration and the hemoglobin saturation (SaO_2). In the normal infant with a hemoglobin level of 15 g/100 mL and SaO_2 of 100%, approximately 20 mL O_2 is bound to the hemoglobin in 100 mL of blood.

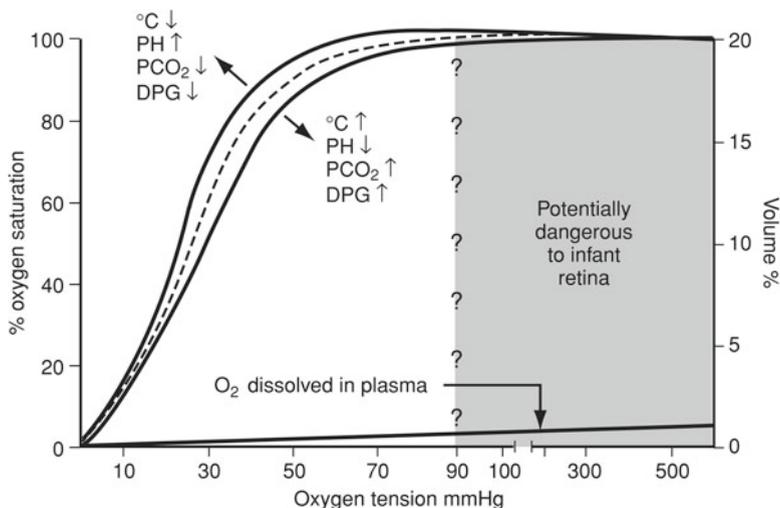


Fig. 19.1 The oxyhemoglobin dissociation curve (From Klaus MH, Fanaroff AA. Care of the high risk neonate. Philadelphia: WB Saunders CO.; 1986. p. 173. Used by permission)

2. Dissolved in plasma. In the normal infant (or adult), the amount of oxygen dissolved in plasma is trivial compared to the amount of oxygen that is bound to hemoglobin (Hb). Approximately 0.3 mL of O_2 is dissolved in 100 mL plasma per 100 Torr O_2 partial pressure.
- B. Significantly increasing PaO_2 beyond that which is needed to fully saturate Hb will slightly increase the amount of O_2 dissolved in plasma, but will not increase the amount of O_2 bound to Hb.
- C. The PaO_2 that is required to fully saturate Hb is dependent upon the oxygen-hemoglobin dissociation curve (Fig. 19.1). This curve is dependent upon many factors, including the relative amount of fetal Hb in the blood (fetal Hb is fully saturated at a lower PaO_2 than is adult Hb). For this reason, arterial saturation (SaO_2) is a better indicator of the amount of oxygen in the blood than is PaO_2 .

III. Oxygen delivery and mixed venous oxygen saturation

- A. The amount of oxygen delivered to the tissues depends on the amount of oxygen in the blood (CaO_2) and cardiac output (CO). Oxygen delivery is the product of oxygen content and blood flow.
 1. Assume an average infant has a CaO_2 of 20 mL O_2 /100 mL blood and a cardiac output of 120 mL/kg/min.
 2. Therefore, the amount of oxygen available for delivery to the body can be calculated as the product of CaO_2 and CO.
 3. (20 mL O_2 /100 mL blood) \times (120 mL/kg/min) = 24 mL O_2 /kg/min available for delivery to tissues.

- B. Under stable conditions, oxygen consumption for the average infant is approximately 6 mL/kg/min.
- C. If an infant is delivering oxygen to the systemic circulation at a rate of 24 mL/kg/min and is utilizing oxygen at a rate of 6 mL/kg/min, then 25% of the oxygen in the blood is utilized by tissues; 75% of the oxygen (18 mL/kg/min) is not utilized by the tissues, so blood returning to the right atrium from the systemic circulation is 75% saturated. This is the normal mixed venous saturation (SvO_2) in a healthy infant.
 1. SvO_2 is the saturation of blood as it enters the pulmonary artery. It is referred to as “mixed” venous blood because it represents the average of the blood returning to the right atrium from the superior vena cava and from the inferior vena cava. SvO_2 can be measured directly with a pulmonary artery catheter, or can be approximated by a sample of blood from the right atrium.
 2. SvO_2 is an important measurement in patients with questionable cardiac output. A low SvO_2 (<75%) means that an unusually large fraction of the available oxygen has been extracted by the tissues. This usually indicates inadequate delivery of oxygen to the tissues.
 3. Causes of low SvO_2 include inadequate oxygenation of the blood, anemia, or low cardiac output. The presence of low SvO_2 in a patient with normal SaO_2 and normal Hb is diagnostic of cardiac output inadequate to meet tissue oxygen demands.
 4. SvO_2 is typically used to monitor the adequacy of tissue perfusion in patients receiving ECMO (Chap. 56) and can be useful in any patient, where adequacy of cardiac output is uncertain.

IV. Arterial, capillary, and venous blood

- A. As blood flows through the systemic capillary bed, O_2 is extracted and CO_2 and lactic acid are added to it. Thus, venous blood has a lower PO_2 , a lower pH, and a higher PCO_2 than arterial blood. Unfortunately, the size of the PO_2 , PCO_2 , and pH gradients between arterial and venous blood are dependent upon multiple factors, including Hb, cardiac output, and metabolic demand. Essentially, the only useful information from a venous blood sample (other than mixed venous sample) is that the $PaCO_2$ is lower than the $PvCO_2$.
- B. Capillary blood gases are typically “arterialized” samples, where the capillary bed has been warmed to increase blood flow. The assumption is that increased blood flow leads to decreased exchange of O_2 , CO_2 , and lactic acid between the tissue bed and the capillaries. However, this is not a consistent effect, and the correlation between capillary and arterial values is poor. In addition, capillary sampling is painful and usually causes infants to cry and change their respiratory pattern, raising the question of how reflective of baseline state a capillary sample truly is. In general, capillary blood gases should be used only to provide a rough approximation of arterial CO_2 , with the understanding that they may overestimate $PaCO_2$ by 5–10 Torr (or more).

V. Noninvasive estimation of blood gases (Chaps. 17 and 18)

- A. Pulse oximeters are the clinical “gold standard” for measuring oxygenation.
- B. Transcutaneous monitors provide an estimate of PaO_2 and PaCO_2 . They can be cumbersome to use, and both the adhesives used to attach the probes to the skin and the elevated temperature can cause mild skin injury to extremely preterm infants. However, they are a useful tool for continuously monitoring critically ill infants, or infants with labile PaCO_2 . In general, transcutaneous CO_2 monitors are as accurate as capillary blood gas samples.
- C. End-tidal CO_2 monitors can provide useful information about PaCO_2 in some infants. The concentration of CO_2 at the end of exhalation is close to PaCO_2 in patients with healthy lungs and low respiratory rates. This makes end tidal CO_2 monitoring a useful tool for term postoperative babies, or other big babies with only minimal lung disease. For patients who are small, tachypneic, or have severe lung disease, end-tidal monitoring can provide a useful measure of trends in PaCO_2 , although not an accurate measure of absolute PaCO_2 values.

VI. Errors in blood gas measurements

- A. An air bubble in a blood gas sample will cause the blood to equilibrate with room air.
 - 1. PaCO_2 will be artificially lowered.
 - 2. PaO_2 will move closer to the partial pressure of O_2 in room air (approximately 140 Torr or 18.7 kPa, depending on altitude and humidity).
- B. Dilution of a blood gas sample with IV fluid of any sort will cause both CO_2 and O_2 to diffuse from the blood into the diluting fluid.
 - 1. PaO_2 will be artificially lowered.
 - 2. PaCO_2 will be artificially lowered.
 - 3. Because of the buffering capability of the blood, pH will not change as much as will PaCO_2 . The combination of relatively normal pH and decreased PaCO_2 will appear to be a respiratory alkalosis with metabolic acidosis.
- C. If a blood gas sample is left for a long period at room temperature, the blood cells will continue to metabolize oxygen and produce CO_2 .
- D. Most blood gas machines calculate SaO_2 from PaO_2 , assuming that all of the Hb is adult Hb. In an infant with a significant amount of fetal Hb, this calculated value will be much lower than the actual measured SaO_2 .
- E. Capillary blood gas values are frequently assumed to approximate arterial blood gas values. However, there is marked variation in the correlation of capillary and arterial values. Capillary blood gases should always be interpreted with caution.
- F. Blood gases obtained by arterial puncture or capillary stick are painful and disturb the infant, frequently causing agitation, desaturation, or hyperventilation. They should be interpreted with caution.

VII. Clinical interpretation of blood gases. Blood gas values, by themselves, convey relatively little information; they must be interpreted in a clinical context. When interpreting blood gas results, a number of other factors must be assessed simultaneously.

- A. How hard is the infant working to breathe?
 1. A normal blood gas in an infant who is clearly struggling to breathe is not necessarily reassuring.
 2. An elevated PaCO_2 in an infant with BPD, who is comfortable, is not necessarily concerning.
- B. Does a recent change in blood gas values represent a change in the patient, or is it an artifact?
- C. If a blood gas result is used to make decisions about ventilator strategy, how much of the total respiratory work is being done by the patient, and how much is being done by the ventilator?
- D. Where is the patient in the course of the disease? A PaCO_2 of 65 Torr (8.7 kPa) may be very concerning in an infant in the first few hours of life, but perfectly acceptable in an infant with BPD.
- E. When deciding whether to obtain a blood gas sample, ask yourself whether you will learn anything from it that you cannot learn from a clinical examination of the patient. Clinical or ventilator-derived information includes:
 1. Respiratory rate
 2. Minute volume (ventilation)
 3. Lung compliance
 4. Hemodynamic status (heart rate, blood pressure, perfusion)

VIII. Target ranges for blood gases. A wide range of blood gas values is seen in newborn infants, depending upon their gestational age, postnatal age, and disease state. In most infants with a respiratory disease, the goal is not to make blood gases entirely normal, but to keep them within an acceptable “target range.” There are little controlled data to guide the choice of these “target ranges;” instead they have gradually evolved, and are continuing to evolve.

- A. pH. In most newborns, the goal is to keep the arterial pH between 7.25 and 7.4. However, in some patients it is appropriate to allow an arterial pH as low as 7.2, or even lower. An alkalotic pH (>7.4) should almost always be avoided.
- B. PaCO_2 . In the healthy term newborn, the normal PaCO_2 is approximately 35–40 Torr.
 1. However, infants with any significant lung disease will exhibit alveolar hypoventilation and develop an elevated PaCO_2 and respiratory acidosis.
 2. Over the last two decades, there has been a gradual shift toward tolerating higher PaCO_2 levels (“permissive hypercapnia”).

3. Partially because of the data suggesting a link between hypocarbia and decreased cerebral blood flow and resultant possible brain injury, PaCO₂ levels much below 40 Torr should be avoided.
 4. With time, respiratory acidosis will be matched by a compensatory metabolic alkalosis, and the arterial pH will move toward the normal range.
 5. Because of the complex interaction of disease severity, ventilatory support, and duration of hypercapnea, many clinicians find it easier to define a “target pH” rather than a “target PaCO₂.”
- C. PaO₂. PaO₂ is not nearly as important a physiologic parameter as SaO₂, and because of the variable amount of fetal Hb in an infant’s blood, it is also widely variable. Many neonatologists think of oxygenation only in terms of SaO₂, not in terms of PaO₂.
- D. SaO₂. In the healthy term infant SaO₂ is close to 100%. However, the oxygen content of blood is adequate for tissue oxygen delivery at much lower levels of SaO₂. In patients with cyanotic heart disease SaO₂ of 70–75% is sufficient to ensure adequate tissue oxygenation. Because of the association between high SaO₂ with an increased risk of both retinopathy of prematurity and BPD, most premature infants should be managed with SaO₂ <95%. The ideal target range for SaO₂ remains uncertain, and is the subject of ongoing clinical trials.
- E. Base deficit.
1. In the healthy term infant, the base deficit is usually around 3–5 mEq/L.
 2. However, base deficit is a calculated value, and can vary significantly.
 3. In most patients with a base deficit between 5 and 10 mEq/L, assuming good tissue perfusion on clinical examination, no acute intervention is needed. A base deficit in this range in a very preterm infant may suggest renal bicarbonate wasting, and may prompt an increase in the amount of base administered in the maintenance fluids.
 4. A base deficit of more than 10 mEq/L should prompt a careful examination of the infant for signs of under-perfusion. In the patient with a significant base deficit and clinical under-perfusion, correcting the cause of the under-perfusion should be the primary goal. In most cases, correcting the underlying cause of metabolic acidosis is far more effective than is administering extra base.

Suggested Reading

- Ambalavanan N, Carlo W. Hypocapnia and hypercapnia in respiratory management of newborn infants. *Clin Perinatol*. 2001;28:517–31.
- Aschner JL, Poland RL. Sodium bicarbonate: basically useless therapy. *Pediatrics*. 2008;122:831–5.
- Chen ML, Guo L, Smith LEH, Dammann CEL, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. *Pediatrics*. 2010;125:e1483–92.

- Courtney SE, Weber KR, Breakie LA, et al. Capillary blood gases in the neonate: a reassessment and review of the literature. *Am J Dis Child.* 1990;144:168–72.
- Dennis RC, Ng R, Yeston NS, Statland B. Effect of sample dilutions on arterial blood gas determinations. *Crit Care Med.* 1985;13:1067–8.
- Dudell G, Cornish JD, Bartlett RH. What constitutes adequate oxygenation? *Pediatrics.* 1990;85:39–41.
- Molloy EJ, Deakins K. Are carbon dioxide detectors useful in neonates? *Arch Dis Child Fetal Neonatal Ed.* 2006;91:F295–8.
- SUPPORT Study Group. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362:1959–69.
- Tobias JD. Transcutaneous carbon dioxide monitoring in infants and children. *Paediatr Anaesth.* 2009;19:434–44.

Chapter 20

Neonatal Pulmonary Graphics

Joanne Nicks

I. Indications

A. Optimizing mechanical ventilation parameters

1. Peak inspiratory pressure (PIP)
2. Positive end expiratory pressure (PEEP)
3. Inspiratory and expiratory tidal volume (V_{T_I} or V_{T_E})
4. Inspiratory time (T_I)
5. Expiratory time (T_E)
6. Flow rate
7. Synchronization

B. Evaluation of infant's spontaneous effort

1. Spontaneous V_T
2. Minute ventilation (MV)
3. Respiratory pattern
4. Readiness for extubation

C. Therapeutic response to pharmacologic agents

1. Surfactant
2. Bronchodilators
3. Diuretics
4. Steroids

D. Evaluation of respiratory waveforms, loops, and mechanics

1. Waveforms
 - a. Pressure

J. Nicks, RRT, AAS (✉)
Pediatric Respiratory Care, C.S. Mott Children's Hospital,
1540 East Hospital Dr. SPC 4208, Ann Arbor, MI 48109, USA
e-mail: jnicks@med.umich.edu

- b. Flow
 - c. Volume
 - 2. Loops
 - a. Pressure–volume loop
 - b. Flow–volume loop
 - 3. Mechanics
 - a. Dynamic compliance (C_D) or static compliance (C_{ST})
 - b. Resistance (inspiratory and expiratory)
 - c. Time constants
 - E. Disease evaluation
 - 1. Restrictive
 - 2. Obstructive
 - 3. Severity
 - 4. Recovery
- II. Graphical user interfaces
- A. Graphical user interfaces (GUI) provide continuous, real-time feedback of the interaction between the patient and the ventilator.
 - B. They are also an excellent teaching tool.
 - C. Graphics Monitors have been available for the last two decades. Initially they could be added to ventilators as an option, but now the latest generation of ventilators have touch screen interfaces with color displays that are integral to the ventilator.
 - D. It is important to know where and how data are collected for the graphics. One very important consideration is location of the flow sensor.
 - 1. If the flow sensor is proximal (close to the patient’s airway), the waveforms, loops, and data are more reflective of what is actually occurring in the lung.
 - 2. If the flow sensors are distal (within the machine), the waveforms, loops, and data include circuit compliance and resistance and may not accurately reflect the pulmonary system. Even if the ventilator employs circuit compliance compensation, the waveforms/loops may still be displayed inaccurately because of volume expansion and compression within the circuit.
 - E. Flow sensors
 - 1. Heated wire anemometer. Measures the amount of current required to keep a heated wire at a constant temperature as gas flows past the wire and heat is convected. This current can be converted to volume measurement.
 - 2. Differential pressure pneumotachometer. As gas flows through the sensor across an element, a differential pressure is created between the upstream and downstream sensing ports. The change in pressure across the element is proportional to flow.

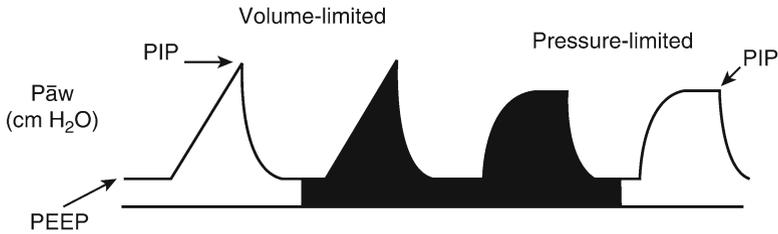


Fig. 20.1 Pressure waveform for both volume- and pressure-limited breaths

F. Neonatal-capable ventilators with integral GUI

1. Avea (CareFusion, Yorba Linda, CA)
2. Draeger Babylog VN500, Evita XL, Evita Infinity V500 (Draeger Medical, Inc, Telford, PA)
3. Puritan Bennett 840 (Covidien-Puritan Bennett, Mansfield, MA)
4. Servo-i (Maquet Critical Care, Wayne, NJ)
5. Hamilton C-2 and S-1 (Hamilton Medical, Reno, NV)
6. SLE 4000 and 5000 (SLE, Ltd., Surrey, UK)
7. Newport e360T and Newport WAVE (if Compass added) (Newport Medical Instruments, Newport Beach, CA)

G. Neonatal-pediatric ventilators that are still in use, but not currently being manufactured

1. VIP BIRD/GOLD with Bird Graphic Monitor (CareFusion Health Care, Yorba Linda, CA)
2. Bear Cub 750 with Ventilator Graphics Monitor (CareFusion Healthcare, Yorba Linda, CA)
3. Draeger Babylog 8000+ (Draeger, Telford, PA)

III. Graphic waveforms

A. Pressure

1. Pressure waveform (Fig. 20.1)
 - a. The upsweep of the waveform represents inspiration and the down-sweep represents expiration.
 - b. PIP is the maximum pressure point on the curve (A).
 - c. PEEP is the baseline pressure level (B).
 - d. The area under the curve represents the mean airway pressure (shaded).
 - e. The shape of the curve represents the breath type, e.g., volume (triangular) or pressure (square).
 - f. The presence of a plateau at peak pressure is caused by an inflation hold or prolonged inspiratory time. This may improve distribution of

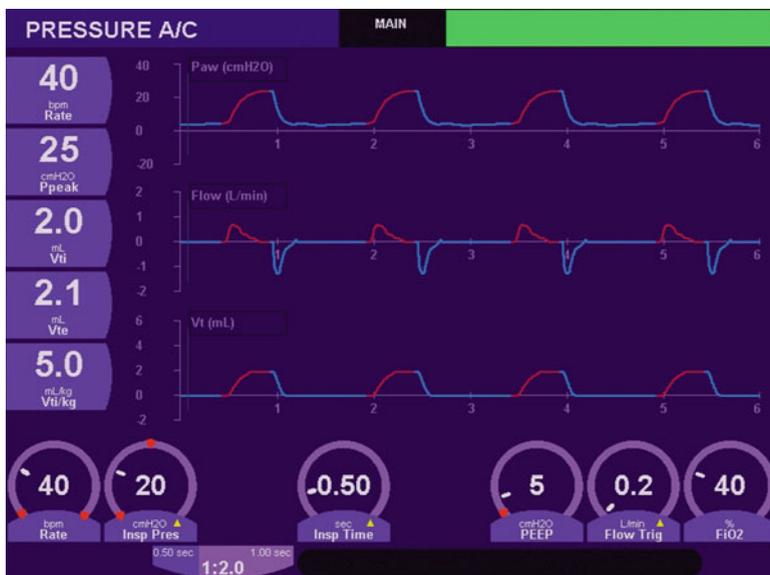


Fig. 20.2 Pressure and flow waveforms showing a prolonged inspiratory time. Note the pressure plateau on the pressure waveform caused by a prolonged time before expiratory flow occurs

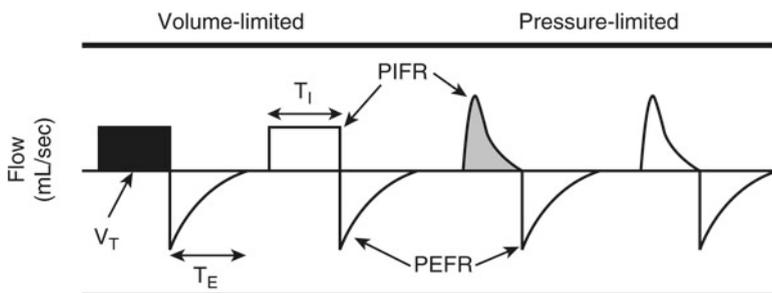


Fig. 20.3 Flow waveforms for both volume- and pressure-limited breath types. Inspiratory flow is above the baseline; expiratory flow is below. Peak inspiratory (PIFR) and peak expiratory (PEFR) flow rates are shown

ventilation but is not usually desirable in infants because it may disrupt synchrony and results in a higher mean airway pressure (Fig. 20.2).

B. Flow waveform (Fig. 20.3)

1. Horizontal line is the zero (no) flow point. Upsweep of the flow waveform above this line is inspiratory flow, and downsweep is expiratory flow.
2. Greatest deflection above reference equals peak inspiratory flow.
3. Greatest deflection below reference equals peak expiratory flow.



Fig. 20.4 This flow waveform illustrates flow cycling. Note that on the monitor display, the actual inspiratory time is shorter than the set inspiratory time. The breaths are being cycled by flow rather than inspiratory time

4. Shape of the flow waveform is typically square or constant flow waveform seen in volume ventilation, or a decelerating flow seen in pressure ventilation.
5. Inspiratory time is measured from the initial flow delivery until expiratory flow begins.
6. Inflation time of the lung is measured from initial inspiratory flow delivery to the point when flow returns to zero. When ventilating newborns, clinicians should evaluate this time interval to set an appropriate inspiratory time.
7. At the point on the waveform when flow is zero, no additional volume can be delivered to the infant. If the inspiratory time is set too long, the time at zero flow may be prolonged.
8. Flow cycling allows a mechanical breath to be triggered (cycled) into expiration by a specific algorithm (usually 5–25% of peak inspiratory flow). The ability of a patient to control inspiratory time and cycle a breath to expiration may lead to improved synchronization. This feature is available on the newer generation ventilators and on any ventilator having pressure support (Fig. 20.4).
9. Expiratory time is the point where expiratory flow begins until the next inspiration begins.
10. When expiratory flow returns to zero, lung deflation is complete. This is represented on a waveform from the point where expiration begins to where expiratory flow returns to zero (Fig. 20.5).

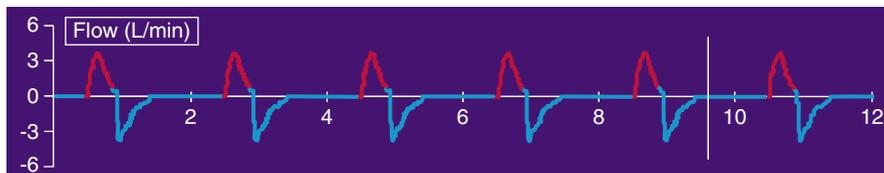


Fig. 20.5 Flow waveform demonstrating complete exhalation. Note that expiratory flow completely returns to baseline

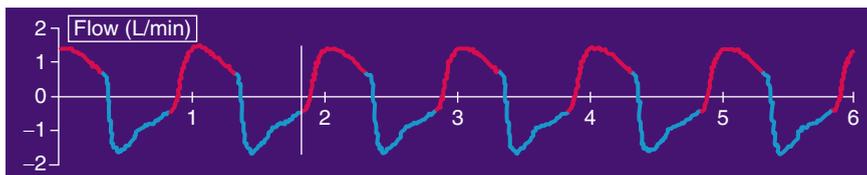


Fig. 20.6 Flow waveform demonstrating incomplete exhalation. Note that expiratory flow does not completely return to baseline before the next breath

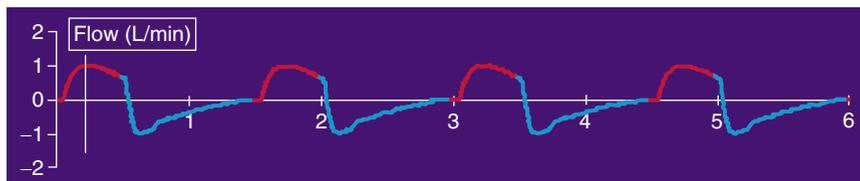


Fig. 20.7 Higher resistance is seen in this flow waveform. Air trapping is not present, but with this slow return of flow on expiration, air trapping could occur with a small increase in respiratory rate

11. If flow has not reached zero before the next breath is delivered, gas trapping may occur (Fig. 20.6).
 12. Gas trapping is more likely to occur in airways with increased resistance showing slow emptying time (Fig. 20.7).
- C. Volume waveform (Fig. 20.8)
1. Inspiration is represented as the waveform sweeps upward and expiration as the waveform sweeps downward.
 2. The dashed line represents delivered inspiratory tidal volume.
 3. An endotracheal tube leak is observed when the expiratory portion of the waveform fails to return to the zero baseline (Fig. 20.9).
 4. The relationship between mechanical volumes vs. spontaneous volumes in SIMV ventilation may be helpful in determining readiness to wean (Fig. 20.10).

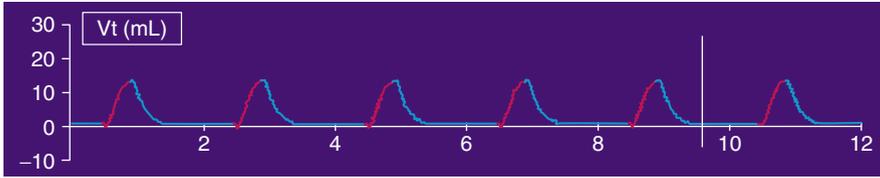


Fig. 20.8 On the volume waveform, inspiration is represented by the upsweep of the waveform and expiration by the downsweep. No leak is present in this waveform, as expiratory volume returns to baseline

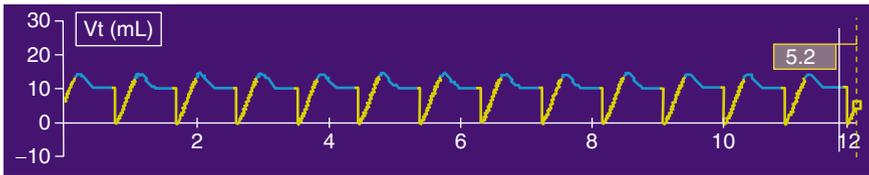


Fig. 20.9 Leak is shown on this volume waveform because the expiratory volume does not return to zero baseline

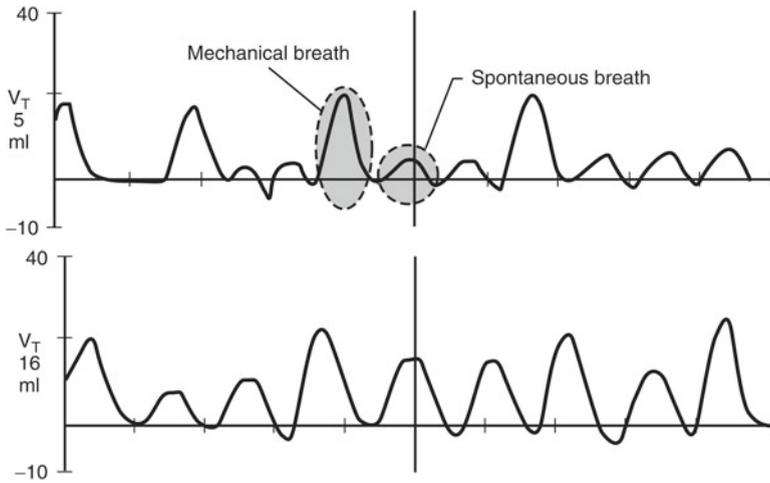


Fig. 20.10 The relationship between mechanical V_T and spontaneous V_T in SIMV may be helpful in determining readiness to wean. (From Nicks JJ: Graphics Monitoring in the Neonatal Intensive Care Unit. Palm Springs, CA, Bird Products, 1995, with permission)

- Asynchronous ventilation may be observed with the volume waveform. Dysynchrony may result in ineffective delivery of mechanical breaths. Synchronized ventilation (such as SIMV) results in much more consistent delivery of volumes and breaths will be more effective (Fig. 20.11).

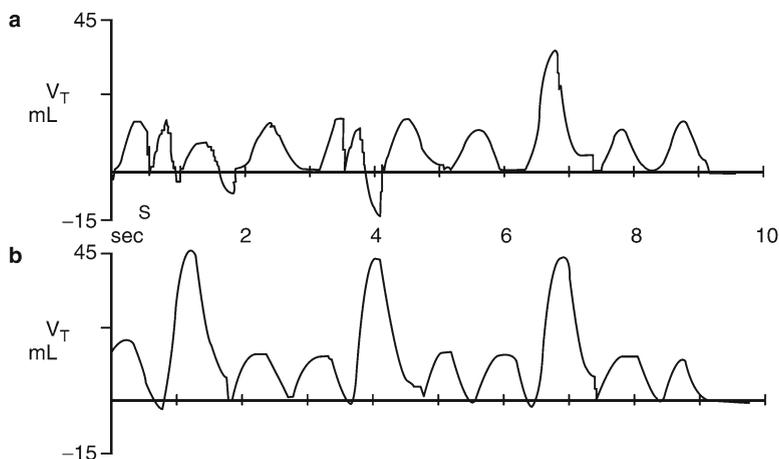


Fig. 20.11 Waveforms may be helpful in assessing patient-ventilator interaction (synchrony). If the infant fights the ventilator (a), inconsistent volume delivery may be present. When the infant demonstrates synchrony (b) volumes are much more consistent

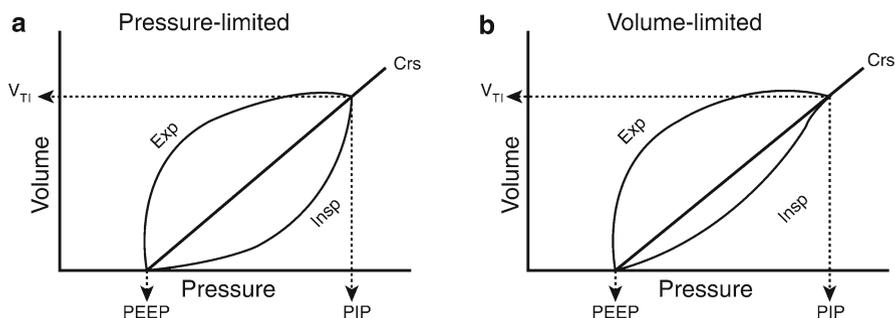


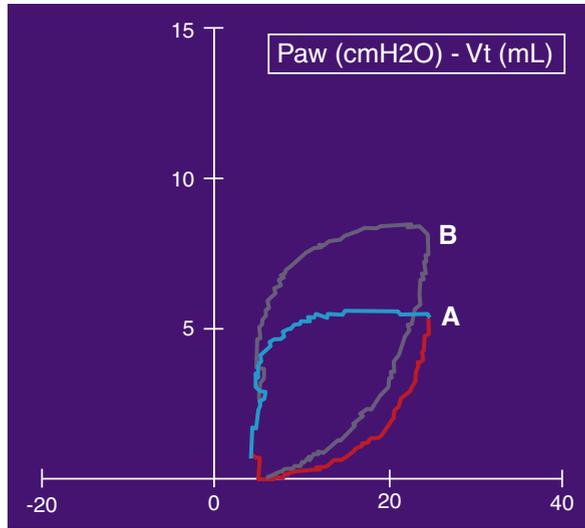
Fig. 20.12 Pressure–volume loops for both pressure-limited (a) and volume-limited (b) breath types. Note the inspiratory (Insp) and expiratory (Exp) limbs, origin (PEEP), peak inspiratory pressure (PIP), tidal volume (V_T), and compliance line (Crs) drawn by connecting the origin with the point of PIP

IV. Graphic loops

A. Pressure–Volume (P – V) loop (Fig. 20.12)

1. A pressure–volume loop displays the relationship of pressure to volume (compliance).
2. Pressure is displayed along the horizontal axis and volume is displayed on the vertical axis.
3. Inspiration is represented by the upsweep from the baseline (PEEP) terminating at PIP and V_{TI} . Expiration is the downsweep from PIP and V_{TI} back to baseline.
4. A line drawn from each endpoint represents compliance ($\Delta V/\Delta P$).

Fig. 20.13 On these pressure volume loops, note the change in compliance that occurred with surfactant delivery. *PV* loop A was obtained presurfactant and shows a much lower volume and *PV* loop B was postsurfactant with an increased volume. Both breaths were delivered with the same pressure



5. On a $P-V$ loop, poor compliance is represented by a lower volume in Pressure control ventilation or an increase in pressure in volume control ventilation. Recovery from RDS or response to surfactant therapy demonstrates improvement in compliance (Fig. 20.13).
6. Graphic monitoring is useful in identifying appropriateness of pressure delivery. A “beaking” of the $P-V$ loop often indicates overdistension. This occurs when pressure continues to rise with minimal change in volume (Fig. 20.14). Note that the compliance of the last 20% of the $P-V$ loop is lower than the C_D of the entire loop. This relationship is often expressed as a mechanics calculation (C_{20}/C_D ratio). A ratio of less than one usually indicates overdistension. When this is seen, it is appropriate to evaluate the PIP or V_T and attempt to reduce either of these.
7. $P-V$ loops can help evaluate whether flow delivery from the ventilator is adequate to meet the needs of the patient. Inadequate flow is represented by cusping of the inspiratory portion of the curve. Severe flow limitation may appear as a “figure-eight” on the $P-V$ loop (Fig. 20.15).

B. Flow–volume ($\dot{V} - V$) loop (Fig. 20.16)

1. A $\dot{V} - V$ loop displays the relationship between volume and flow. Volume is plotted on the horizontal axis and flow is plotted on the vertical axis.
2. In this example of a $\dot{V} - V$ loop (may vary with monitor type), the breath starts at the zero axis and moves downward and to the left on inspiration, terminating at the delivered inspiratory volume and upward, to the right, back to zero on expiration. Note the constant flow delivered with a volume breath type yields a square inspiratory pattern (a) vs. decelerating inspiratory flow (b) with a pressure breath type.
3. The $\dot{V} - V$ loop is useful in evaluating airway dynamics. During conditions of high airway resistance, peak flow is lower for a given volume.

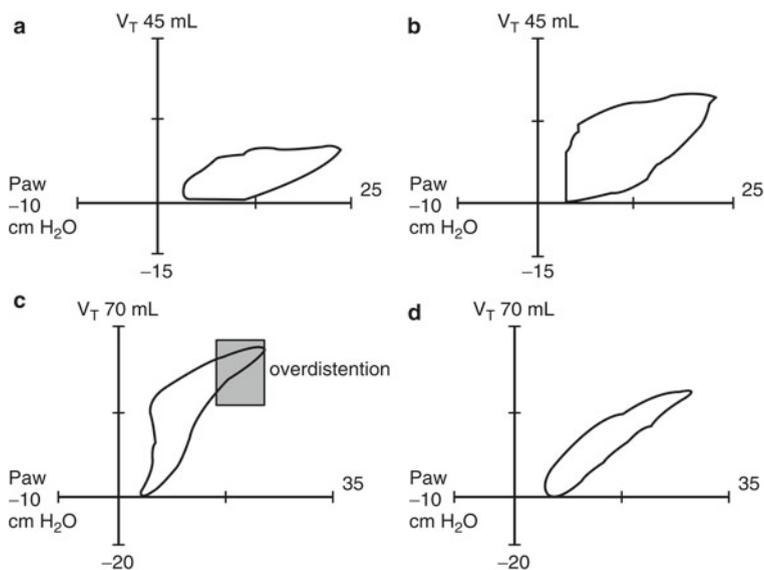


Fig. 20.14 In pressure–volume monitoring, a pressure change should result in a linear change from the low volume shown in **a**, as seen in **b** and **d**. On the loop in **c**, however, the last third of the curve is flattened, indicating that pressure continues to be delivered with only a minimal increase in volume. This is a sign of overdistention. (From Nicks JJ: *Graphics Monitoring in the Neonatal Intensive Care Unit*. Palm Springs, CA, Bird Products, 1995, with permission)

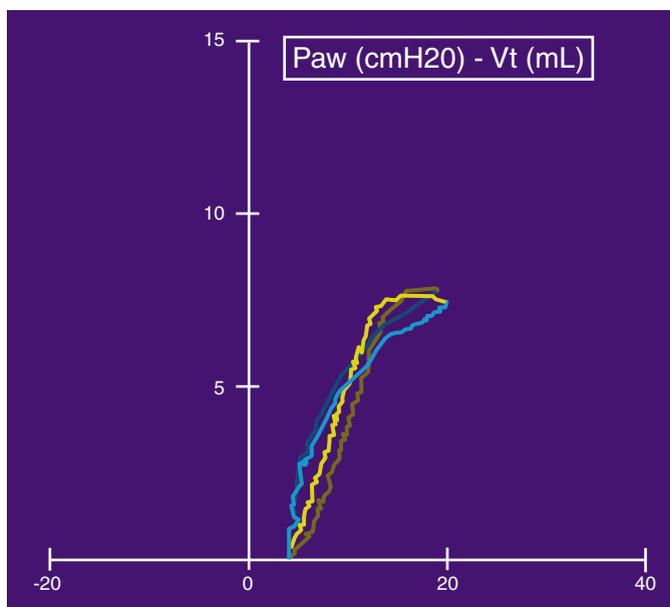


Fig. 20.15 Flow–volume loop displaying inadequate flow, with cusping of the inspiratory portion of the loop. This figure-eight loop indicates flow starvation

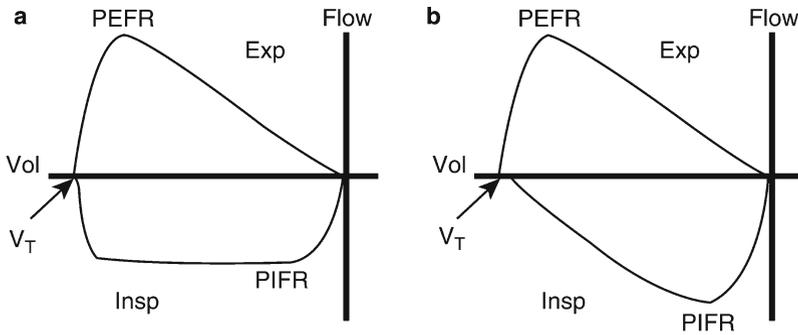


Fig. 20.16 Flow–volume loops. (a) Inspiratory flow limitation is demonstrated by flattening of the loop. The peak inspiratory flow rate (PIFR) is lower for a given volume. (b) Decreasing the resistance (such as by using a bronchodilator) results in improved (PIFR) and a more normal appearance of the inspiratory flow–volume loop



Fig. 20.17 Flow–volume and pressure volume loops displaying high airway resistance on expiration. Notice the low expiratory peak flow on the flow–volume loop, in comparison to the inspiratory flow. Also note the bowing out on the expiratory side of the pressure–volume loop, which also illustrates high expiratory resistance

Typically, expiratory resistance is higher with airway collapse or bronchospasm.

4. Conditions in the newborn that often result in increased expiratory resistance from airway obstruction include meconium aspiration syndrome (MAS) and bronchopulmonary dysplasia (BPD) (Fig. 20.17).

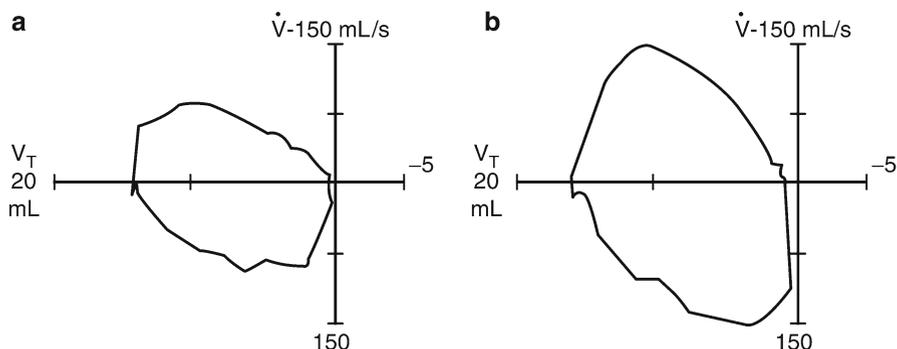


Fig. 20.18 Another example of evaluating a treatment using pulmonary graphics: (a) flow-volume loop before administration of a bronchodilator; (b) the same loop following treatment. Note the marked improvement in inspiratory and expiratory flow rates in this patient. (From Nicks JJ: Graphics Monitoring in the Neonatal Intensive Care Unit. Palm Springs, CA, Bird Products, 1995, with permission)

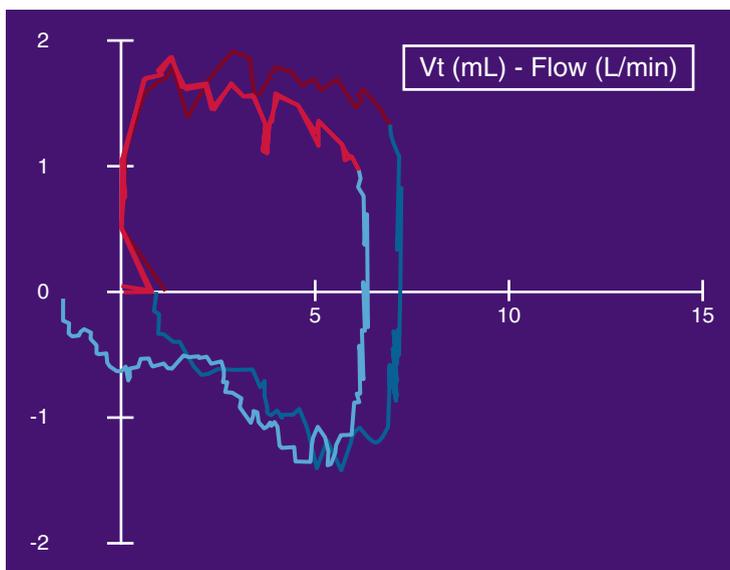


Fig. 20.19 Flow-volume loop on an infant in need of suctioning

5. The $\dot{V}-V$ loop is useful for evaluating the effectiveness of bronchodilators in treating airway reactivity. In Fig. 20.18, increased expiratory flow is seen in the loop on the right compared to the loop on the left.
6. The presence of secretions or water in the ventilator tubing or flow sensor can be seen on the loop displays. Since suctioning should only be

performed as indicated, loops are a useful way to evaluate need for suctioning or draining water from circuit (Fig. 20.19).

V. Dynamics measurements/calculations

- A. Tidal volume is measured on inspiration and expiration. Normal delivered V_T is 4–8 mL/kg.
- B. Minute ventilation is the product of V_T and respiratory rate. The normal range is 240–360 mL/kg/min.
- C. Pressure may be measured as peak inspiratory pressure (PIP) or static pressure. Static pressure is obtained by doing an inflation hold maneuver, which measures pressure obtained by closing the exhalation valve and stopping flow delivery during a mechanical breath.
- D. Compliance is the relationship between a change in volume and a change in pressure.
 1. Dynamic compliance (C_D) is the measurement of compliance based on peak pressure.

$$C_D = \frac{V_{Ti}}{PIP - PEEP}$$

2. Static compliance is the measurement based on static pressure

$$C_{ST} = \frac{V_{Ti}}{P_{ST} - PEEP}$$

3. C_{20}/C_D is the ratio of compliance of the last 20% of the P – V curve to the compliance of the entire curve. With overdistension, this ratio will be less than 1.0.
- E. Resistance is the relationship of pressure to flow. The pressure may be dynamic or static, and flow measurements are taken from various measurements.
 1. Peak flow is the maximum flow on either inspiration or expiration.
 2. Average flow is based on multiple point linear regression.
 3. Mid-volume flow is based on the flow measured at a point of mid-volume delivery.

$$R_{AW}(\text{cm H}_2\text{O/L/s}) = \frac{PIP - PEEP}{\text{Flow}}$$

Suggested Reading

Cannon ML, Cornell J, Trip-Hamel D, et al. Tidal volumes for ventilated infants should be determined with a pneumotachometer placed at the endotracheal tube. *Am J Respir Crit Care Med.* 2000;62:2109–12.

- Cunningham MD, Wood BR. Monitoring of pulmonary function. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 3rd ed. Philadelphia: W.B. Saunders Co.; 1996. p. 273–89.
- Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1998.
- Nicks JJ. Graphics monitoring in the neonatal intensive care unit: maximizing the effectiveness of mechanical ventilation. Palm Springs, CA: Bird Products Corp; 1995.
- Sinha SK, Nicks JJ, Donn SM. Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. *Arch Dis Child*. 1996;75:F213–8.
- Wilson BG, Cheifetz IM, Meliones JN. Mechanical ventilation in infants and children with the use of airway graphics. Palm Springs, CA: Bird Products Corp; 1995.

Chapter 21

Radiography

Ramon Sanchez and Peter J. Strouse

I. Introduction

- A. Conventional chest radiography is the primary imaging modality used for the evaluation of the neonatal chest.
- B. Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and fluoroscopy are less commonly used but are valuable in selected cases.

II. Conventional radiography

A. Introduction

1. With conventional radiography, electrical energy is received and converted into X-rays. These X-rays create an image after penetrating an object.
2. Chest radiographs are usually done portably at the bedside.
3. Most incubators incorporate X-ray tray devices to minimize manipulation of patients.
4. Conventional film screen radiography has largely been replaced by digital radiology systems. This new technology allows almost immediate availability of images, different visualization options, electronic archiving, transmission in networks and have the potential to decrease the radiation dose.
5. The anteroposterior (AP) view is the primary projection used. Lateral and cross table views can be obtained in selected cases.

B. Common indications

1. Respiratory distress
2. Abnormal blood gases

R. Sanchez, MD (✉) • P.J. Strouse, MD
Section of Pediatric Radiology, University of Michigan, C.S. Mott Children's Hospital,
1540 East Hospital Dr. SPC 4208, Ann Arbor, MI 48109-4252, USA
e-mail: ramonsan@umich.edu

3. Sepsis and/or pneumonia
4. Cardiac anomalies
5. Suspected congenital anomalies
6. Postsurgical evaluation
7. Assessment of catheters and tubes

III. Computed tomography

- A. Introduction. A thin X-ray beam is projected through the body. The radiation is measured by X-ray detectors. The X-ray beam and the detectors rotate around the patient while the examination table and patient moves through the scanner. Sophisticated computer software reconstructs the images for display on a monitor.
- B. Common indications.
 1. Developmental lung anomalies
 2. Cardiovascular anomalies
 3. Vascular rings and slings and tracheal anomalies
 4. Acute or chronic lung parenchyma disease
 5. Postsurgical evaluation
- C. Advantages.
 1. Good tissue characterization within the thorax
 2. Newer generation multidetector scanners with short acquisition times have decreased the need of sedation or anesthesia
 3. Multiplanar and 3D capabilities
- D. Disadvantages.
 1. Higher dose of ionizing radiation than conventional radiography
 2. Requires transport to the scanner
 3. May require sedation or anesthesia
 4. May require intravenous iodinated contrast administration

IV. Magnetic resonance imaging

- A. Introduction. MRI makes use of the magnetic properties of protons. Protons of different tissues to resonate at different frequency when subjected to an electromagnetic field. MRI *does not* use ionizing radiation.
- B. Common indications.
 1. Pre- and postsurgical evaluation of cardiovascular anomalies incompletely evaluated on echocardiogram
 2. Suspected vascular rings
 3. Mediastinal masses
- C. Advantages.
 1. *No ionizing radiation*
 2. Multiplanar capabilities

3. Exquisite tissue characterization
4. Dynamic evaluation (multiple phases of contrast, cardiac motion, functional assessment)

D. Disadvantages.

1. The role of MRI is limited in the evaluation of lung parenchyma disease
2. Need for transport, sedation, and/or anesthesia and, in many circumstances, intravenous gadolinium-based contrast
3. Vital signs may be difficult to monitor during long acquisition time
4. Expensive
5. Not available in all institutions
6. Magnet incompatibility with monitor equipment
7. Requires continuous monitoring of patient temperature secondary to environment and length of scan

V. Ultrasound

A. Introduction. Ultrasound waves propagate similarly to sound waves through a medium. Transmitted ultrasound waves reflect off interfaces with tissue back to the transducer to be detected. Different tissues have different acoustic properties. With diagnostic ultrasound, a body part is exposed to sound waves to produce images of the inside of the body. Ultrasound *does not* use ionizing radiation.

B. Common indications.

1. Pleural or pericardial effusions
2. Intrathoracic and mediastinal masses
3. Assessment of blood flow
4. Evaluation of diaphragmatic motion
5. Guidance for vascular access and other minor procedures

C. Advantages.

1. *No ionizing radiation*
2. Can be performed at the bedside
3. Dynamic evaluation of structures
4. Does not require sedation or contrast administration

D. Disadvantages.

1. Operator dependent.
2. Limited value for lung parenchyma disease. There is no transmission of sound waves through normal lung parenchyma.
3. Superimposed structures such as air, dressing, hardware, and osseous structures can limit the field of view and cause imaging artifacts.
4. Incomplete coverage; limited by scan planes and points of access.

VI. Fluoroscopy

- A. Introduction. Fluoroscopy uses a continuous (or preferably a pulsed) X-ray beam to produce a set of images. A television-like system is used to transfer the images from the source of the image to a monitor screen.
- B. Common indications.
 - 1. An esophagogram for tracheal, esophageal, or vascular anomalies
 - 2. Pre- and postsurgical evaluation of tracheoesophageal anomalies
 - 3. Evaluation of diaphragmatic motion
 - 4. Evaluation of swallowing
- C. Advantages.
 - 1. Dynamic evaluation
 - 2. Multiplanar capabilities
 - 3. High contrast resolution
- D. Disadvantages.
 - 1. Ionizing radiation
 - 2. Cannot be performed at the bedside and requires transport
 - 3. Requires immobilization
 - 4. May require administration of contrast material

VII. Common clinical scenarios

- A. Lung disease in the preterm infant
 - 1. Respiratory distress syndrome (RDS)
 - a. Typical radiographic pattern is a diffuse, bilateral, and symmetric granular pattern with air bronchograms and low volumes. This pattern results from a combination of collapsed alveoli and dilated terminal bronchioles (Fig. 21.1).
 - b. Atelectasis may cause complete whiteout of the lung.
 - c. Assisted ventilation may produce aerated lungs.
 - d. Nonhomogeneous distribution of surfactant may cause an asymmetric appearance of the typical radiographic pattern.
 - e. A left-to-right shunt from a patent ductus arteriosus (PDA) may cause worsening of the radiological pattern despite adequate treatment (Fig. 21.2).
- B. Bronchopulmonary dysplasia (BPD)
 - 1. A form of chronic lung disease (CLD).
 - 2. The most common radiographic appearance is the presence of diffuse, coarse, bilateral interstitial markings with lung hyperinflation with little change over the time (Fig. 21.3).
 - 3. If pulmonary hypertension is present, cardiomegaly can occur.

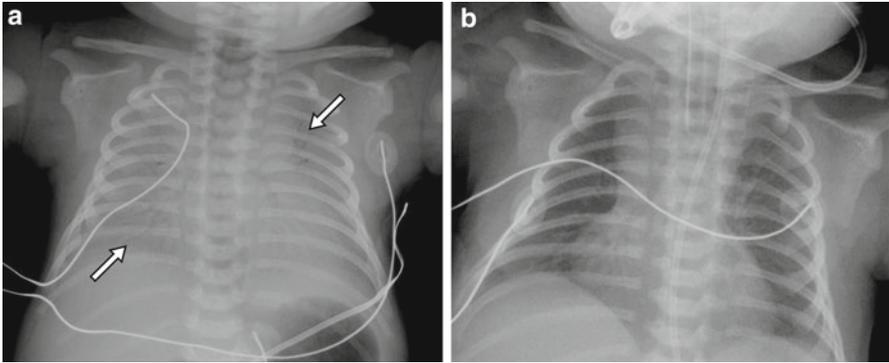


Fig. 21.1 Respiratory distress syndrome. (a) Chest radiograph shows hypoventilated lungs with symmetrical, bilateral granular opacities and air bronchograms (*white arrows*). (b) Exam performed 24 h later after endotracheal intubation and surfactant treatment. Lung aeration has improved. Diffuse bilateral granular pattern persists

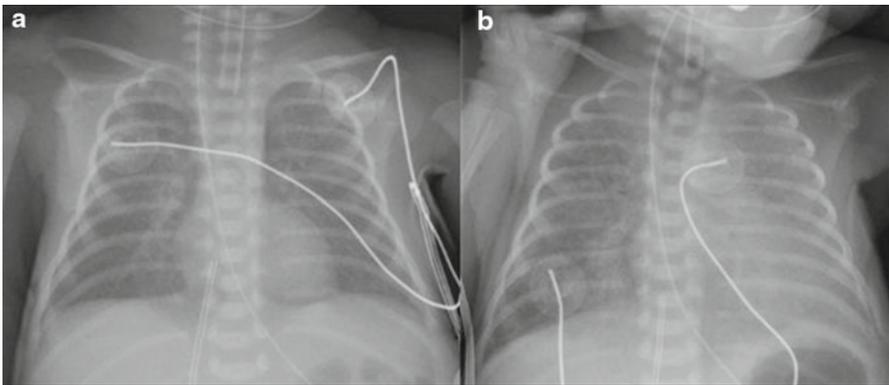


Fig. 21.2 Respiratory distress syndrome. (a) 4-day-old neonate. Diffuse and bilateral granular pattern consistent with respiratory distress syndrome are noted. (b) On day of life eight, there was significant worsening of his respiratory status. Diffuse, bilateral air space opacities and cardiomegaly are noted. The patient had a large PDA causing significant left-to-right shunt

4. Early stages simulate and overlap RDS. End stage disease causes cystic lung changes, with linear opacities representing fibrosis, atelectasis, and lung hyperinflation.
5. Limited thin slice chest CT can be used to evaluate the disease. Septal thickening, parenchymal bands, scars, atelectasis, and cystic changes are common findings (Fig. 21.4).

VIII. Lung disease in the term infant

A. Transient tachypnea of the newborn (TTN; TTNB).

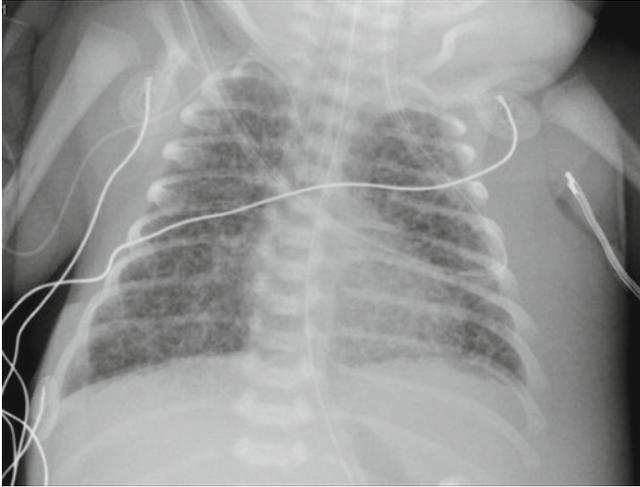


Fig. 21.3 Bronchopulmonary dysplasia. Hyperventilated lungs with diffuse, bilateral interstitial coarse opacities and small cystic changes are the typical radiographic findings



Fig. 21.4 Bronchopulmonary dysplasia. Axial CT image shows diffuse septal thickening and multiple right lung thin wall cysts (*arrows*)

1. Typical radiographic findings include mildly overinflated lungs with prominent interstitial markings, pleural thickening, and small pleural effusions. The latter are more common on the right side (Fig. 21.5).
2. Findings are usually symmetric and the heart may be mildly enlarged.
3. Radiographic findings usually resolve in 12–24 h.

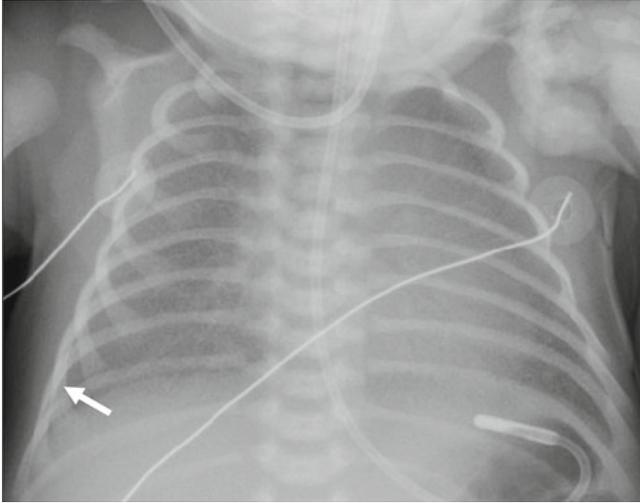


Fig. 21.5 Transient tachypnea of the newborn. Radiograph shows diffuse and bilateral prominent interstitial markings, and a small right pleural effusion (*arrow*). Note hyperinflation of the lungs

B. Meconium aspiration syndrome.

1. The syndrome consists of aspirated meconium, respiratory distress, and a characteristic chest radiograph.
2. Aspiration of meconium causes coarse patchy nodular opacities representing atelectasis and lung consolidation (Fig. 21.6).
3. Lung hyperinflation and air leaks, pleural effusion, and cardiomegaly can also be present. Meconium aspiration is a common cause of secondary persistent pulmonary hypertension (PPHN).

C. Persistent pulmonary hypertension (PPHN). Idiopathic persistent pulmonary hypertension causes hyperlucent lungs with decreased pulmonary vascularity (Fig. 21.7).

IX. Other forms of neonatal respiratory distress

A. Neonatal pneumonia

1. Radiographic patterns of neonatal pneumonia are nonspecific. Differentiating pneumonia from TTN, RDS, pulmonary edema, and pulmonary hemorrhage can be difficult, if not impossible.
2. Common radiographic manifestations are bilateral coarse or scattered air space opacities. Lungs are usually normally aerated and pleural effusions may occur (Fig. 21.8).
3. Isolated air opacities with air bronchograms are uncommon in this age group.

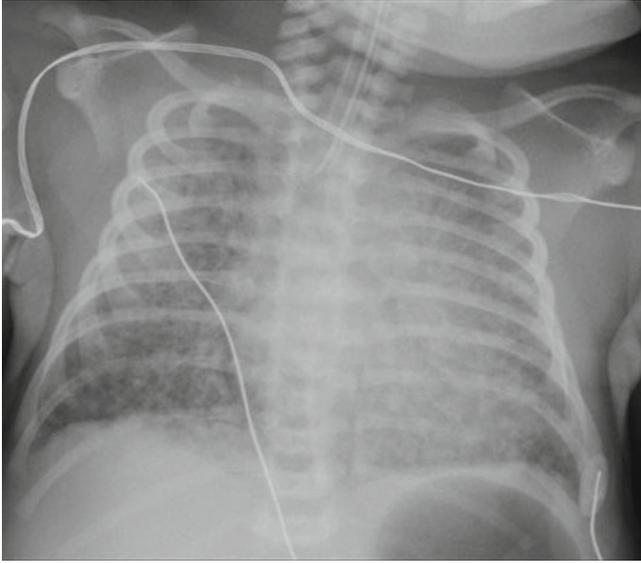


Fig. 21.6 Meconium aspiration. Diffuse, bilateral patchy opacities representing atelectasis and consolidation are seen on this chest radiograph. Note that the patient is intubated and that the heart is mildly enlarged

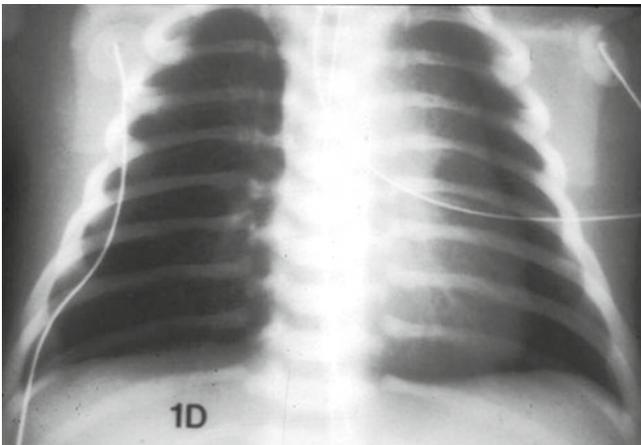


Fig. 21.7 Persistent pulmonary hypertension (PPHN). Radiograph shows hyperlucent lungs and decreased pulmonary vascularity in a 1-day-old neonate

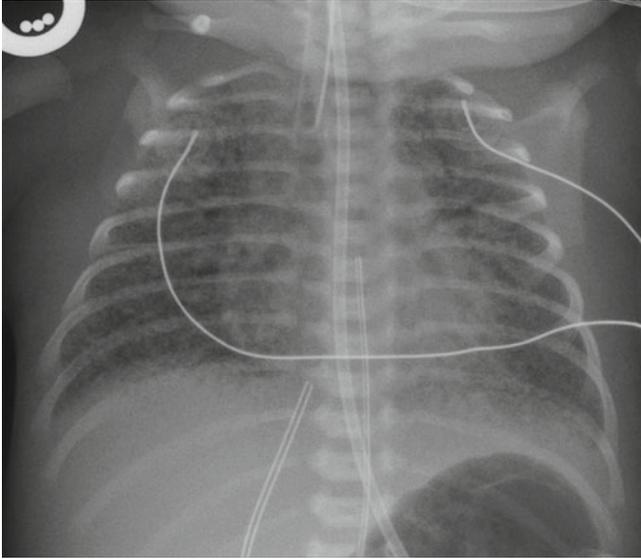


Fig. 21.8 Neonatal pneumonia. Neonate with group B streptococcal pneumonia. Diffuse and bilateral mixed interstitial and alveolar opacities. Thickening of the minor fissure is also noted

4. Ultrasound can be used to differentiate focal lung consolidation from other lung parenchymal opacities (Fig. 21.9). Ultrasound also visualizes pleural fluid (see below).
5. CT may be used in specific circumstances to rule out uncommon complications such as lung abscesses and bronchopleural fistula formation (Fig. 21.10).

B. Atelectasis

1. Atelectasis may be segmental, lobar, or total. Segmental atelectasis is seen as areas of lung opacification with volume loss and mediastinal shift proportional to degree of lung collapse. This is most common with endotracheal tube malposition and after extubation and typically resolves rapidly. Rapid resolution differentiates atelectasis from other causes of lung opacification (Fig. 21.11).
2. Poor radiographic technique (expiratory images) may simulate atelectatic lungs.
3. A normal thymus may simulate lung atelectasis. Ultrasound has been used to differentiate atelectasis from normal thymus simulating a collapsed lobe (Fig. 21.12).

C. Pleural effusion

1. Large pleural effusions are seen as increased opacification of the contralateral hemithorax with adjacent lung collapse and possible mediastinal shift (Fig. 21.13a).

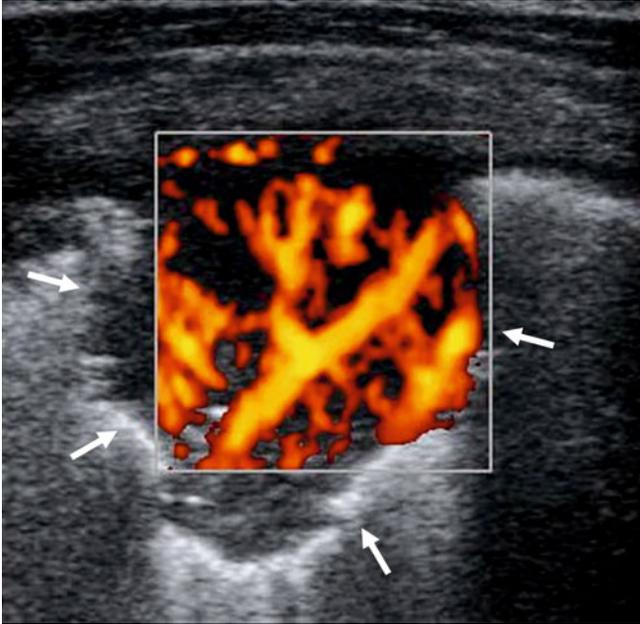


Fig. 21.9 Pneumonia. Ultrasound findings. Ultrasound image shows a hypoechoic area (*arrows*) representing an area of lung consolidation with increased vascular flow. No anomalous vessel to suggest sequestration

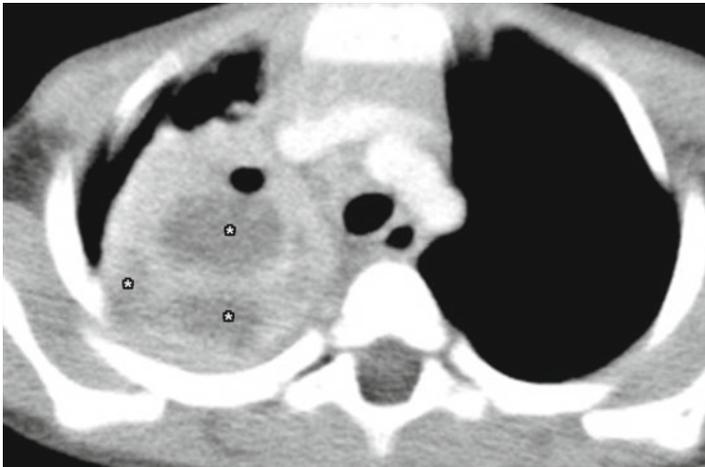


Fig. 21.10 Pneumonia. CT. Axial CT image performed after intravenous contrast administration. Note a right upper lobe air space opacification with nonenhancing areas (*asterisks*) and an air fluid level representing necrotizing pneumonia

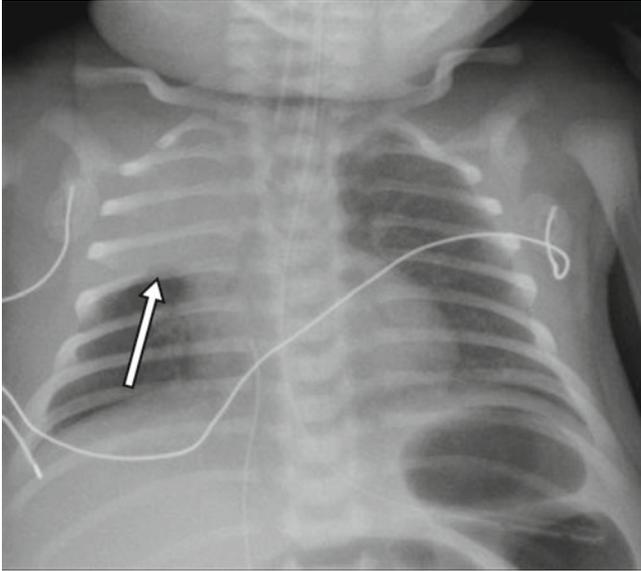


Fig. 21.11 Atelectasis. Right upper lobe atelectasis (*arrow*). Note the trachea is slightly deviated to the right

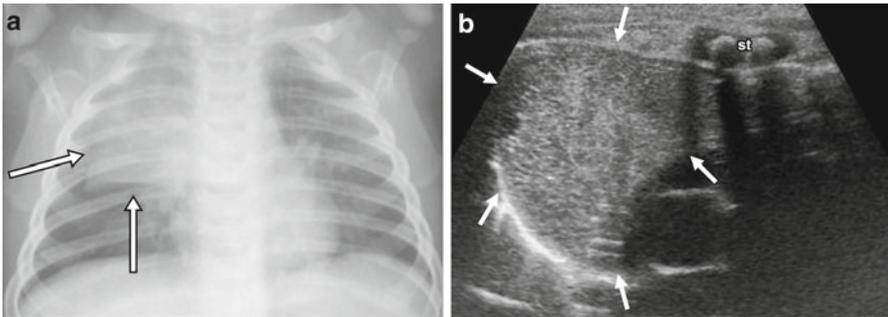


Fig. 21.12 Normal thymus simulating atelectasis. **(a)** Chest radiograph shows a right upper lobe opacity (*arrows*) mimicking lung collapse. **(b)** Transverse ultrasound image at the level of the upper mediastinum shows that the area of lung opacity on radiograph corresponds to normal thymus (*arrows*). *ST* sternum

2. Smaller effusions may be subtle on supine films. Increased lung density, blurring of the diaphragm and heart contour, and thickening of the fissures are typical findings.
3. Lateral decubitus views may be used to better delineate the presence of a pleural effusion, and may confirm motility of effusions, but do not allow characterization of pleural effusions (Fig. 21.13b, c).

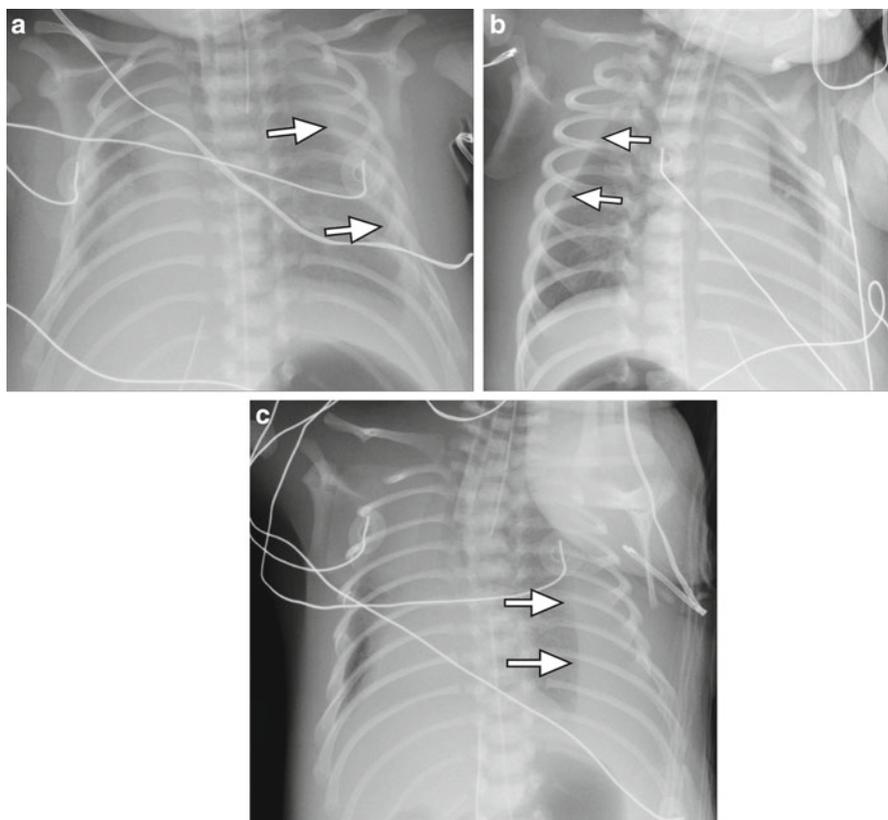


Fig. 21.13 Neonate with pulmonary lymphangiectasis with chylous effusions. (a) Supine radiograph of the chest shows diffuse and bilateral lung haziness with a moderate left pleural effusion (arrows). Right side down (b) and left side down (c) lateral decubitus views better delineate the presence of effusions. Note that the nasogastric tube tip is in the mid esophagus. The patient has been intubated in the interval between the supine to the lateral decubitus views

4. Ultrasound can be used to detect, quantify, and characterize pleural effusions. Echogenic pleural fluid and septations are seen in complex pleural effusions (Fig. 21.14).

D. Air leaks

1. Pneumothorax

- a. Imaging appearance depends on the size, location, and projection.
- b. On supine chest radiographs, pneumothoraces are typically seen as radiolucent spaces without vascular margins (Fig. 21.15; see also Figs. 21.16 and 21.17).
- c. Small pneumothoraces can be subtle on supine views, since air accumulates anteriorly, causing increased sharpness of the mediastinal edge and a hyperlucent lung (Fig. 21.16). Decubitus views can be

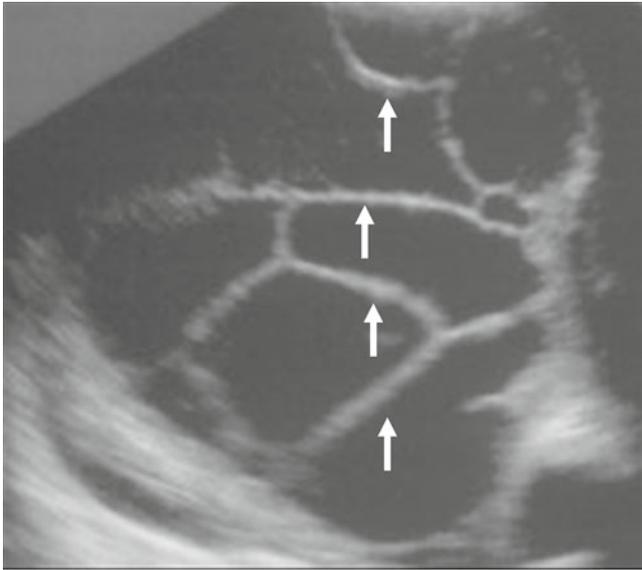


Fig. 21.14 Pleural effusion. Ultrasound image shows a large pleural effusion with multiple septations (*arrows*) representing fibrin bands in a patient with empyema

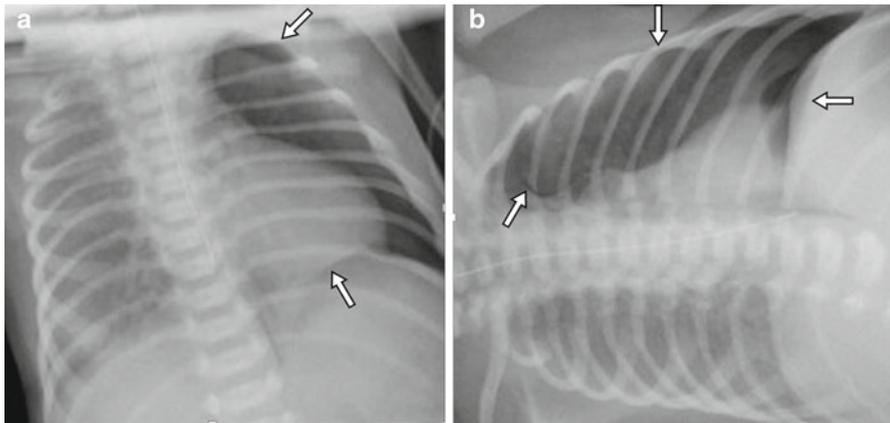


Fig. 21.15 Pneumothorax. (a) Supine view of the chest in a patient with left pneumothorax (*arrows*). The left hemithorax appears hyperlucent from predominantly left anterior pneumothorax. (b) Right side down lateral decubitus view in the same patient better delineates the presence of a pneumothorax

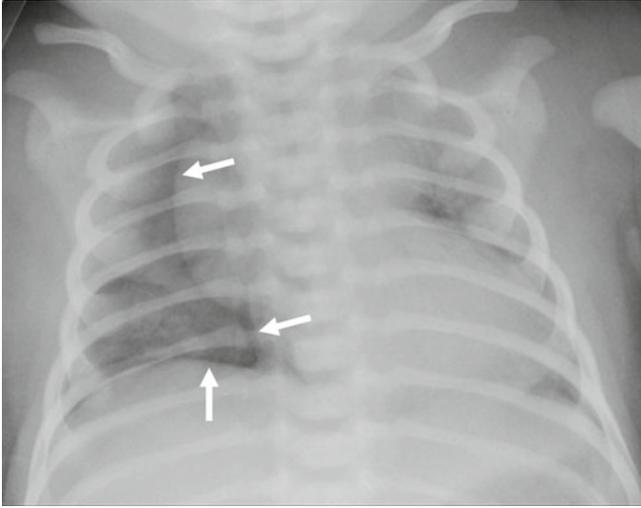


Fig. 21.16 Pneumothorax. Right pneumothorax. Supine chest radiograph shows a sharp right mediastinal borders and diaphragm (*arrows*). The pneumothorax is predominantly medial and anterior in location

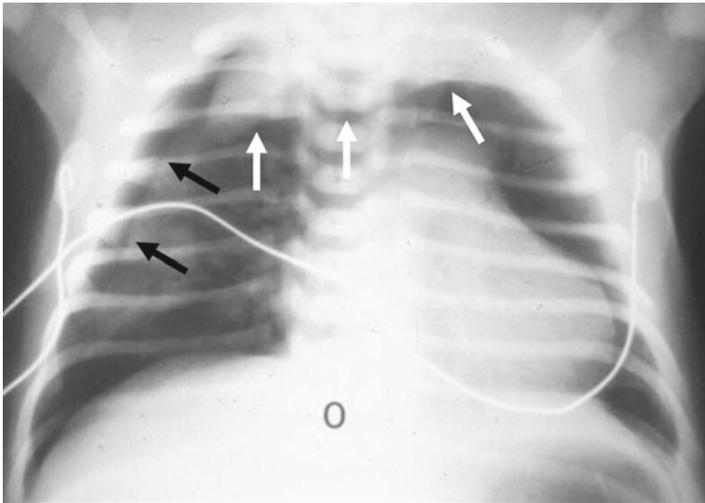


Fig. 21.17 Pneumomediastinum. Air in the mediastinum displaces the thymus superiorly (*white arrows*). Associated right pneumothorax (*black arrows*)

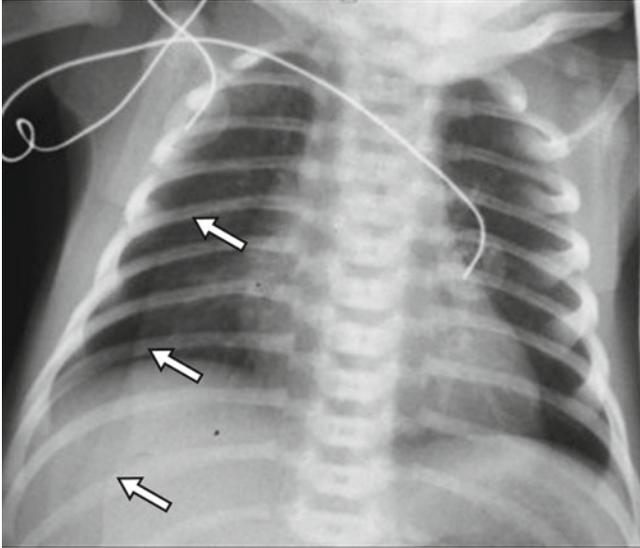


Fig. 21.18 Skin fold mimicking pneumothorax. Vertically oriented linear density (*arrows*) projecting over the right hemithorax. Note the extension of the density below the diaphragm and the presence of pulmonary vessels lateral to its edge

- useful in some circumstances and are preferred to cross table lateral views, which do not differentiate side and are limited by overlying structures (Fig. 21.15b).
- d. Medial pneumothorax (Fig. 21.16) can be difficult to differentiate from a pneumomediastinum (Fig. 21.17).
 - e. Normal skin folds may mimic pneumothoraces. Skin folds usually extend beyond the lung edge (Fig. 21.18).
 - f. Tension pneumothoraces are seen as hyperlucent lungs with lung collapse and mediastinal shift (see also Fig. 21.20).
2. Pneumomediastinum
 - a. Mediastinal air collections are usually asymptomatic and rarely require intervention.
 - b. Anteriorly located pneumomediastinum usually outlines or delineates the thymus (“angel” or “bat wing” sign) (Fig. 21.18).
 - c. Posteriorly located pneumomediastinum may dissect into the subcutaneous tissues of the neck.
 3. Pulmonary interstitial emphysema (PIE)
 - a. PIE projects as linear and cystic lucencies radiating from the hilum toward the periphery of the lung (Fig. 21.19).
 - b. May be localized, unilateral, or bilateral. May cause significant mass effect and mediastinal shift.

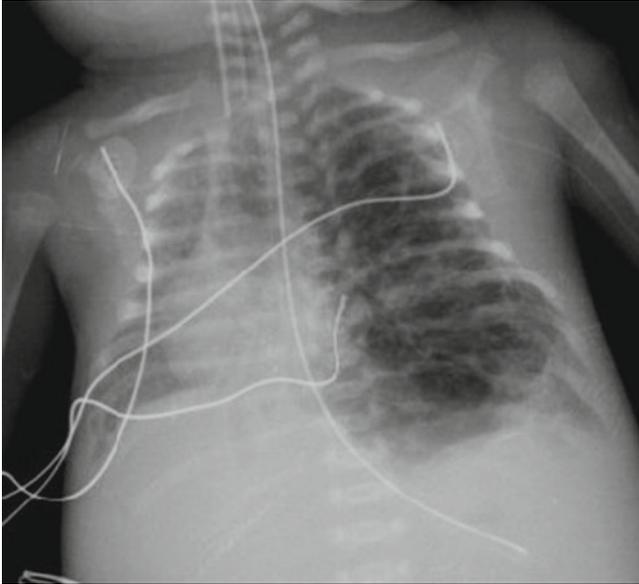


Fig. 21.19 Pulmonary interstitial emphysema (PIE). Multiple linear and cystic lucencies are identified in the left lung. Note the hyperexpansion of the left lung with flattening of the diaphragm and mediastinal shift to the right

4. Pneumopericardium. Pneumopericardium is recognized by the presence of a curvilinear lucency completely surrounding the heart which conforms to the pericardial sac (Fig. 21.20).

E. Congenital cardiovascular anomalies

1. Chest radiography.

- a. A cardiothoracic index (ratio of the transverse diameter of the heart to the maximum internal diameter of the thorax) $>60\%$ suggests cardiomegaly (Fig. 21.22a). Lateral views also help to assess heart size. From radiography, determination of which heart chamber is enlarged and the shape of the heart is usually not very useful. Expiratory films may simulate cardiomegaly.
- b. A normal thymus may mimic cardiomegaly (Fig. 21.21).
- c. The aortic arch may be hidden by the thymus, but the descending aorta is usually visible (see also Fig. 21.21). Assessment of aortic arch may be suggested by the position of the trachea.
- d. Left-to-right shunts $>2:1$ usually cause increased pulmonary vascularity (Fig. 21.22), while right-to-left shunts cause oligemia and decreased pulmonary flow. These radiographic changes are not usually apparent in the first week of life.
- e. Skeletal abnormalities and cardiac position should also be assessed.

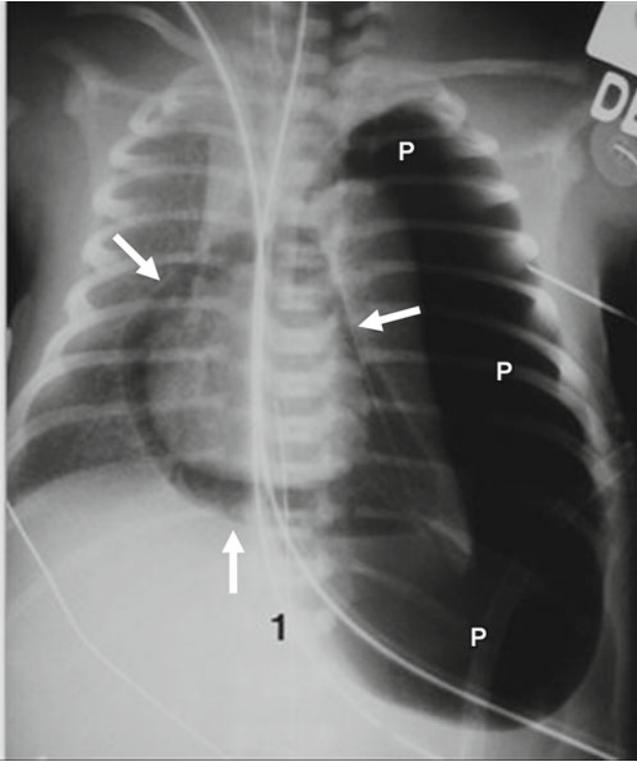


Fig. 21.20 Pneumopericardium. The heart is surrounded by air (*white arrows*). Note the presence of a left-tension pneumothorax (P) which causes left lung collapse, inversion of the left diaphragm, and mediastinal shift to the right

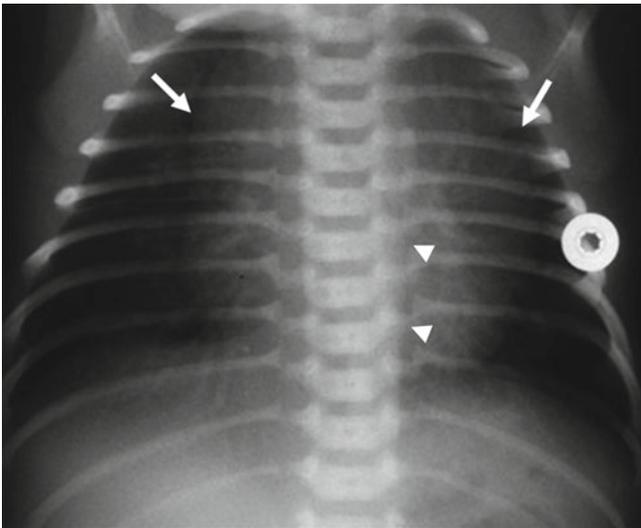


Fig. 21.21 Thymus simulating cardiomegaly. The heart and mediastinum appear widened secondary to the presence of a prominent thymus. Note the undulating appearance of the lateral aspect of the thymus due to the impressions caused by the ribs (*white arrows*). Descending aorta (*arrowheads*)

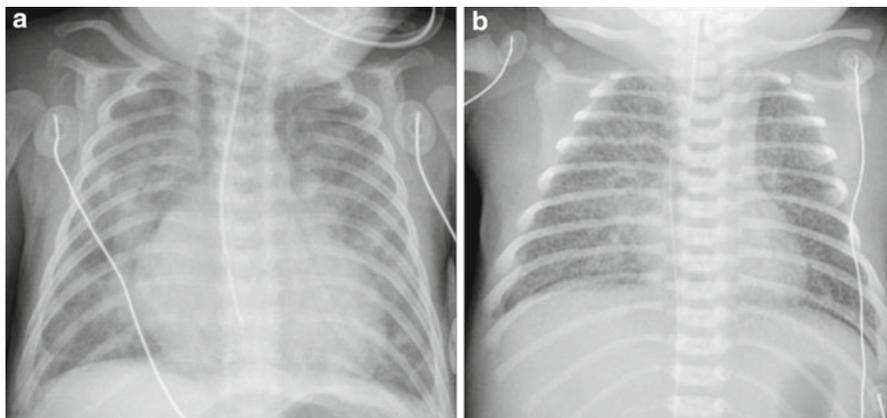


Fig. 21.22 Increased vascular flow. **(a)** Neonate with ventricular septal defect. Chest radiograph shows cardiomegaly and increased vascular flow. Note that the tip of the nasogastric tube is malpositioned in the distal esophagus. **(b)** Chest radiograph in a neonate with total anomalous pulmonary venous return and interstitial edema. The heart is not significantly enlarged. Bilateral pulmonary vessels are ill defined representing venous congestion. Prominent and bilateral interstitial markings are seen suggesting edema. Associated small right pleural effusion is noted

2. Esophagogram. An esophagogram may be performed when there is a suspicion of a vascular anomaly causing airway compression (Fig. 21.23).
3. CT and MRI.
 - a. Echocardiography remains the primary imaging modality for cardiovascular anomalies in the neonate.
 - b. Magnetic resonance imaging (MRI) and computed tomography (CT) are excellent minimally invasive imaging modalities which allow pre and postoperative evaluation of vascular anomalies, as well as complex cardiovascular anomalies. CT and MRI are specifically useful in determining caliber and patency of small vessels or surgical shunts (Fig. 21.24). MRI also allows dynamic evaluation of cardiac function.

F. Developmental lung anomalies

1. Congenital pulmonary airway malformation (CPAM)
 - a. Previously referred to as congenital cyst adenomatoid malformation (CCAM).
 - b. CPAM represents the most common lung malformation and is often diagnosed on prenatal ultrasound.
 - c. Imaging appearance is variable and depends on the size and composition of the lesion. Lesions may be solid and/or cystic in composition (Fig. 21.25a). Most CPAMs are solitary with no lobar predilection and multiple lobes may be affected by one lesion.

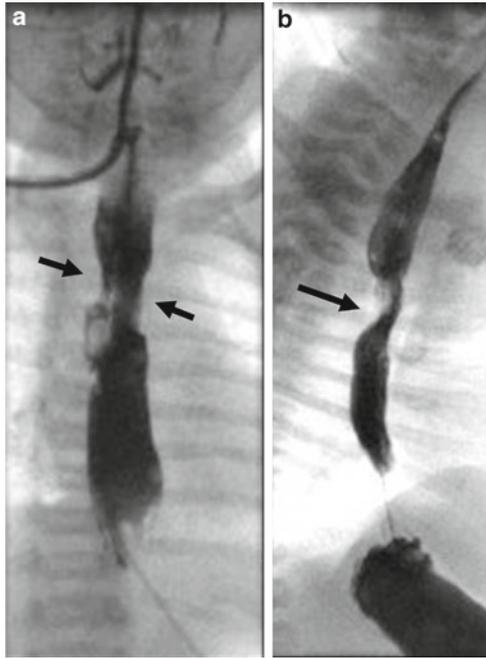


Fig. 21.23 Double aortic arch. AP (**a**) and lateral (**b**) views from an esophagogram show extrinsic compressions (*arrows*) posterior and to both sides of the esophagus caused by a double aortic arch



Fig. 21.24 Neonate with hypoplastic left heart syndrome status post Norwood procedure. Coronal MR angiogram reconstruction shows patency of modified Blalock–Taussig shunt (*arrow*) extending from the neo-aorta to the right pulmonary artery

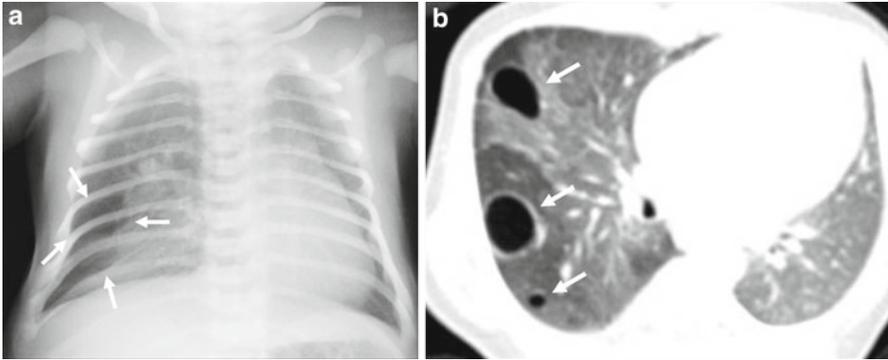


Fig. 21.25 CPAM. (a) Chest radiograph shows right lower lobe multi-cystic lesion (*arrows*). (b) Axial CT image through the lung bases shows multiple well-defined air-filled cysts lesions (*arrows*) involving middle and lower lobes

- d. CT is mainly used to evaluate size and location and is usually performed with intravenous contrast administration to evaluate the vascular anatomy (Fig. 21.25b).
- e. Pre- or postnatal MRI also evaluates anatomy and extension.

2. Pulmonary sequestration

- a. Pulmonary sequestration represents an area of dysplastic, nonfunctional lung with a systemic arterial supply that typically arises from the aorta. The most common location is the left lower lobe followed by the right lower lobe. Most neonatal sequestrations are extralobar and have their own pleura and systemic venous return. Intralobar sequestrations have pulmonary venous drainage and are invested within the pleura of the affected side.
- b. On conventional radiography, sequestrations are seen as dense and persistent focal masses (Fig. 21.26a).
- c. It is also often diagnosed on prenatal ultrasound. Fetal MRI also allows evaluation of anatomy and extension.
- d. Presurgical evaluation with CT, MRI and ultrasound is performed to evaluate the extent and to identify the systemic vascular supply, which arises from below the diaphragm in 20% of cases (Fig. 21.26b).
- e. Pulmonary sequestration may occur in conjunction with CPAM (“hybrid lesions”), cardiac, diaphragmatic, skeletal, and other lung anomalies.

3. Congenital lobar overinflation

- a. Formerly referred to as congenital lobar emphysema (CLE).
- b. Initially, after birth, the overdistended lobe is filled with fluid and is opaque.

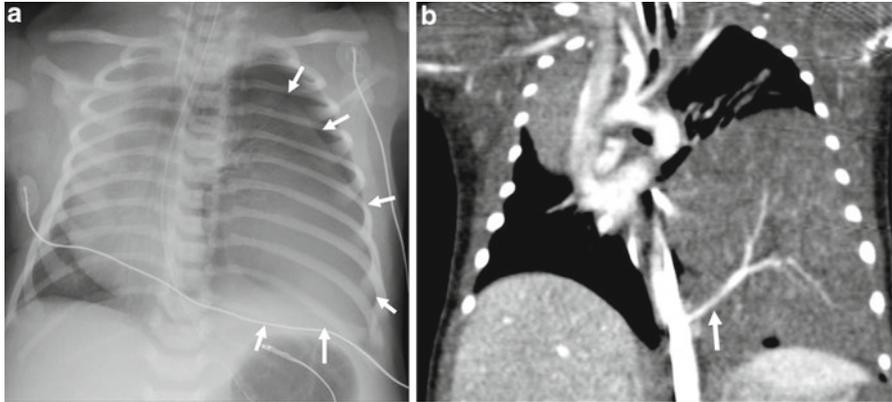


Fig. 21.26 Pulmonary sequestration. (a) Chest radiograph shows a well-defined left lung opacity (*arrows*) and significant mediastinal shift to the right. (b) Coronal CT image shows a large left lower lobe solid mass and a feeding vessel (*arrow*) arising from the aorta

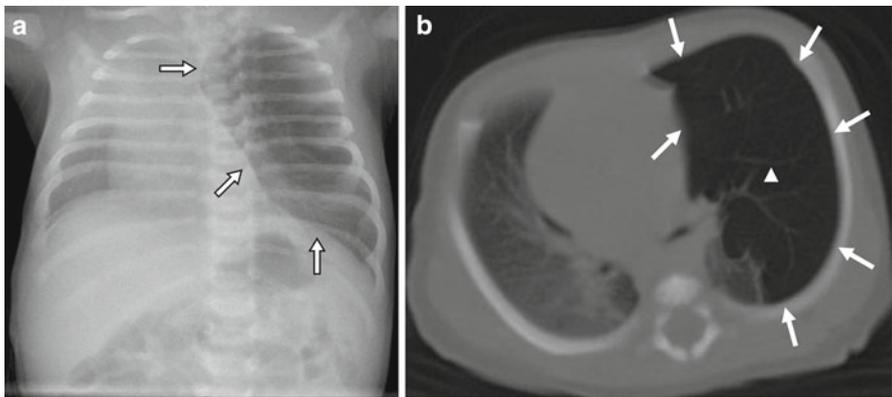


Fig. 21.27 Congenital lobar overinflation. (a) Chest radiograph shows a left upper lobe lucency (*arrows*) with mediastinal shift to the contralateral side and compressive right lung atelectasis. (b) Axial CT image in the same patient. Marked hyperinflation of the left upper lobe (*arrows*) with significant mediastinal shift and right lung atelectasis. Note that the vascularity (*arrowhead*) in the affected lobe is attenuated

- c. Subsequently, the typical appearance is that of an overdistended lung, which, depending on the size, may cause adjacent atelectasis and mediastinal shift to the contralateral side (Fig. 21.27a).
- d. CT may be performed for presurgical evaluation to better evaluate the anatomy (Fig. 21.27b).

G. Congenital diaphragmatic hernia (CDH)

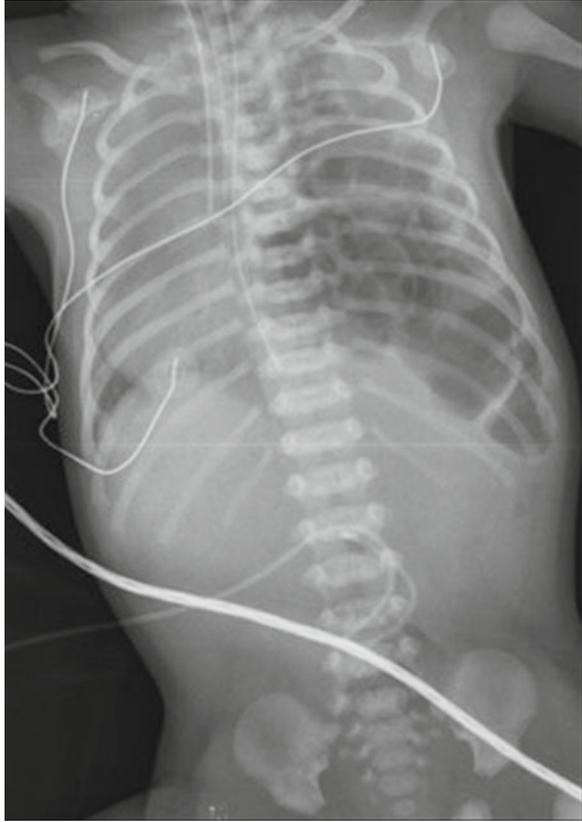
1. Congenital diaphragmatic hernias are usually diagnosed on prenatal ultrasound.

Fig. 21.28 Left-sided congenital diaphragmatic hernia. Coronal T2 weighted fetal MRI image shows herniation of part of the left hepatic lobe (L), stomach (S), and small and large bowel (SB) into the chest. Note the presence of a hypoplastic left lung (*arrow*)



2. Fetal MRI now plays an important role in the presurgical and initial neonatal management. MRI characterizes the herniated structures, quantifies the degree of lung hypoplasia, and evaluates for the presence of associated anomalies (Fig. 21.28).
3. On initial radiographs, herniated abdominal contents are seen as an opaque mass, more common on the left side, with ipsilateral lung hypoplasia and a contralateral mediastinal shift. During the following hours, air fills the herniated loops of bowel giving the typical appearance of multiple lucencies in the chest (Fig. 21.29).
4. After surgical correction, “ex vacuo” pneumothorax is a frequent finding.

Fig. 21.29 Left-sided congenital diaphragmatic hernia. Radiograph of the chest and abdomen shows lack of abdominal gas and multiple gas filled loops of bowel occupying the left hemithorax. The mediastinum is shifted to the right. Note the nasogastric tube tip in the distal esophagus and selective intubation of the right bronchus



H. Esophageal atresia, tracheoesophageal fistula, tracheal stenosis

1. A coiled gastric tube in the proximal esophagus suggests esophageal atresia in the adequate clinical setting. The presence of abdominal gas suggests the presence of an associated distal tracheoesophageal fistula (Fig. 21.30).
2. Cardiac, renal, vertebral, anal, and osseous anomalies are common associated findings.
3. Contrast studies can be performed in equivocal cases, when pharyngeal perforation is in the differential diagnosis and for postsurgical evaluation (Fig. 21.31).
4. Rapid acquisition time, multiplanar, and volumetric capabilities make CT an excellent noninvasive diagnostic tool when airway anomalies such as tracheal stenosis (Fig. 21.32), abnormal tracheal-bronchial tree development, or extrinsic compression are suspected.

Fig. 21.30 Esophageal atresia and distal tracheoesophageal fistula. Radiograph of the chest and upper abdomen shows a coiled nasogastric tube (*arrow*) in the upper esophagus. The presence of abdominal gas determines the presence of a distal tracheoesophageal fistula

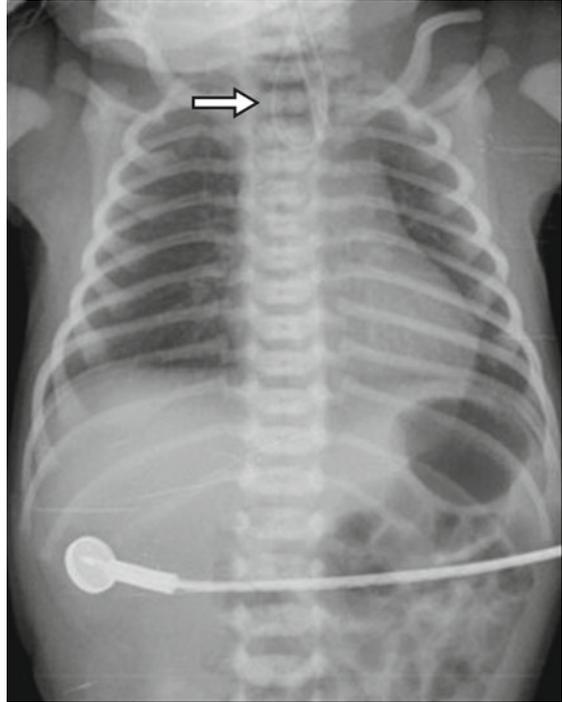
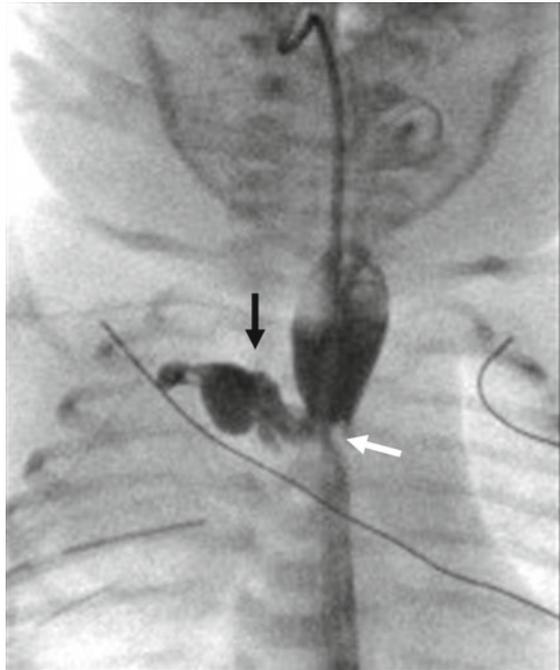


Fig. 21.31 Tracheoesophageal fistula status post repair. Postsurgical leak. Esophagram performed after surgical correction shows an area of narrowing (*white arrow*) at the level of the surgical anastomosis and leak of contrast (*black arrow*) into the right pleural space. Note the presence of three right chest tubes



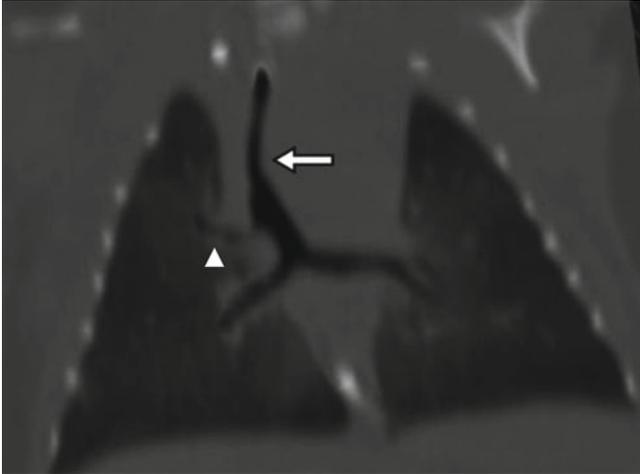


Fig. 21.32 Tracheal stenosis and accessory tracheal bronchus. Reconstructed coronal CT image shows a long segment area of tracheal narrowing (*arrow*) and an accessory right bronchus (*arrow-head*) arising from the trachea

I. Assessment of tubes and catheters (Fig. 21.33)

1. Endotracheal tube (ETT)

- a. Endotracheal tube tip should be located in the mid to distal trachea.
- b. The position of the patient's head and neck may alter the ETT position: the tube tip moves caudally (toward the carina), with neck flexion and cephalic (toward the glottis) with neck extension and lateral rotation.
- c. Unintentional right main bronchus intubation is a common radiologic finding.

2. Vascular catheters, gastric drainage tubes, and surgical drains

- a. Placement of vascular catheters, gastric drainage and chest tubes, may require additional imaging to assess correct position.
- b. Umbilical venous catheter (UVC) tip is ideally located above the diaphragm and below the right atrium.
- c. Umbilical arterial catheters (UAC). A high line tip is usually located at T7–T10 vertebral level. A low line tip is ideally located at L3–L4 vertebral body interspace.
- d. Ultrasound can be used to guide peripherally inserted central catheter (PICC) placement.

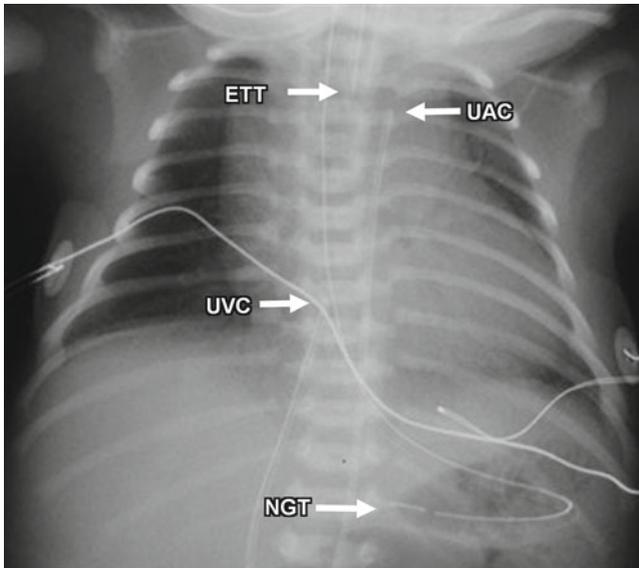


Fig. 21.33 Catheters and tubes. Neonate with RDS. Note the tip of the endotracheal tube (ETT), umbilical venous catheter (UVC), umbilical arterial catheter (UAC), and gastric drainage tube (NGT)

3. Extracorporeal membrane oxygenation (ECMO) cannulas and liquid ventilation
 - a. ECMO Cannulas may be venoarterial (V-A) or venovenous (V-V).
 - b. For V-A ECMO, the tip of the venous cannula should project within the right atrium, while the tip of the arterial cannula should be within the aortic arch at the expected location of the origin of the innominate artery (Fig. 21.34).
 - c. After bypass, a whiteout of the lungs is a common radiological finding.
 - d. A rapidly increasing pleural effusion is suggestive of anticoagulation-induced hemothorax.
 - e. Conventional radiographs are used to evaluate the distribution of perflubron when liquid ventilation is used (Fig. 21.35).
- J. Chest wall deformities causing respiratory distress
 1. Neuromuscular disease, skeletal dysplasia, and congenital osseous anomalies may be responsible for restrictive lung disease (Figs. 21.36 and 21.37a). Lung hypoplasia, atelectasis, and aspiration contribute to the development of respiratory distress.
 2. CT and MRI can be performed to evaluate extent of the deformity and to evaluate lung volume (Fig. 21.37b).

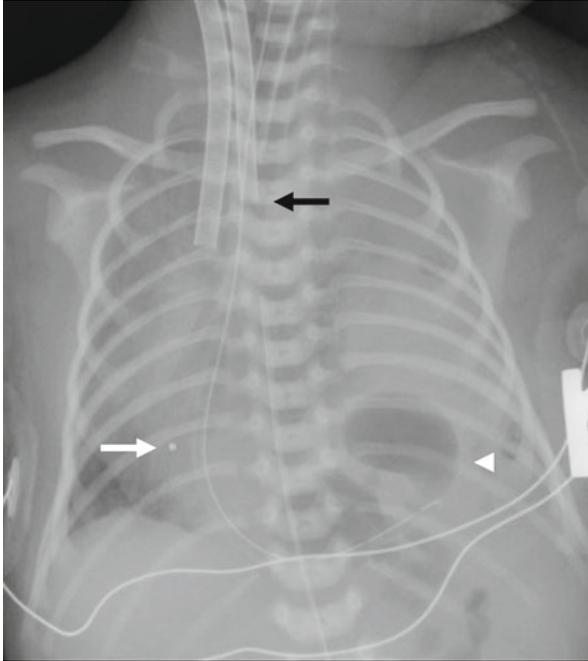


Fig. 21.34 ECMO cannulas. Chest radiograph in a neonate with left congenital diaphragmatic hernia on ECMO. The venous cannula tip (*white arrow*) is located at the expected location of the right atrium. The arterial cannula tip (*black arrow*) is located at the innominate artery/aorta junction. Note the tip of the NG tube (*arrowhead*) in the herniated stomach

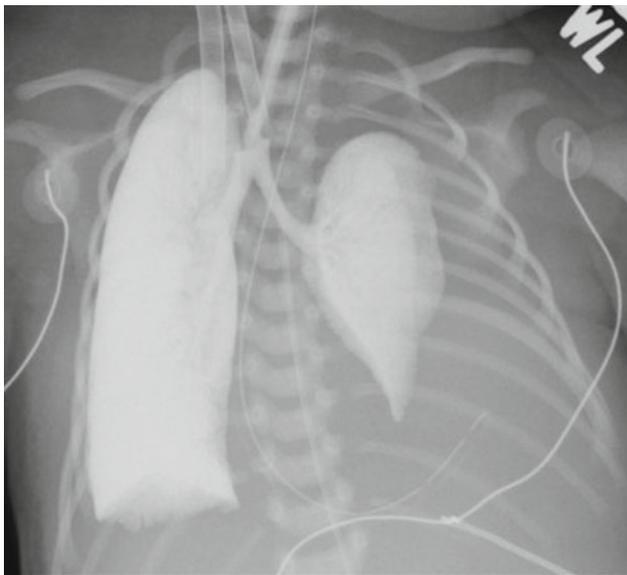


Fig. 21.35 Liquid ventilation. Chest radiograph performed in newborn with left congenital diaphragmatic hernia (CDH) on ECMO and liquid ventilation. Note the presence of ECMO cannulas, NG tube tip in stomach located in the left hemithorax, ascending vascular catheter (UAC), and perflubron within trachea-bronchial tree and the lungs. The left lung is hypoplastic secondary to left side CDH

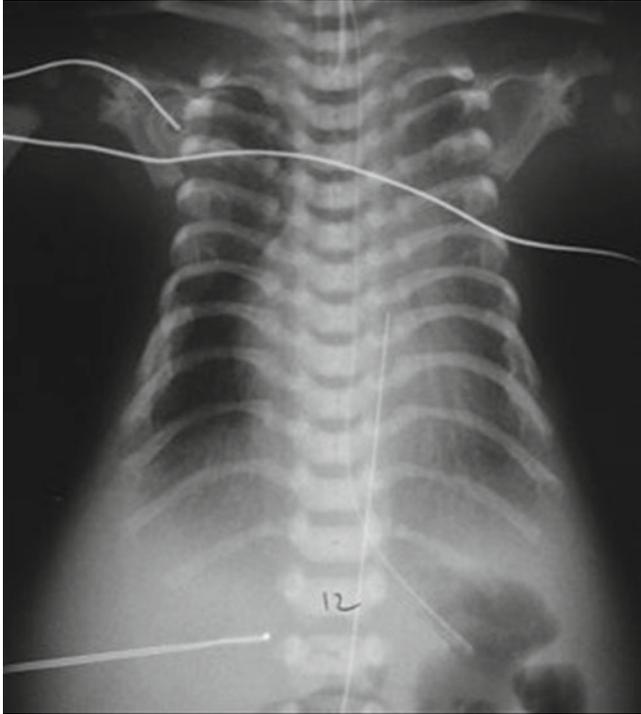


Fig. 21.36 Chest wall deformity. Chest radiograph of a patient with Jeune syndrome. Small chest with short, horizontally oriented ribs and irregular anterior ends. Note the NG tube tip in the stomach, an UAC with tip at the level of T6 vertebral body and an ETT tip at the level of the cervicothoracic junction

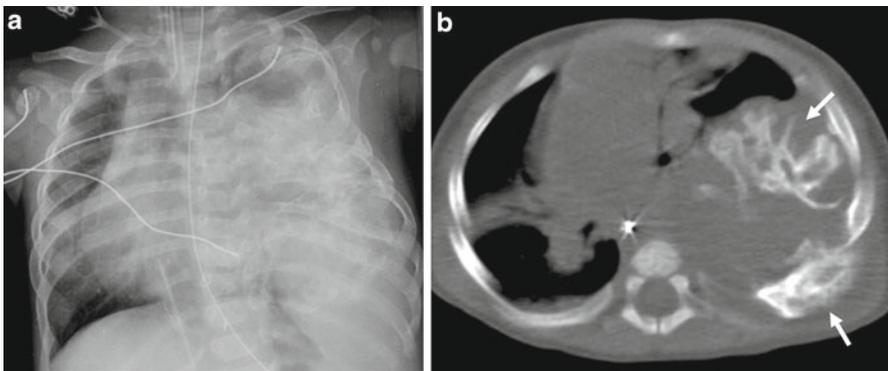


Fig. 21.37 Chest wall deformity. Supine chest radiograph (a) and axial CT image (b) in a neonate with large left mesenchymal hamartoma involving multiple ribs and causing significant mediastinal shift. CT delineates degree of osseous involvement and soft tissue components (*arrows*)

Suggested Reading

- Agrons GA, Courtney SE, Stocker JT, Markowitz RI. From the archives of the AFIP: lung disease in premature neonates: radiologic–pathologic correlation. *Radiographics*. 2005;25:1047–73.
- Bedard MP. Anatomy, embryology, and physiology. In: Slovis TL, Bulas DI, Faerber EN, Brent H, Adler BH, Hernanz-Schulman M, Coley BD, Strouse PJ, Bloom DA, Donaldson JS, Frush DP, editors. *Caffey’s pediatric diagnostic imaging*. 11th ed. Philadelphia, PA: Mosby; 2008. p. 73–7.
- Bulas DI, Farmer DL. Prenatal diagnosis and therapy of chest anomalies. In: Slovis TL, Bulas DI, Faerber EN, Brent H, Adler BH, Hernanz-Schulman M, Coley BD, Strouse PJ, Bloom DA, Donaldson JS, Frush DP, editors. *Caffey’s pediatric diagnostic imaging*. 11th ed. Philadelphia, PA: Mosby; 2008. p. 78–92.
- DiPietro MA. A radiological atlas on neonatal emergencies. In: Donn SM, Faix RG, editors. *Neonatal emergencies*. Mount Kisco, NY: Futura Publishing; 1991. p. 123–206.
- Donoghue V, editor. *Radiological imaging of the neonatal chest*. Berlin, Heidelberg, New York: Springer; 2002.
- Hernanz-Schulman M, Coley BD, Strouse PJ, Bloom DA, Donaldson JS, Frush DP, editors. *Caffey’s pediatric diagnostic imaging*. 11th ed. Philadelphia, PA: Mosby; 2008. p. 93–132.
- Humes RA, Walter III HL, Slovis TL. Neonatal congenital heart disease requiring intervention in the first 28 days. In: Slovis TL, Bulas DI, Faerber EN, Brent H, Adler BH, Hernanz-Schulman M, Coley BD, Strouse PJ, Bloom DA, Donaldson JS, Frush DP, editors. *Caffey’s pediatric diagnostic imaging*. 11th ed. Philadelphia, PA: Mosby; 2008. p. 364–76.
- Slovis TL, Bulas DI. Tumors, tumor-like conditions (masses) and miscellaneous lesions. In: Slovis TL, Bulas DI, Faerber EN, Brent H, Adler BH, Hernanz-Schulman M, Coley BD, Strouse PJ, Bloom DA, Donaldson JS, Frush DP, editors. *Caffey’s pediatric diagnostic imaging*. 11th ed. Philadelphia, PA: Mosby; 2008. p. 134–8.
- Strife JL, Lucaya J, editors. *Neonatal chest imaging. Chest imaging in infants and children*. Springer: New York, Berlin, Heidelberg; 2007.
- Taylor GA, Atalabi OM, Estroff JA. Imaging of congenital diaphragmatic hernias. *Pediatr Radiol*. 2009;39:1–16.
- Newman B. Imaging of medical disease of the newborn lung. *Radiol Clin North Am*. 1999;37:1049–65.

Chapter 22

Transillumination

Steven M. Donn

I. Description

Use of a high-intensity light to help define normal from abnormal structure or function. Using transillumination, the density and composition of tissue are assessed by its diffusion of light.

II. Clinical applications

- A. Diagnosis of air leaks
- B. Distinguishing cystic from solid masses
- C. Locating veins or arteries for blood sampling or catheter insertion
- D. Initial diagnosis of central nervous system abnormalities which involve formation of fluid collections

III. Technique

- A. Prepare light source.
 - 1. Check power supply or batteries
 - 2. Connect fiber-optic cable if necessary
 - 3. Practice good infection control by disinfecting light probe with antiseptic solution
- B. Darken room as much as possible. Allow some time for dark adaptation.
- C. Apply light probe to infant's skin surface in the area to be examined; contralateral side can be used as control.

S.M. Donn, MD, FAAP (✉)
Division of Neonatal–Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

- D. Normally, extent of visible light corona around probe tip is 2–3 cm; the presence of air (or fluid) in light path substantially increases the degree of lucency. A significant collection of air enables the entire hemithorax to “glow.”
 - E. Pneumomediastinum.
 - 1. Suggested if cardiac pulsations are clearly evident in lucent area
 - 2. Best seen if light probe is placed next to costal margin
 - 3. High predictive value (94%) if >20 mL air
 - F. Pneumothorax.
 - 1. Generally, expand uniformly in anterior direction
 - 2. Best demonstrated if light probe is placed on anterior chest wall
 - 3. Can be diagnosed with >95% accuracy under favorable conditions
 - G. Pneumopericardium.
 - 1. Place light probe in third or fourth intercostal space in left mid-clavicular line
 - 2. Angle light probe toward xiphoid process
 - 3. When probe is moved over thorax, corona appears brightest over the pericardial sac, and silhouette of heartbeat may be seen
 - H. All three collections may be aspirated under transillumination guidance.
- IV. Special considerations
- A. Care must be taken to avoid burning the patient with the high-intensity light. This is accomplished by using a red filter inserted in front of the light source and limiting contact of the light probe with the skin.
 - B. Cross-contamination of patients is avoided by covering light with cellophane.

Suggested Reading

- Cabatu EE, Brown EG. Thoracic transillumination: aid in the diagnosis and treatment of pneumopericardium. *Pediatrics*. 1979;64:958–60.
- Donn SM. Historical perspective: neonatal transillumination. *NeoReviews*. 2005;6:e1–3.
- Donn SM. Transillumination. In: Donn SM, editor. *The Michigan manual: a guide to neonatal intensive care*. 2nd ed. Armonk, NY: Future Publishing Co; 1997. p. 27–8.
- Donn SM, Kuhns LR. *Pediatric transillumination*. Chicago: Chicago Year Book Medical Publishers; 1983.
- Wyman ML, Kuhns LR. Accuracy of transillumination in the recognition of pneumothorax and pneumomediastinum in the neonate. *Clin Pediatr*. 1977;16:323–4.

Chapter 23

Echocardiography

Jonathan Wyllie

I. Background

- A. Until the advent of echocardiography, cardiac function in the ventilated baby was monitored by clinical assessment and invasive monitoring, which is limited by the size of the patient.
- B. Tissue perfusion is the most relevant parameter in assessing cardiovascular function. This depends upon peripheral vascular resistance and cardiac output. Previously, heart rate and blood pressure have been utilized as indicators of these parameters, but these have significant limitations.
- C. Echocardiography now offers a number of different modalities which can be used to assess cardiac function in the ventilated infant and provide more information upon which to base clinical decisions.

II. Influences on newborn cardiovascular adaptation

- A. Preterm delivery
- B. Surfactant deficiency
- C. Ventilation
- D. Hypoxemia
- E. Acidosis

III. Effects of prematurity and respiratory disease on cardiovascular adaptation

- A. Delayed fall in pulmonary vascular resistance
- B. Myocardial dysfunction
- C. Ductal patency
- D. Ventilation and diminished venous return
- E. Hypovolemia

J. Wyllie, BSc(Hons), MB ChB, FRCPCH, FRCP, FERC (✉)
Department of Neonatology, The James Cook University Hospital,
Marton Road, Middlesbrough, Cleveland TS4 3BW, UK
e-mail: jonathan.wyllie@stees.nhs.uk

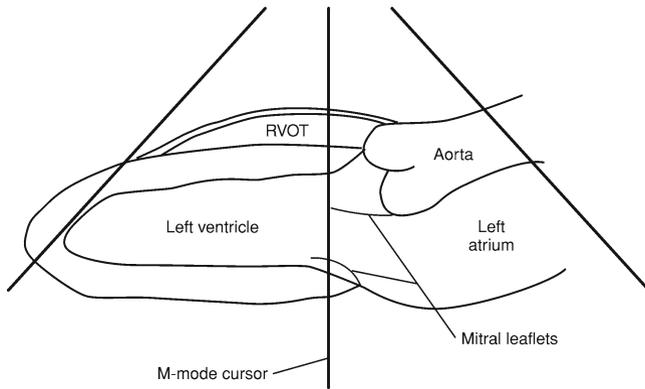


Fig. 23.1 Long-axis parasternal view. Positioning of M-mode cursor for left ventricular measurements is shown. *RVOT* right ventricular outflow tract

IV. Ideal cardiac assessment

- A. Right and left ventricular outputs
- B. Cardiac function
- C. Pulmonary resistance
- D. Tissue perfusion
- E. Systemic vascular resistance

V. Echocardiographic assessment

A. Echocardiographic principles

1. Cross-sectional echocardiography is used to assess anatomy, allow accurate positioning of an M-mode, continuous wave Doppler, or pulsed wave Doppler beam, and to give a subjective impression of function. Views used include:

- a. Long-axis parasternal (Fig. 23.1)
- b. Short-axis parasternal mitral (Fig. 23.2)
- c. Short-axis parasternal pulmonary (Fig. 23.3)
- d. Apical four chamber (Fig. 23.4)
- e. Subcostal
- f. Suprasternal view of aortic arch or ductal arch
- g. Subcostal short axis (Fig. 23.5); useful if lungs are overdistended

- B. M-mode obtains detailed echocardiographic information along a thin beam. It is simplest to first position using a cross-sectional image (Fig. 23.1) and then switch to M-mode. It is used to obtain views of the left ventricle at the level of the mitral leaflets in assessment of left ventricular function and measurement of left ventricular dimensions (Fig. 23.6). It is also used in measurement of the left atrium and aorta (Fig. 23.7a, b).

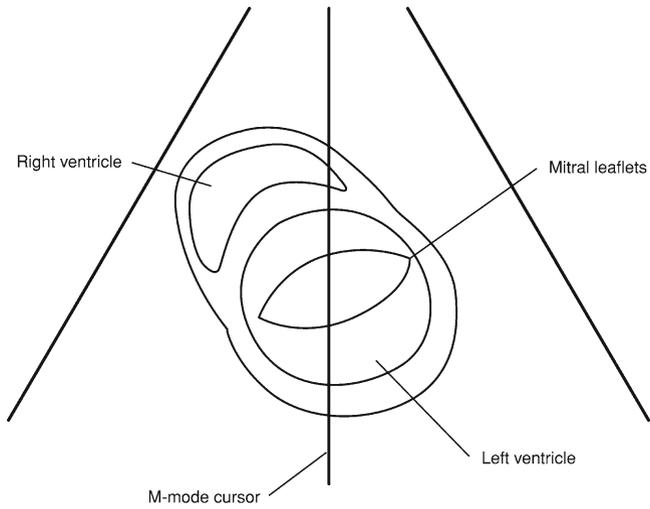


Fig. 23.2 Short-axis parasternal mitral view. Positioning of M-mode cursor for left ventricular measurements is shown

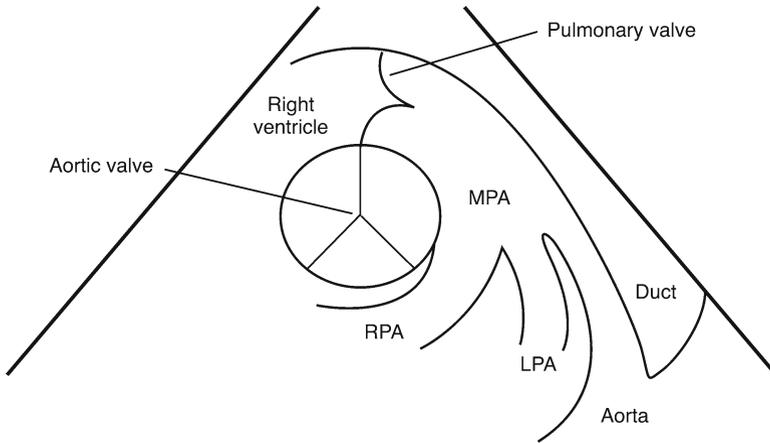


Fig. 23.3 Short-axis parasternal pulmonary view. *MPA* main pulmonary artery; *RPA* right pulmonary artery; *LPA* left pulmonary artery

- C. Pulsed wave Doppler uses Doppler shift of sound waves from moving red blood cells to assess flow velocity. It can sample the velocity at a point specified on a cross-sectional image (range gated), but is often only useful for relatively low velocities. It is useful for velocity measurement in the pulmonary artery, ductus arteriosus (Fig. 23.8), foramen ovale, superior vena cava, aortic arch, celiac axis, and superior vena cava.

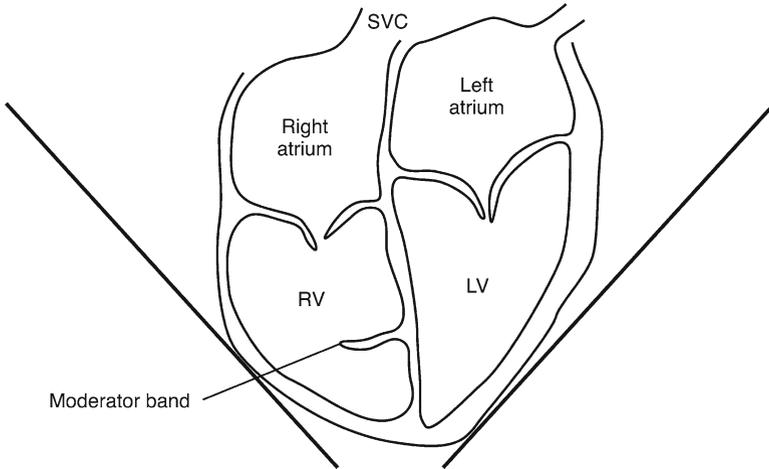


Fig. 23.4 Four-chamber apical view. Offset of tricuspid and mitral valves is seen. *SVC* superior vena cava; *RV* right ventricle; *LV* left ventricle

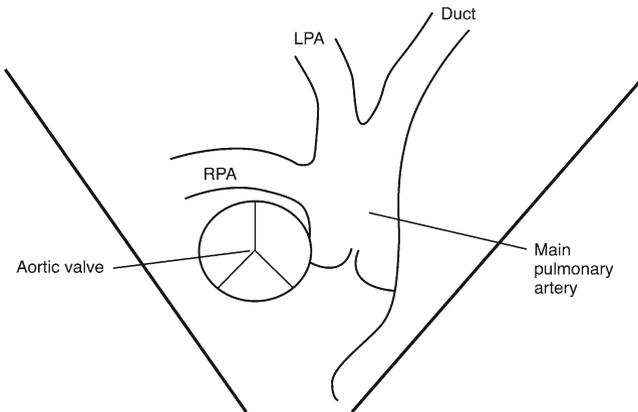


Fig. 23.5 Subcostal short-axis pulmonary view. *RPA* right pulmonary artery; *LPA* left pulmonary artery

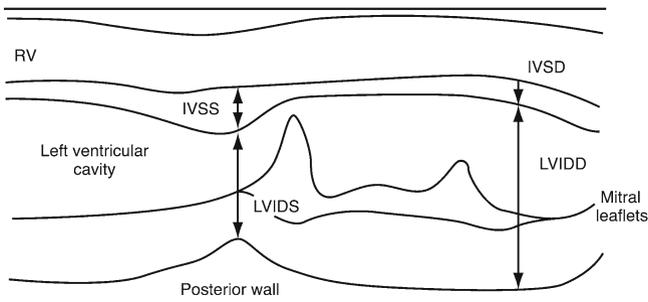


Fig. 23.6 M-mode view of left ventricle showing measurements. *RV* right ventricle; *IVSS* intra-ventricular septum systole; *LVSS* left ventricular internal diameter systole; *LVIDS* left ventricular internal diameter systole; *LVIDD* left ventricular internal diameter diastole; *IVSD* intra-ventricular septum diastole; *Mitral leaflets*

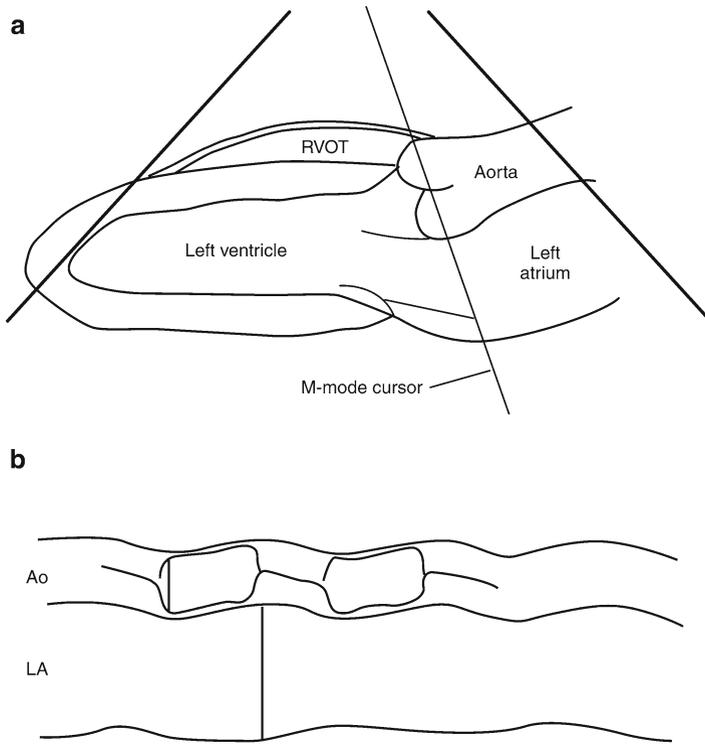


Fig. 23.7 Long-axis parasternal view with M-mode cursor across aorta (Ao) and left atrium (LA) (a) M-mode of aorta and left atrium showing measurements of each (b) M-mode of aorta (Ao) and left atrium (LA) showing measurements of each

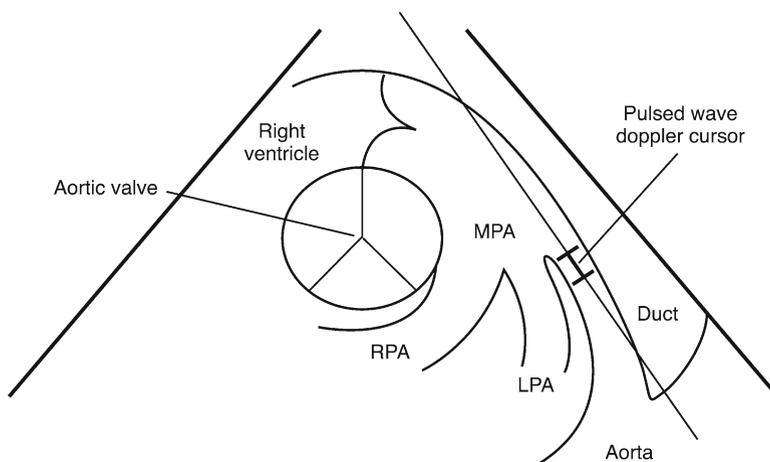


Fig. 23.8 Short-axis parasternal pulmonary view showing the position of the pulsed-wave Doppler cursor for sampling ductal flow velocity

- D. Continuous wave Doppler also uses Doppler shift of sound waves from moving red blood cells to assess flow velocity, but is not range gated and samples velocities along the cursor line (Fig. 23.8). It can be used in line with cross-sectional views or using a stand-alone “pencil” probe. Both continuous and pulsed wave Doppler beams must be within 15° of the direction of flow to be accurate. Continuous wave Doppler is useful for measuring faster flow velocities.
- E. Color Doppler simplifies accurate diagnosis and delineation of ductal patency. It also enables identification of tricuspid regurgitation and patency of the foramen ovale, as well as the direction of flow. Flow velocity measurement is possible when used in conjunction with continuous or pulsed wave Doppler. It is used to measure ductal dimension.

VI. Indications for echocardiographic assessment

- A. Suspected congenital heart disease
- B. Suspected persistent pulmonary hypertension
- C. Suspected patent ductus arteriosus (60% patency <28 weeks’ gestation)
- D. Hypotension or shock
- E. Asphyxia
- F. Suspected cardiac dysfunction
- G. Use of high PEEP
- H. High-frequency oscillatory ventilation

VII. Cardiac function

- A. Depressed ventricular function may occur in neonatal disease processes, such as hypoxia, sepsis, hemolytic disease, hyaline membrane disease (RDS), persistent pulmonary hypertension, and transient tachypnea.
- B. Half of premature babies who develop hypotension have cardiac dysfunction in the first 24 h of life. A dysfunctional heart may be tachycardic, bradycardic, or have a normal rate.
- C. In hypotensive newborns, cardiac function may be depressed, normal, or even hyperdynamic.

VIII. Left ventricular assessment

- A. Cross-sectional and M-mode assessment.
- B. Cross-sectional echocardiography permits accurate positioning of the M-mode beam just at the mitral leaflet tips in the long axis (parasternal, Fig. 23.1) or centered in the short-axis parasternal views (Fig. 23.2) of the left ventricle. Measurements must be taken from standard and reproducible positions; otherwise, increased variability will obscure the results.
- C. On the M-mode picture (Fig. 23.6), the interventricular septal (IVS), left ventricular internal diameter (LVID), and posterior wall dimensions are measured at end-systole (S) and end-diastole (D). From these measurements, several parameters of ventricular function can be calculated.
- D. The apical four-chamber view (Fig. 23.4) allows subjective assessment of both left and right ventricular function. This can be appreciated without

taking the measurements above. It is useful in understanding clinical situations and taking a logical approach. However, it is much less helpful in monitoring the response to treatment.

1. Fractional shortening characterizes left ventricular contractility, although it is also affected by preload and afterload.

$$\text{Fractional shortening (\%)} = \frac{\text{LVIDD} - \text{LVIDS}}{\text{LVIDD}} \cdot 100\%.$$

Normal ranges
25–45% Adults
25–41% Term babies
23–40% Preterm babies

Errors in fractional shortening estimation may occur in early preterm life from distortion of the left ventricle and abnormal septal motion. Fractional shortening cannot be measured if there is paradoxical septal motion.

2. Circumferential fiber shortening: Mean velocity of circumferential fiber shortening (VCF) has been suggested as a simple alternative measurement of left ventricular contractility. It is less sensitive to minor dimensional discrepancies and involves no assumptions about ventricular shape, offering a reproducible measurement of neonatal ventricular contractility.

To calculate VCF, LVIDD and LVIDS are measured as above, but ejection time is measured from the time of mitral valve closure to the onset of mitral valve opening.

$$\text{VCF} = \frac{\text{LVIDD} - \text{LVIDS}}{\text{LVIDD}} \cdot \text{Ejection time}.$$

The units are circumferences per second.

3. Stroke volume
 - a. Stroke volume (SV) measurement assumes an ellipsoidal ventricle. This is a reasonable assumption in adults but less so in neonates. Using measurements of LVID in diastole (LVIDD) and systole (LVIDS), the stroke volume can be calculated:

$$\text{SV} = \text{LVIDD}^3 - \text{LVIDS}^3$$

- b. Similarly, a proportion of ventricular contents or ejection fraction (EF) can be calculated:

$$\text{EF} = \frac{\text{Stroke volume}}{\text{End diastolic volume}} = \frac{(\text{LVIDD}^3 - \text{LVIDS}^3)}{\text{LVIDD}^3}.$$

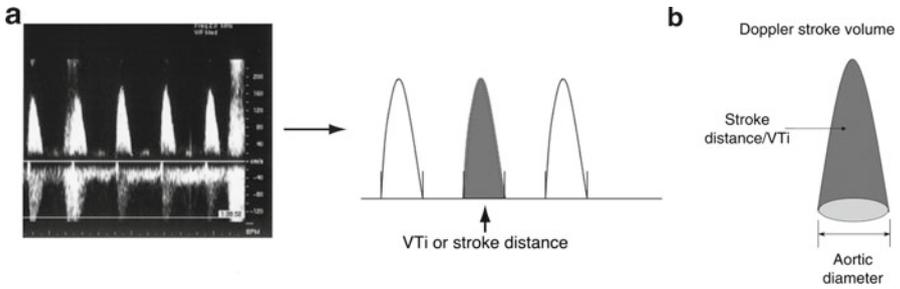


Fig. 23.9 (a) Aortic Doppler trace showing the measurement of the integral of the velocity time curve (VTi) or stroke distance. (b) Calculating stroke volume using the aortic diameter calculated from the diameter

4. Volume load assessment

- a. M-mode assessment of the left ventricle and atrial size provides information about changes in ventricular preload. The ratio of these chambers to the aorta is used to assess the effect of shunts upon the heart, especially the ductus arteriosus.
- b. Normal left atrial:aortic ratio is 0.84 to 1.39 in preterm infants and 0.95 to 1.38 in term infants.
- c. Left atrial:aortic ratio >1.5 suggests volume loading.
- d. Left ventricular internal diastolic diameter:aortic ratio >2:1 suggests ventricular volume loading.
- e. It is important to realize that apparant volume loading may also result from poor contractility in a normovolemic neonate.

IX. Doppler assessment of systolic function

A. Stroke volume: Calculated from the product of the integral of the Doppler velocity–time curve (VTI, also known as stroke distance) (Fig. 23.9a, b) and the cross-sectional area of the aorta derived from the M-mode diameter:

$$SV = VTI \cdot p \frac{\square \text{Aortic diameter} \square^2}{2} \square$$

B. Cardiac output

1. Left ventricular output: Multiplying SV by the heart rate (HR) produces the left ventricular output (LVO)

$$LVO = VTI \cdot p \frac{\square \text{Aortic diameter} \square^2}{2} \square \cdot HR.$$

Note: Minute distance (MD=VTI×HR) is directly related to cardiac output but removes the aortic diameter from the calculation, which is the major source of error. This can be used to assess changes in therapy in an individual.

Normal ranges	
Preterm	221 ± 56 mL/kg/min
Term	236 ± 47 mL/kg/min
Range	158 – 325 mL/kg/min

2. Right ventricular output: In a similar way, right ventricular output (RVO) can be measured. Pulmonary artery diameter is measured in the short-axis pulmonary view (Fig. 23.3). RVO is less affected by ductal shunting; however, the pulmonary artery diameter varies more than the aorta during the cardiac cycle introducing more error into this measurement. The pulmonary VTI is obtained from the pulmonary Doppler velocity–time curve taken in the short-axis view (Fig. 23.3).

$$RVO = VTI \cdot p \frac{\square \text{pulmonary diameter} \square^2}{2 \square} \cdot HR.$$

A useful screening measurement, which can give an indication of RVO in the first 48 h, is the maximum pulmonary velocity taken as above:

$$<0.35 \text{ mps} = \text{RVO likely to be less than } 150 \text{ mL/kg/min}$$

3. Superior vena caval (SVC) flow measurements: SVC flow has been used as representative of systemic flow unaffected by ductal shunting. SVC diameter is measured in a parasternal view; however, it is known that the SVC becomes crescent shaped during the cardiac cycle making accuracy of measurement an issue. SVC VTI is measured from the subcostal view.

$$SVC \text{ (cardiac output)} = VTI \cdot p \frac{\square \text{SVC diameter} \square^2}{2 \square} \cdot HR.$$

A measurement of less than 40 mL/kg/min in the first 24 h of life has been associated with intraventricular hemorrhage and death or disability at 3 years of age.

X. Right ventricular assessment

- A. The normal shape of the right ventricle is more complex than the left.
- B. It consists of inflow, outflow, and apical segments and is wrapped around the left ventricle. This makes quantitative evaluation by M-mode difficult at any age and not useful in the newborn. However, qualitative information about right ventricular systolic function can be obtained by the experienced operator from cross-sectional views.
- C. Paradoxical movement of the intraventricular septum is seen in right ventricular dysfunction. Such movement prevents any assessment of left ventricular fractional shortening.

XI. Doppler assessment of systolic function

One of the most important determinants of right ventricular systolic function in newborns is pulmonary arterial pressure. This can be estimated in several ways.

- A. Tricuspid regurgitation: If present, the most accurate assessment of right ventricular (and therefore pulmonary) pressure is obtained by measuring the velocity of the regurgitant jet (V). Then, assuming right atrial pressure is low, pulmonary pressure = $4V^2$.
- B. Pre-ejection period-to-right ventricular ejection time is related to pulmonary pressure and requires ECG monitoring while echoing the subject. It is useful for assessment of babies with chronic lung disease but difficult to interpret acutely.
- C. Time to peak velocity (TPV)-to-right ventricular ejection time is inversely related to pulmonary pressure but does not require ECG monitoring to measure. A ratio of >0.3 indicates normal pulmonary pressures and <0.2 pulmonary hypertension. Between these two, it is likely that the pulmonary pressure is mildly elevated.
- D. Ductal flow: If the ductus arteriosus is patent, the direction of flow (as well as the pattern) gives an indication of pulmonary pressure (i.e., right-to-left indicates pulmonary $>$ systemic) (Fig. 23.10a–d). However, the velocity of flow cannot accurately predict pulmonary pressure.
- E. Foramen ovale: Right-to-left flow is suggestive of high right-sided pressures or dysfunction. It is seen best in the subcostal view.
- F. Diastolic function: Few studies of diastolic function have been carried out in children or infants. Right ventricular filling is modified by positive pressure ventilation and especially by high positive end-expiratory pressure and oscillatory ventilation.

XII. Assessment of the patent ductus arteriosus (Chap. 73)

- A. The ductus arteriosus is best seen in the parasternal short-axis view (Fig. 23.3), although the suprasternal and subcostal approaches may be needed in babies with overdistended lungs. Color Doppler simplifies identification and allows subjective assessment of flow and velocity. Doppler interrogation of the ductus arteriosus (Fig. 23.8) demonstrates the pattern of flow and the velocity profile. Velocity depends upon both the size of the vessel and the pressure difference between aorta and pulmonary artery. The classical flow pattern associated with a large shunt is high in systole and low in diastole. The size can be estimated in cross-sectional view in relation to the branch pulmonary arteries or aorta.
- B. Ductal diameter can be assessed by measuring the narrowest waist of the ductal color flow when the picture is frozen. Ensure maximal color Doppler scale, optimize the color gain, and measure. In some units, this is used to predict which ducts are likely to be significant and require treatment. Diameter >1.5 mm in the first 30 h has an 83% sensitivity and a 90% specificity for needing treatment.

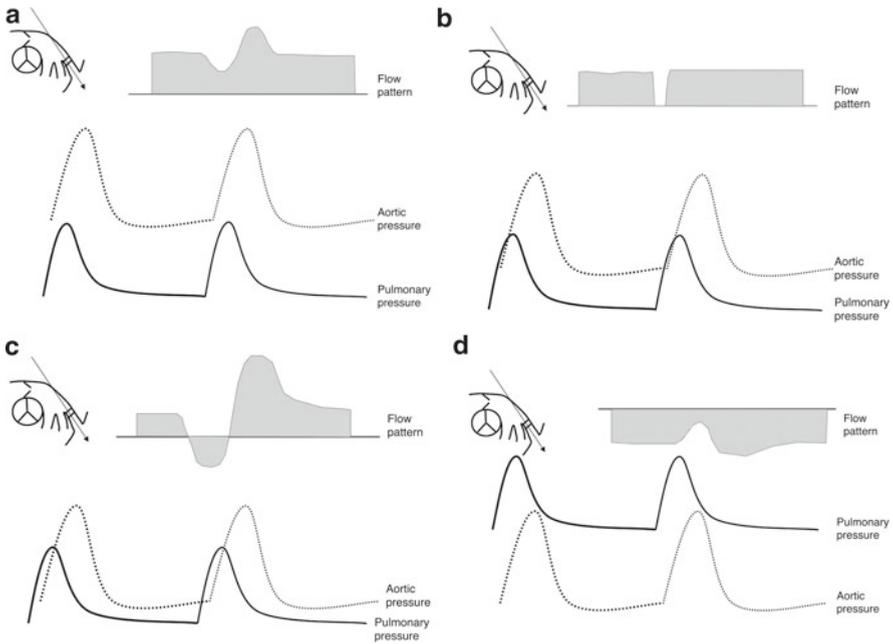


Fig. 23.10 Ductal flow patterns associated with differing systemic and pulmonary pressures (a) Aortic > pulmonary pressure. (b) Pulmonary = aortic pressure in early systole. (c) Bidirectional flow with pulmonary > aortic pressure in early systole. (d) Pulmonary > aortic pressure

- C. Measurement of the left atrium:aortic ratio (see above) gives some indication of flow, but may not be accurate if the left atrium decompresses through the foramen ovale. A ratio >1.5 after the first day has a sensitivity of 88% and a specificity of 95%.
- D. A 60% increase in LVO predicts development of a significant PDA.
- E. Echocardiographic evidence of a significant ductus arteriosus precedes clinical evidence. On day 3 of life, it can predict significance with a 100% sensitivity and an 85% specificity.
- F. Assessment of descending aortic or celiac axis diastolic flow beyond ductal insertion.
 1. Normal: Continuous antegrade flow
 2. Abnormal: Absent or reversed diastolic flow

XIII. Accuracy and reproducibility

- A. M-mode measurements have been made using both leading and trailing edges. In measurements of the left ventricle, both leading and trailing edges are used. Intraobserver variability for these measurements ranges from 5% for distances to 10% for calculated volumes. Interobserver variability is greater, ranging from 7 to 25% for volume measurements.

- B. Measurement of the aorta and left atrium by M-mode is more reproducible in newborns if it is made from trailing-to-leading echo edge (i.e., the internal aortic diameter). Accuracy is vital, as a 1-mm error in the measurement of a 10-mm aorta produces a 17% error in cardiac output.
- C. The main sources of error in Doppler measurement are from the site of sampling and the angle of incidence of the Doppler wave. If the angle is less than 15°, the error will be <3%. A further source of error in calculating cardiac output is coronary artery flow, which may cause a 10–15% underestimate in flow.

Suggested Reading

- Evans N, Kluckow M. Early determinants of right and left ventricular output in ventilated preterm infants. *Arch Dis Child*. 1996;74:F88–94.
- Gill AB, Weinding AM. Echocardiographic assessment of cardiac function in shocked very low birthweight infants. *Arch Dis Child*. 1993;68:17–21.
- Hudson I, Houston A, Aitchison T, et al. Reproducibility of measurements of cardiac output in newborn infants by doppler ultrasound. *Arch Dis Child*. 1990;65:15–9.
- Hunt R, Evans N, Reiger I, Kluckow M. Low superior vena cava flow and neurodevelopmental outcome at 3 years in very preterm infants. *J Pediatr*. 2004;145:588–92.
- Kluckow M, Evans NJ. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child*. 2000;82:F188–94.
- Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. *J Pediatr*. 1995;127:774–9.
- Skinner J, Alverson D, Hunter S, editors. *Echocardiography for the neonatologist*. London: Churchill Livingstone; 2000.
- Skinner JR, Boys RJ, Hunter S, Hey EN. Pulmonary and systemic arterial pressure in hyaline membrane disease. *Arch Dis Child*. 1992;67:366–73.

Chapter 24

Bronchoscopy

Neil N. Finer

I. Equipment

- A. Flexible 2.2- or 2.7-mm bronchoscope
- B. Appropriate light source (preferably Xenon)
- C. Optional video camera and recorder
 1. Bronchoscope passes through 2.5- or 3.0-mm ETT.
 2. Optional equipment includes video camera and recorder as well as a microphone (allows determination of the phase of respiration).
 3. 2.2-mm scope does not have suction channel.
- D. Consider use of video laryngoscope to evaluate upper airway
 1. Useful for infants >1 kg
 2. Provides large clear image
 3. Easier to use for inexperienced operators

II. Patient preparation

- A. Suction airway thoroughly.
- B. Medications:
 1. Atropine (0.01 mg/kg) can be used to decrease secretions and block vagal-mediated bradycardia.
 2. Morphine (0.05–0.1 mg/kg) or meperidine (0.5–1.5 mg/kg) may be given for analgesia at least 10–15 min prior to procedure.
 3. For nonintubated patients, apply topical xylocaine to one naris.
 4. For intubated infants, utilize a bronchoscopic adapter on the ETT connector to maintain FiO_2 , airway pressure, and support during procedure.

N.N. Finer, MD (✉)
Pediatrics, Division of Neonatology, San Diego Medical Center, University of California,
402 Dickinson Street MPF 1-140, Hillcrest, San Diego, CA 92103, USA
e-mail: nfiner@ucsd.edu

5. Inject Xylocaine (4–7 mg/kg) at the tip of ETT, using a feeding catheter, 3 min prior to procedure. Suction again just prior to procedure.

C. Follow principles of conscious sedation; monitor continuously.

1. Pulse oximetry
2. Blood pressure, if available
3. Heart rate
4. Respiratory rate

III. Indications: emergent (can be done in under 2 min by experienced operator)

A. Acute/subacute suspected airway obstruction or misplacement

1. Mucus
2. Blood
3. Dislodged ETT, tube in main stem bronchus, usually right sided, esophageal
4. Check ETT position after intubation if infant is unstable

B. Evaluation of airway obstruction in recently extubated baby

C. To perform fiber-optic nasotracheal intubation in conditions with associated airway anomalies:

1. Pierre-Robin
2. Goldenhar, Treacher Collins
3. Other

D. Procedure

1. Premedicate—Use only topical xylocaine and smallest dose of narcotic for fiber-optic intubation; try initially awake following atropine.
2. Provide oxygen using a single nasal cannula or use laryngeal mask.
3. Monitor as above.
4. Have equipment available to secure airway—oral airway, nasopharyngeal tube or endotracheal tube, and/or nasal trumpet to be used to maintain airway patency, and selection of appropriate masks.
5. Slide proper-size nasotracheal tube with proximal connector removed over bronchoscope and lodge at the proximal end of scope.
6. Visualize larynx via nares.
7. Pass bronchoscope through vocal cords to carina during inspiration.
8. Have an assistant hold bronchoscope as straight as possible without pulling back.
9. Slide ETT over scope until in trachea, check position as bronchoscope is withdrawn, remove bronchoscope, and tape tube in place.
10. After taping, recheck ETT position to be approximately 1 cm above carina in 3-kg infant.

IV. Indications: intubated patient

- A. Confirm ETT placement, rule out plug, tracheal narrowing, tracheomalacia
- B. Persistent or recurrent atelectasis or wheezing in an intubated patient
- C. Evaluation of known or suspected tracheo-esophageal fistula
- D. Assist placement of ETT for unilateral lung ventilation or placement of Fogarty catheter for unilateral ventilation for pulmonary interstitial emphysema.

V. Indications: nonintubated patient

- A. Evaluation of stridor, noisy breathing
- B. Evaluation for evidence of reflux—inflammation around upper airway

VI. Practical clinical hints

- A. Take time out to properly identify patient and ensure that consent form is signed.
- B. Examine patient and review procedure with staff. It is essential in patients with a concern for a dysmorphic airway than one evaluates whether there is a cleft palate—best done by digitally palpating the palate.
- C. Always preoxygenate patient and provide continuous oxygen during procedure using a single nasal cannula.
- D. Use either oximeter-audible tone or heart rate monitor-audible tone to be aware of patient status during procedure.
- E. Video camera recording can decrease procedure time.
- F. Consult with pediatric otolaryngologist when findings in doubt, and always for suspect vocal cord lesions or other laryngeal abnormalities.

VII. Common neonatal diagnoses amenable to bronchoscopy (Table 24.1)

Table 24.1 Common neonatal diagnoses amenable to bronchoscopy

Upper airway lesions	Lower airway lesions
Unilateral and bilateral choanal atresia	Tracheomalacia
Laryngomalacia	
Laryngeal dyskinesia	
Subglottic narrowing, secondary to edema, web, stenosis	Bronchomalacia
Vocal cord paralysis, unilateral or bilateral	Tracheal or bronchial granulations, mucus plugs, blood clots (especially in ECMO patients)
Laryngeal hemangioma, cystic hygroma	Obstructed, malpositioned, or dislodged ETT or tracheotomy tube
Laryngeal edema and/or inflammation	
Gastroesophageal reflux	Tracheo-esophageal fistula
Laryngotracheoesophageal cleft	Tracheal stenosis or Web abnormal tracheal anatomy, tracheal bronchus

Suggested Reading

- Berkowitz RG. Neonatal upper airway assessment by awake flexible laryngoscopy. *Ann Otol Rhinol Laryngol.* 1998;107:75–80.
- Bloch ED, Filston HC. A thin fiberoptic bronchoscope as an aid to occlusion of the fistula in infants with tracheoesophageal fistula. *Anesth Analg.* 1988;67:791–3.
- Ellis DS, Potluri PK, O'Flaherty JE, Baum VC. Difficult airway management in the neonate: a simple method of intubating through a laryngeal mask airway. *Paediatr Anaesth.* 1999;9:460–2.
- Etches PC, Finer NN. Use of an ultrathin fiberoptic catheter for neonatal endotracheal tube problem diagnosis. *Crit Care Med.* 1989;17:202.
- Finer NN, Etches PC. Fiberoptic bronchoscopy in the neonate. *Pediatr Pulmonol.* 1989;7:116–20.
- Finer NN, Muzyka D. Flexible endoscopic intubation of the neonate. *Pediatr Pulmonol.* 1992;12(1):1248–51.
- Lee YS, Soong WJ, Jeng MJ, et al. Endotracheal tube position in pediatrics and neonates: comparison between flexible fiberoptic bronchoscopy and chest radiograph. *Zhonghua Yi Xue Za Zhi.* 2002;65:341–4.
- Reeves ST, Burt N, Smith CD. Is it time to reevaluate the airway management of tracheoesophageal fistula? *Anesth Analg.* 1995;81:866–9.
- Rotschild A, Chitayat D, Puterman ML, et al. Optimal positioning of endotracheal tubes for ventilation of preterm infants. *Am J Dis Child.* 1991;145:1007–17.
- Shinwell ES, Higgins RD, Auten RL, Shapiro DL. Fiberoptic bronchoscopy in the treatment of intubated neonates. *Am J Dis Child.* 1989;143:1064–5.
- Vanderhal AL, Berci G, Simmons CF, Hagiike Jr M. A videolaryngoscopy technique for the intubation of the newborn: preliminary report. *Pediatrics.* 2009;124(2):e339–46.
- Vauthy PA, Reddy R. Acute upper airway obstruction in infants and children. Evaluation by the fiberoptic bronchoscope. *Ann Otol Rhinol Laryngol.* 1980;89:417–8.

Part V
Non-invasive Ventilatory Techniques

Chapter 25

Nasal Cannula Therapy

Andrea L. Lampland and Mark C. Mammel

- I. Humidified high-flow nasal cannula (HFNC) to deliver noninvasive, positive-pressure respiratory support
 - A. Continuous positive airway pressure (CPAP) provides noninvasive positive-pressure respiratory support in spontaneously breathing infants with a goal of preventing alveolar collapse and allowing sufficient gas exchange.
 1. Avoidance of intubation and use of nasal CPAP is an effective strategy for treating respiratory distress syndrome.
 2. Early use of nasal CPAP has been associated with decreased incidence of bronchopulmonary dysplasia in premature infants.
 - B. Multiple devices are available. Continuous positive airway pressure (CPAP) provides noninvasive positive-pressure respiratory support in spontaneously breathing infants with a goal of preventing alveolar collapse and allowing sufficient gas exchange. Multiple devices are available through which CPAP can be delivered.
 - C. Nasal cannulas are a common means of providing supplemental oxygen to neonates. However, recent investigations have shown potential for delivering positive distending pressure via nasal cannulas with utilization of higher gas flow rates and larger diameter cannulas.
 1. $\text{Pressure} = \text{flow} \times \text{resistance}$
 2. The term “HFNC” relates to the use of >1 L/min of gas flow, most commonly 2–8 L/min.

A.L. Lampland, MD (✉)

Department of Newborn Medicine, Children’s Hospitals and Clinics of Minnesota – St. Paul,
347 N Smith Ave., Ste. 505, St. Paul, MN 55102, USA
e-mail: lampl002@umn.edu

M.C. Mammel, MD

Department of Newborn Medicine, Children’s Hospitals and Clinics of Minnesota,
University of Minnesota, 347 N Smith Ave, Rm 505, St. Paul, MN 55102, USA

- a. Humidified HFNC systems are commercially available.
 - b. Typically, these prepackaged systems have an internal pressure-limiting mechanism as a safety measure to prevent excessive pressure delivery to the patient; however, the exact pressure limits vary and are different among systems.
3. Closure of the infant's mouth allows more optimal delivery of positive-distending pressure.
- D. Proposed mechanisms of action of humidified HFNC:
1. Flushing of dead space in the nasopharyngeal cavity leading to improved respiratory efficiency
 2. Adequate gas flow reduces inspiratory resistance in the nasopharynx and reduces work of breathing
 3. Heated and humidified air improves pulmonary mechanics and prevents airway water loss and cooling
 4. Delivery of positive-distending pressure
- II. Potential risks and benefits of humidified HFNC
- A. Benefits
1. Avoidance of nasal septal trauma by using small nasal cannula interface
 2. Avoidance of nasal mucosa irritation and decrease in thickened secretions by heating and humidification of air
 3. Studies suggest no significant changes in work of breathing compared to nasal CPAP
 4. Easy to administer and well-tolerated by patients
 5. Allows the care provider easy access to and interaction with the patient with minimal impediments related to the device
 6. Lower cost than nasal CPAP
- B. Limitations and risks
1. Inability to consistently predict the actual level of positive-distending pressure delivered to the patient:
 - a. Improved delivery of continuous positive-distending pressure if infant has mouth closed to minimize leak
 - b. Significant inpatient and interpatient variability of the amount of positive-distending pressure delivered at same gas flow rates because of variable leaks around the nares and mouth as well as differences in patient physiology
 - c. Necessitates the calculation of effective FiO_2 delivery to accurately predict oxygen delivery to the patient
 - d. Nasal cannula oxygen is a blend of the supplemental oxygen delivered by the nasal cannula and of room air inhaled through the mouth and nose

2. HFNC devices direct gas flow straight to the patient:
 - a. Commercially available HFNC systems typically have pressure-limiting controls; however, each system has a different pressure level limit. Some systems do not specifically quantify the upper pressure limit—the pressure above which the pressure-limiting valve opens and deflects direct pressure from the gas flow away from the patient
 - b. Handmade high-flow systems (those not commercially produced) do not have pressure-limiting controls and therefore, the only pressure-limiting “valves” are at the patient, most commonly at the nose and mouth
 - c. Subcutaneous scalp emphysema, pneumo-orbitis, and pneumocephalus have been reported with use of humidified HFNCs
3. Historical data with concern for increased rates of infection, in particular, Gram-negative bacteremia
4. Limited data set with predominance of observational and retrospective studies:
 - a. Very few randomized trials
 - b. Very few studies have directly compared nasal CPAP (standard of care) and varying levels of HFNC within the same population
 - c. Difficult to compare and generalize current data to all neonatal populations secondary to variables related to the type of HFNC that was used (commercially available versus homemade systems), the presence or absence of a pressure-limiting valve, and the diameter of the nasal cannula
 - d. No studies to date with adequate power to assess long-term major clinical and neurodevelopmental outcomes

III. Potential clinical applications

- A. Humidified HFNC to provide positive-distending pressure after extubation
 1. Limited data with very few randomized controlled trials: Data vary with regard to study design, use of different devices and equipment, and unknown severity of patient respiratory status.
 2. Randomized controlled trials:
 - a. Campbell et al. (2006) compared rates of reintubation in preterm infants with birth weight $\leq 1,250$ g who were extubated to nasal CPAP versus humidified HFNC.
 - (1) Extubation failure rates within 7 days were 60% with HFNC and 15% with nasal CPAP
 - (2) Increased oxygen use and more apnea and bradycardia in the babies extubated to humidified HFNC
 - b. Woodhead et al. (2006) compared rates of extubation failure in infants exposed to HFNC versus Vapotherm 2000i®-heated, humidified

HFNC in the first 24 h after extubation. Extubation failure rates were 47% in the HFNC group versus 0% in the Vapotherm group.

- c. Miller and Dowd (2010) compared rates of extubation failure in infants 26–29 weeks of age extubated to either Fisher and Paykel® or Vapotherm HFNC. There were no differences in extubation failure rates.

3. Retrospective studies:

- a. Shoemaker et al. (2007) compared a retrospective cohort of infants <30 weeks' gestation who received nasal CPAP or humidified HFNC within 96 h of birth. Extubation failure was higher in the nasal CPAP group.
- b. Holleman-Duray et al. (2007) compared a retrospective cohort of infants 25–29 weeks' gestation before and after the introduction of an early extubation protocol to Vapotherm; there were no differences in extubation failure rates or oxygen use.

B. Humidified HFNC to prevent apnea of prematurity and increased work of breathing

1. Sreenan et al. (2001) compared stable premature infants in a crossover study of nasal CPAP and humidified HFNC.
 - a. There were no significant differences between the modes with respect to apnea, bradycardia, and desaturation events.
 - b. Infant oxygen requirements were no different between the two modes.
2. Saslow et al. (2006) evaluated the effects of nasal CPAP and Vapotherm HFNC on respiratory parameters and work of breathing indices in a crossover study of stable preterm infants requiring nasal CPAP or HFNC and weighing <2.0 kg at birth. There were no significant differences in work of breathing between the two groups.

Suggested Reading

- Abdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in pre-term infants in associated with prolonged oxygen requirement: a randomized controlled trial. *Early Hum Dev.* 2011;87:205–8.
- Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for preterm infants. *J Perinatol.* 2006;26:546–9.
- Dani C, Pratesi S, Migliori C, Bertini G. High flow nasal cannula therapy as respiratory support in the preterm infant. *Pediatr Pulmonol.* 2009;44:629–34.
- Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respir Med.* 2009;103:1400–5.
- Frizzola M, Miller TL, Rodriguez ME, Zhu Y, Rojas J, Heseck A, Stump A, Shaffer TH, Dysart K. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. *Pediatr Pulmonol.* 2011;46:67–74.

- Holleman-Duray D, Kaupie D, Weiss MG. Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. *J Perinatol.* 2007;27:776–81.
- Jasin LR, Kern S, Thompson S, Walter C, Rone JM, Yohannan MD. Subcutaneous scalp emphysema, pneumo-orbitis, and pneumocephalus in a neonate on high humidity high flow nasal cannula. *J Perinatol.* 2008;28:779–81.
- Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? *Pediatrics.* 2008;121:82–8.
- Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. *J Pediatr.* 2009;154:177–82.
- Miller SM, Dowd SA. High-flow nasal cannula and extubation success in the premature infants: a comparison of two modalities. *J Perinatol.* 2010;30:805–8.
- Saslow JG, Aghai ZH, Nakhla TA, Hart JJ, Lawrysh R, Stahl GE, Pyon KH. Work of breathing using high-flow nasal cannula in preterm infants. *J Perinatol.* 2006;26:476–80.
- Shoemaker MT, Pierce MR, Yoder BA, DiGeronimo RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. *J Perinatol.* 2007;27:85–91.
- Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics.* 2001;107:1081–3.
- Wilkinson D, Andersen C, O'Donnell CPF, De Paoli AG (2011) High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database of Syst Rev* (5): CD006405.
- Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal intubation: a prospective, randomized, masked cross-over trial. *J Perinatol.* 2006;26:481–5.

Chapter 26

Continuous Positive Airway Pressure

Colin J. Morley

I. Definitions

- A. Continuous positive airway pressure (CPAP) is positive pressure applied to the airways of a spontaneously breathing baby throughout the respiratory cycle.
- B. Positive end-expiratory pressure (PEEP) is pressure applied to the airways through an endotracheal tube during positive-pressure mechanical ventilation during the expiratory phase of ventilation (see Chap. 28).
- C. CPAP and PEEP are used to treat babies with acute respiratory difficulty, mainly premature infants with RDS. In particular, they are used to facilitate the formation of a functional residual capacity (FRC) at birth, then maintain lung volume, and improve oxygenation. CPAP is also used to treat premature infants with apnea or airway obstruction.

II. CPAP and PEEP are needed to support the airways and avoid alveolar collapse to below FRC for the following reasons

- A. The full-term newborn baby normally maintains a small positive end-expiratory pressure in the airways in the first few hours and possibly days after birth by slight adduction of the larynx.
- B. The newborn infant with lung disease and a low lung volume has two mechanisms to maintain FRC. First, he/she can breathe fast and shorten the expiratory time to stop the lung from emptying completely. Second, he/she can “grunt” during expiration. During these breaths, the baby inspires rapidly as much as possible, and then closes the larynx to maintain any lung volume that has been achieved. Simultaneously, he/she contracts the abdominal muscles to increase intrathoracic pressure, help clear lung fluid,

C.J. Morley, MB Bchir, DCH, MD, FRCPCH, FRACP (✉)
Neonatal Research, The Royal Women’s Hospital, Melbourne, VIC, Australia
The Rosie Maternity Hospital, Cambridge, UK
e-mail: colin@morleys.net

and prevent the alveoli and airways from collapsing. He/she then opens the larynx slightly and rapidly exhales through a narrowed larynx to maintain pressure in the airway and create the grunting expiration. This can be so forceful that it raises the CPAP pressure if this is being used. If the baby tires, cannot maintain adequate laryngeal tone, or the larynx is bypassed by an endotracheal tube, he/she may rapidly lose FRC and become hypoxic.

- C. Fluid is secreted by the alveolar epithelium before birth and there is as much fluid in the lungs before birth as there is gas after birth. During labor, adrenergic hormones inhibit secretion and promote some fluid absorption. In term infants, the lung fluid leaves the air spaces soon after birth. Inflation of the lungs moves the liquid from the lung lumen into distensible perivascular spaces and away from the sites of gas exchange. The postnatal clearance of lung liquid is slower after premature birth and after cesarean delivery. The premature lung may even continue to secrete fluid into the alveoli adding to the problems of maintaining alveolar patency. Elevated left atrial pressure and low plasma protein concentration also slow the rate at which lung liquid is removed from potential air spaces. This means that the very premature infant has considerable difficulty producing and maintaining FRC. This problem can be helped by CPAP or PEEP.
- D. The newborn lung has an FRC that is close to airway closing volume. Premature babies may have to work hard with each breath to maintain lung volume. This can be helped by CPAP or PEEP.
- E. Term infants generate large, negative pressures (up to -80 cm H_2O) with the first few breaths to open the lung. Very premature infants are not able to exert as much negative pressure because they are not strong enough to expand their stiff, surfactant-deficient, fluid-filled lungs, and their chest wall retracts with each inspiration.
- F. The upper airway in the term infant is supported by a fat, laden, superficial fascia and also actively held open by the pharyngeal muscles. In the premature infant, the pharynx is not as well-stabilized and is more likely to collapse. Pharyngeal closure or narrowing can occur with relatively small changes in airway pressure. If the infant has large, negative pharyngeal pressure during inspiration, this may collapse the extrathoracic airway. Infants with periodic breathing easily develop obstruction of the pharynx, which is reversible by CPAP.
- G. The premature infant has an immature lung structure with a relatively undeveloped internal architecture to maintain lung volume so that it is not held open by internal support. The immature lung also has thicker and fewer alveolar septa. This reduces gas exchange.
- H. The newborn's chest wall is very compliant, probably five times more than the normal lung tissue. The chest wall of the premature baby is so soft and flexible that it is incapable of holding the lung open during excessive inspiratory efforts, and contraction of the diaphragm and the negative pressure generated distort the chest wall and reduce tidal volume.
- I. The round shape of the premature infant's chest wall with horizontal ribs also reduces the potential for lung expansion. The diaphragm of the preterm

infant is relatively flat and potentially less effective. During REM sleep, there is loss of intercostal muscle activity. This destabilizes the chest wall so that rib cage and abdominal respiratory movements are out of phase. This results in a further loss of end-expiratory lung volume. Atelectasis and airway closure develop easily, especially considering the relative paucity of collateral ventilation channels in the newborn.

- J. Premature babies often have a patent ductus arteriosus (PDA) (Chap. 73). If they have a high pulmonary artery pressure, blood is shunted away from the lungs through the ductus arteriosus. As the pulmonary artery pressure falls, the ductus arteriosus shunts extra blood from the aorta to the pulmonary arteries and lungs on top of the blood flow from the right ventricle. This may increase fluid in the lungs making them less compliant and may predispose to pulmonary edema.
- K. Surfactant in normal lungs has two important functions.
 - 1. It lowers the surface tension and facilitates lung expansion at birth.
 - 2. It “solidifies” on the alveolar surface, increasing the surface pressure, and helps hold the lung open during expiration.
 - 3. Very immature lungs lack adequate surfactant, so they tend to have a low lung volume or even airway collapse during expiration.
 - 4. This results in a further loss of surfactant from the alveolar surface by “squeeze out” as the surface area falls.
- L. The epithelium of repeatedly collapsing lung is easily damaged and plasma proteins exude onto the surface. These compound the problem of inadequate surfactant by inhibiting its function. These proteins form the hyaline membranes seen on the surface of the alveoli in the pathology of RDS.
- M. A decrease in lung volume is associated with inadequate oxygenation, a persistently elevated alveolar-arterial oxygen gradient, and ventilation/perfusion mismatch. Oxygenation is related to the surface area of the lung. If this is reduced, oxygenation is compromised. Carbon dioxide diffuses more easily and elimination is primarily related to minute volume. This can be compromised by low lung volume and atelectasis.
- N. Reduced arterial oxygen availability impairs the respiratory pump, including the diaphragm.

III. How CPAP improves respiratory function

- A. CPAP reduces the chance of upper airway occlusion and decreases upper airway resistance by mechanically splinting it open. It increases the pharyngeal cross-sectional area, reducing upper airway resistance, and decreases genioglossus activity.
- B. CPAP alters the shape of the diaphragm, making it flatter, and increases diaphragmatic activity.
- C. CPAP improves lung compliance and decreases airway resistance in the infant with unstable lung mechanics when the lung is stiff and FRC low. The distending pressure enables a greater tidal volume for a given negative pressure with subsequent reduction in the work of breathing.

- D. For a baby with stiff lungs, CPAP increases the mean airway pressure. The associated increase in FRC improves lung surface area, ventilation/perfusion mismatch, and reduces oxygen requirements.
- E. CPAP increases the radius of curvature of the alveolus, thus decreasing the amount of pressure necessary to overcome surface tension, in accordance with LaPlace's law.
- F. CPAP conserves surfactant on the alveolar surface.
- G. Successful extubation may be more likely to succeed if the baby is treated with nasal CPAP immediately after extubation.

IV. Indications for treating a baby with CPAP

- A. For very preterm babies, CPAP should be started as soon as resuscitation is started to facilitate the early formation of an FRC and thereby improve oxygenation.
- B. Increased work of breathing:
 - 1. Increased respiratory rate, usually more than 60/min, is an indication that the baby is trying to maintain lung volume by shortening the expiratory time.
 - 2. Retractions of the lower ribs and sternum, where the diaphragm is inserted, are an indication of strong diaphragmatic contractions pulling on a compliant chest wall.
 - 3. Grunting expiration results from the baby trying to maintain positive pressure in the lungs during expiration by adducting the larynx during active expiration.
- C. The need for increased inspired oxygen: This is a good sign of low lung volume.
- D. A chest radiograph showing inadequately expanded or infiltrated lung fields, atelectasis, or pulmonary edema.
- E. Recurrent apnea of prematurity.
- F. Recent extubation from ventilation in a preterm baby.
- G. Tracheomalacia or abnormalities of the airways predisposing to airway collapse.

V. How to administer CPAP

- A. The following devices have been used:
 - 1. Face mask:
 - a. This can provide positive pressure throughout the respiratory cycle and has the benefit of no loss of pressure through the mouth. It can be very useful for giving CPAP immediately after birth.
 - b. A face mask has several problems when used long term.
 - (1) It is difficult to get a good seal without excessive pressure on the baby's face.

- (2) The mask has to be removed, and the pressure is lost, when the mouth and nose are cleared by suction.
- (3) It is difficult to have a nasogastric or orogastric tube because of the difficulty with then forming a seal when the tube is in place.

2. Head box with a neck seal:

- a. This was one of the original methods, devised by Gregory.
- b. It was a special head box that sealed around the neck and preset pop-off valves to control the pressure.
- c. It had many problems.
 - (1) It was difficult to get a good neck seal.
 - (2) There was very limited access to the baby's face.
 - (3) Any attention to the baby's face caused a loss of pressure.
 - (4) There was a high flow of gas cooling the baby's head.
 - (5) It was very noisy.

3. Negative-pressure box:

- a. Various types were designed. None are in use now.
- b. A cuirass encircled the chest and abdomen with a tight fit at the top and bottom. It maintained a negative pressure outside the chest to help resist forces causing lung collapse.
- c. Although effective, it had many practical problems.
 - (1) It was difficult to get a good seal.
 - (2) There was poor access to the baby's body.
 - (3) Any attention to the baby's body caused a loss of pressure.
 - (4) There was a high flow of gas cooling the baby.

B. The following devices are commonly used for delivering CPAP because they are easier to use, associated with fewer complications, and are more effective.

1. Short binasal prongs:

- a. This is the most satisfactory (or least unsatisfactory) method of delivering CPAP.
- b. Nasal CPAP is delivered through binasal prongs.
 - (1) Short prongs are inserted into the nostrils and attached to a device for delivering CPAP.
 - (2) Binasal prongs are more effective at delivering CPAP than a long, single prong.
 - (3) A binasal device with a "fluidic flip" when the baby exhales through the device is said to reduce the work of breathing, but there are few clinical data to substantiate superiority over other devices and there is no evidence that babies on binasal CPAP exhale through the device unless their mouth and nose are held closed.

2. A single nasal prong:
 - a. A single prong can be short, inserted into the nostril about 1.5 cm or inserted deep into the pharynx.
 - b. This can be an ETT cut down to about 5 cm long and fixed about 1 cm into the nostril.
 - c. It has higher resistance than binasal prongs.
3. Long nasopharyngeal prongs:
 - a. Long nasal prongs have a higher resistance than short prongs and some of applied pressure is lost.
 - b. They are more likely to become blocked by secretions.
4. Nasal mask:
 - a. This can be effective but is difficult to attach to the baby and get a good seal without undue pressure.
 - b. Several different models are available.
 - c. They can cause damage to the nasal bridge.
5. Endotracheal tube:
 - a. An ETT should not be used solely for the purpose of delivering CPAP because the resistance increases the baby's work of breathing.
 - b. Endotracheal CPAP may be used for a short while, just before extubation, to investigate how well the baby can breathe when extubation is considered.

VI. What CPAP pressures can be used?

- A. As each baby's respiratory problems are unique, the level of CPAP required needs to be individualized and should be altered to suit the baby's problems as they change. Using one pressure for all babies with different problems is common but not appropriate.
 1. Immediately after birth, a pressure of at least 5 cm H₂O is required and up to 8 cm H₂O may be more effective.
 2. If an infant has stiff lungs or low lung volume, increasing CPAP improves oxygenation. Some babies with very stiff lungs may need a higher pressure. However, if the pressure is too high in a baby with compliant lungs, overdistension may occur and oxygenation may be compromised. The maximum pressure is not known but is probably at least 10 cm H₂O for a baby with stiff lungs.
 3. Increasing CPAP may increase PaCO₂ if the pressure is too high and lungs are compliant. There may be a trade-off between improving the oxygenation and increasing the PaCO₂. Also, if a baby with highly compliant lungs is treated with CPAP and the PaCO₂ levels are high, reducing the pressure may improve the PaCO₂.

B. Ways to determine the appropriate level of CPAP:

1. Look at the chest radiograph. Do the lungs look consolidated, atelectatic, edematous, or are they well- or overexpanded? Higher or lower pressures may be required depending on the problem seen.
2. Observe the baby's chest. If the baby is retracting, tachypneic, or grunting, a higher pressure is likely to be needed.
3. If oxygenation is the main problem, it will probably improve if the pressure is increased.
4. If carbon dioxide retention is the main problem, this may be secondary to overinflation from too high a pressure. Consider reducing the pressure, but look at a chest radiograph first.
5. Start CPAP at 4–5 cm H₂O and gradually increase up to 10 cm H₂O as required to improve oxygenation and stabilize the chest wall while maintaining appropriate gas exchange [pH > 7.25 and PaCO₂ < 60 torr (8 kPa)].

VII. Use of CPAP postextubation

- A. Several studies have shown that very premature babies breathe and oxygenate better and are less likely to need reintubation, particularly if they were ventilated for RDS and if they are treated with a nasal CPAP pressure of at least 5 cm H₂O immediately after extubation. This may be because the larynx has been stretched, edematous, and not functioning properly during the few hours after extubation.
- B. Alternatively, CPAP helps to maintain airway patency and alveolar distention and lower the work of breathing.

VIII. Prophylactic CPAP for very preterm babies from birth

- A. Historical, cohort, and randomized controlled trials have shown that many very preterm babies can be successfully started on nasal CPAP from birth and do not need to be intubated, ventilated, and treated with surfactant.
- B. The proportion that succeeds depends upon the gestational age of the infant, the CPAP failure criteria defined, and the experience of the staff.
- C. The outcomes for the babies started on CPAP are similar to babies electively intubated at birth.

IX. When CPAP should not be used?

- A. If a baby is persistently or frequently apneic and bradycardic, he should be intubated and ventilated.
- B. If the baby has respiratory failure—inability to maintain a normal PaCO₂: Intubation and ventilation are required if the PaCO₂ is high and rising; PaCO₂ > 60 torr (8 kPa) and pH < 7.25.
- C. Upper airway abnormalities (cleft palate, choanal atresia, tracheoesophageal fistula).
- D. Severe cardiovascular instability.

X. Hazards/complications of CPAP

- A. Obstruction of the nose or nasal tubes with secretions, so the baby can only breathe through the mouth and does not receive the CPAP pressure.
- B. CPAP applied to a compliant lung may cause overdistension of the lung and reduce the tidal volume. It may also lead to:
 - 1. Air leaks
 - 2. CO₂ retention
 - 3. Hypoxia
 - 4. Increased work of breathing
 - 5. Impedance of pulmonary blood flow with subsequent increased pulmonary vascular resistance and decreased cardiac output
 - 6. Gastric distension (not a big problem as long as the baby has an oro-gastric tube, left open to atmosphere, and any residual gas is aspirated regularly); concern about gastric distension from gas is not a reason to withhold enteral feeding
 - 7. Nasal irritation, damage to the septum, mucosal damage, and possibly sepsis
 - 8. Skin irritation and necrosis or infection of the face from the fixation devices
 - 9. Failure of the disconnect alarms because of the increased resistance in the tube or obstruction in the tubes continuing to measure a high pressure
 - 10. The CPAP device falling out of the nose

XI. Weaning babies from CPAP

- A. There is no good evidence to inform how long CPAP should be used.
- B. The pressure required and the length of time it is used have to be determined by observing the baby and clinical experience.
 - 1. A baby, who is not having apneic or bradycardic episodes, requires a low inspired oxygen concentration and is on a CPAP pressure of 5 cm H₂O or less can be tried without CPAP. It is a matter of trial and error to see how he/she manages.
 - 2. Conversely, a baby who requires a high level of inspired oxygen and is clinically unstable will probably benefit from continuing with CPAP.
- C. Some babies appear to be able to breathe well without CPAP but then tire after a few hours, their FiO₂ increases, and apnea and bradycardia occur.

Suggested Reading

- Alex CG, Aronson RM, Onal E, Lopata M. Effects of continuous positive airway pressure on upper airway and respiratory muscle activity. *J Appl Physiol.* 1987;62(5):2026–30.
- Ammari A, Suri M, Milisavljevic V, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr.* 2005;147:341–7.
- Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birthweight infants preventable? A survey of 8 centres. *Pediatrics.* 1987;79:26–30.
- Buckmaster AG, Arnolda G, Wright IM, Foster JP, Henderson-Smart DJ. Continuous positive airway pressure therapy for infants with respiratory distress in non tertiary care centers: a randomized, controlled trial. *Pediatrics.* 2007;120:509–18.
- Davis P, Davies M, Faber B. A randomised controlled trial of two methods of delivering nasal continuous positive airway pressure after extubation to infants weighing less than 1000 g: binasal (Hudson) versus single nasal prongs. *Arch Dis Child Fetal Neonatal Ed.* 2001;85(2):F82–5.
- Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev.* 2003;2:CD000143.
- De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. *J Paediatr Child Health.* 2001;37(2):161–7.
- De Paoli A, Davis P, Faber B, Morley C. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database Syst Rev.* 2008;1:CD002977.
- De Paoli AG, Morley CJ, Davis PG, Lau R, Hingeley E. In vitro comparison of nasal continuous positive airway pressure devices for neonates. *Arch Dis Child Fetal Neonatal Ed.* 2002;87(1):F42–5.
- Elgellab A, Riou Y, Abbazine A, et al. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. *Intensive Care Med.* 2001;27(11):1782–7.
- Fanaroff AA, Cha CC, Sosa R, Crumrine RS, Klaus MH. Controlled trial of continuous negative external pressure in the treatment of severe respiratory distress syndrome. *J Pediatr.* 1973;82(6):921–8.
- Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med.* 2010;362(21):1970–9.
- Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. *Eur J Pediatr.* 1997;156(5):384–8.
- Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. *N Engl J Med.* 1971;284(24):1333–40.
- Gupta S, Sinha SK, Tin W, Donn SM. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus Infant Flow Driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. *J Pediatr.* 2009;154(5):645–50.
- Kamlin CO, Davis PG, Morley CJ. Predicting successful extubation of very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed.* 2006;91:F180–3.
- Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med.* 2008;358(7):700–8.
- Morley CJ, Davis PG. Continuous positive airway pressure: scientific and clinical rationale. *Curr Opin Pediatr.* 2008;20:119–24.
- Polin RA, Sahni R. Newer experience with CPAP. *Semin Neonatol.* 2002;7(5):379–89.
- Robertson NJ, McCarthy LS, Hamilton PA, Moss AL. Nasal deformities resulting from flow driver continuous positive airway pressure. *Arch Dis Child Fetal Neonatal Ed.* 1996;75(3):F209–12.

- Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics*. 2009;123(1):137–42.
- Sandri F, Ancora G, Lanzoni A, et al. Prophylactic nasal continuous positive airways pressure in newborns of 28–31 weeks gestation: multicentre randomised controlled clinical trial. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(5):F394–8.
- Sandri F, Plavka R, Ancora G, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. *Pediatrics*. 2010;125(6):e1402–9.
- Siew ML, Te Pas AB, Wallace MJ, et al. Positive end-expiratory pressure enhances development of a functional residual capacity in preterm rabbits ventilated from birth. *J Appl Physiol*. 2009;106:1487–93.
- te Pas AB, Davis PG, Hooper SB, Morley CJ. From liquid to air: breathing after birth. *J Pediatr*. 2008a;152:607–11.
- te Pas AB, Spaans VM, Rijken M, Morley CJ, Walther FJ. Early nasal continuous positive airway pressure and low threshold for intubation in very preterm infants. *Acta Paediatr*. 2008b;97:1049–54.
- Vento M, Cheung PY, Aguar M. The first golden minutes of the extremely-low-gestational-age neonate: a gentle approach. *Neonatology*. 2009;95:286–98.
- Verder H. Nasal CPAP has become an indispensable part of the primary treatment of newborns with respiratory distress syndrome. *Acta Paediatr*. 2007;96:482–4.

Chapter 27

Non-invasive Ventilation

Brigitte Lemyre and Haresh Kirpalani

I. Definition

- A. This chapter covers methods of assisted ventilation without an endotracheal tube in the trachea, and using interfaces either just at the nares alone or sealing the entire nose with a mask. These can deliver positive pressure throughout the respiratory cycle with additional intermittent increases in the airway pressure. This additional intermittent airway pressure can be either synchronized to the patient's own breaths or non-synchronized, depending on the delivery system used.
- B. The terminology used for non-invasive ventilation can be confusing. When non-invasive ventilation is provided via a conventional ventilator, it usually delivers short (0.3–0.5 s) but high (20–25 cm H₂O) peak pressure, similar to a ventilator breath.
- C. The following abbreviations denote commonly used synonyms:
 - 1. Nasal ventilation (NV)
 - 2. Nasal intermittent mandatory ventilation (NIMV)
 - 3. Nasal intermittent positive pressure ventilation (NIPPV)
- D. The term NIPPV is used here.
- E. The mode can be synchronized or not. When synchronized, it is prefaced with an “s,” as synchronized NIPPV (sNIPPV).

B. Lemyre, MD, FRCP
University of Ottawa, Division of Neonatology, Department of Pediatrics,
Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON, K1H 8L1 Canada
e-mail: blemyre@toh.on.ca

H. Kirpalani, BM, MRCP, FRCP, MSc (✉)
The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine,
34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA
e-mail: kirpalanih@email.chop.edu

- F. Other devices (Infant Flow, SiPAP) are designed to provide positive pressure throughout the respiratory cycle by alternating between a higher pressure and a lower pressure. In these systems, the duration of the higher pressure is longer (0.5–1.0 s) and the peak pressures are lower (12–15 cm H₂O) than those with modalities described above, which are provided via a ventilator. Patients can breathe at both levels of pressure.
1. Bi-level is used here to refer to non-invasive ventilation delivered via such a device.
 2. Bi-level positive airway pressure (BiPAP).
 3. These biphasic devices are usually operated in a synchronized mode (although they have not yet been approved for use in the USA with the synchronizing device).
- G. In experimental animals, nasal high frequency decreases alveolar damage, showing improved histological appearance compared to intubated ventilated animals. Nasal high-frequency oscillation (HFO) at the nares was first reported in the 1980s and more recently in small series. All reports show efficacy in CO₂ removal but have not yet been adequately tested in randomized trials, although one is in progress now (NCT01277874). One small pilot study showed short-term efficacy with nasal percussive high frequency. Therefore, HFO modes have potential, but are not discussed further for lack of data.

II. Likely physiological mechanism underlying putative benefits of NIPPV

- A. Both continuous positive airway pressure (CPAP) and NIPPV or bi-level may exert benefit by reducing the fatigue resulting from the floppy chest wall of preterm infants. All three also splint the upper airway and reduce obstruction. In summary, they expand the lung, increase functional residual capacity, prevent alveolar collapse, and improve ventilation–perfusion mismatch.
- B. sNIPPV results in a higher tidal volume over nCPAP breaths and non-synchronized NIPPV. Increases in tidal volume possibly result from stimulation of the upper airway.
- C. All forms of nasal ventilation also provide additional positive pressure breaths. These provide slightly higher mean airway pressure and higher tidal volumes. Whether synchronized or not, they reduce thoraco-abdominal asynchrony and improve chest wall stabilization, resulting in a decreased work of breathing. These effects have been shown particularly with synchronized nasal ventilation.

III. Current state of evidence

- A. NIPPV was first tested in an RCT in 1970; however, its use was limited by poor interfaces leading to unacceptable rates of complications, including facial edema and gastrointestinal dilatation.
- B. Modern usage with new silastic interfaces has resulted in a much easier application, with a far less adverse event rate.

- C. The present randomized data, as summarized in the Cochrane review, date from 2002 and need revision. However, although those data suggest benefit in prevention of extubation failure, there are insufficient data to support use in apnea of prematurity or prevention of BPD.
- D. In considering the new trials to date, they also do not unequivocally answer several outstanding questions:
 1. Is synchronization superior for post-extubation, primary mode, or treatment of apnea of prematurity?
 2. Are bi-level devices comparable to NIPPV delivered via a ventilator for important short-term outcomes (failure of extubation, prevention of intubation)?
 3. Are clinically important outcome variables (mortality and bronchopulmonary dysplasia (BPD)) improved with the use of NIPPV or bi-level devices?
- E. In addition, one large retrospective study appears to show clinically important reductions in BPD and neurodevelopmental impairment at age 18 months from the use of sNIPPV; however, these findings were puzzlingly only present in one subgroup of infants (BW 500–750 g). The methodological limitations of this study prevent firm conclusions.
- F. A large, multicenter, international, randomized controlled trial is currently nearing completion, and yield more data (ClinicalTrials.gov Number: NCT00433212). In this trial, infants <1,000 g were randomized to nasal ventilation (via a ventilator or bi-level) or nCPAP, either as a primary mode or post-extubation. The outcome is death or moderate/severe BPD at 36 weeks' corrected gestational age.

IV. How can non-invasive ventilation be delivered?

- A. Nasal interface: Airflow may be delivered by nasal prongs, which can be short (tip in the nose) or long (tip in the nasopharynx), single or bi-nasal, or can be delivered via a nasal mask. If using prongs, short prongs are advocated. Effectiveness—and safety—critically depends upon methods of fixation. Nursing care and minimization of loose fittings with infant head movements are critical (see [Squires AJ](#) and [Hyndman M](#)). It is imperative to avoid movement of the tubing, which can be minimized by anchoring it to the cheek. It is also key to make sure that there is appropriate fit to the nares.
- B. As discussed above, non-invasive ventilation can be delivered in a synchronized or non-synchronized fashion. The advantage of synchronization is theoretical, as no trial has compared the modes yet. Also, using standardized scoring assessments, it has been shown to lead to more discomfort to the baby. Non-synchronized nasal ventilation can be delivered using any ventilator, making it a potentially simple tool.
- C. Synchronized nasal ventilation can be delivered by some ventilators with specific triggering devices. The devices are pneumatic capsules that are

used to detect abdominal movement at the start of inspiration. These, however, have significant trigger delays and are known to be unreliable. Many early studies reported data using this type of device. The availability of sNIPPV has decreased in North America. Newer devices, available in some European countries, are able to trigger using airway-derived flow signals, but are not available in North America as of now.

V. Indications for use

- A. Post-extubation: Five randomized controlled trials have compared nasal ventilation to CPAP after extubation in premature infants. Three used synchronized devices (Infant Star[®]). A meta-analysis of these trials demonstrated a reduction in extubation failure (NNT=3). One small trial used a non-synchronized device and could not demonstrate a reduction in extubation failure. One last unpublished trial used a bi-level device (SiPAP) to provide nasal ventilation and found no benefit in reducing extubation failures.
- B. Apnea of prematurity: Three studies compared CPAP with nasal ventilation (non-synchronized) for the treatment of apnea of prematurity. Trials were short term (hours) and results were conflicting. It is not clear whether NIPPV reduces the frequency of apnea more effectively than nCPAP. However, in post-extubation studies, the reason for reintubation in the nCPAP group was mostly apnea of prematurity, which was reduced in the NIPPV group.
- C. Primary mode of ventilation for respiratory distress syndrome: Four randomized controlled trials, with 448 patients, recently examined this question. All used non-synchronized nasal ventilation delivered via a ventilator. The primary outcome was failure of non-invasive respiratory support with need for intubation (4 h to 1 week). Two trials found no difference between treatment approaches while the other two found less treatment failure with NIPPV.

VI. Settings

- A. The settings depend on the device used and the clinical indication.
 1. In post-extubation trials, settings similar to those on the ventilator just prior to extubation were used. These included rates of 20–30/min, PEEP 5–6 cm H₂O, and peak inspiratory pressures of 16–18 cm H₂O.
 2. Settings for infants with RDS included PIP up to 22 cm H₂O and rates up to 50/min. Inspiratory times varied between 0.3 and 0.5 s.
 3. For apnea of prematurity, settings are generally lower, as lungs are healthier. PIP 10–14 cm H₂O, PEEP of 4–6 cm H₂O, and rates of 20/min.
- B. Bi-level devices cannot achieve such levels of PIP and also require longer inspiratory times. Usually, a T_1 of 0.5–1.0 s is required and PIP is set at 3–4 cm H₂O above PEEP. Rate can start at 10–40/min.

VII. Putative Benefits

- A. Avoidance of reintubation, when used immediately after extubation: This was found consistently in devices providing synchronized nasal ventilation.
- B. Reduction in post-extubation apnea has not been so convincingly shown.
- C. Prevention of intubation in RDS.
- D. Possible reduction in BPD (post-extubation and primary-mode trials).

VIII. Potential complications

- A. Abdominal distention from flow delivered preferentially to the stomach (mainly seen in earlier studies).
- B. Gastric perforation: There was an association between the use of NIPPV and gastric perforation in a case–control study. NIPPV was being used as a primary mode of ventilation for RDS and delivered via a face mask in older interfaces. None of the subsequent randomized controlled trials with newer interfaces has reported this complication.
- C. Pneumothorax or other air leaks (none have been reported in randomized trials to date).
- D. Nasal erosion and injuries may result from the prongs or nasal mask, but this is equally true for nCPAP. Again, nursing care and minimization of movement of the interface are crucial.

Suggested Reading

- Barrington KJ, Bull D, Finer NN. Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. *Pediatrics*. 2001;107:638.
- Bhandari V. Nasal intermittent positive pressure ventilation in the newborn: review of literature and evidence-based guidelines. *J Perinatol*. 2010;30(8):505.
- Bhandari V, Finer NN, Ehrenkranz RA, Saha S, Das A, Walsh MC, Engle WA, VanMeurs KP, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Synchronized nasal intermittent positive-pressure ventilation and neonatal outcomes. *Pediatrics*. 2009;124(2):517–26.
- Bisceglia M, Belcastro V, Poerio F, Raimondi I, Mesurace C, Crugliano C, Pio CU. A comparison of nasal intermittent versus continuous pressure delivery for the treatment of moderate respiratory syndrome in preterm infants. *Minerva Pediatr*. 2007;59(2):91.
- Chang HY, Claire N, D'urgard C, Torres J, Nwajei P, Bancalari E. Effects of synchronization during nasal ventilation in clinically stable preterm infants. *Pediatr Res*. 2011;69(1):84–9.
- Colaizy TT, Younis UM, Bell EF, Klein JM. Nasal high-frequency ventilation for premature infants. *Acta Paediatr*. 2008;97(11):1518–22.
- Davis PG, Lemyre B, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (nCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev*. 2001;3:CD003212.
- Davis PG, Morley CJ, Owen LS. Non-invasive respiratory support of preterm neonates with respiratory distress: continuous positive airway pressure and nasal intermittent positive pressure ventilation. *Semin Fetal Neonatal Med*. 2009;14:14.

- De Paoli AG, Davis PG, Lemyre B. Nasal continuous positive airway pressure versus nasal intermittent positive pressure ventilation for preterm neonates: a systematic review and meta-analysis. *Acta Paediatr.* 2003;92:70.
- Dumas De La Roque E, Bertrand C, Tandonnet O, Rebola M, Roquand E, Renesme L, Elleau C. Nasal high frequency percussive ventilation versus nasal continuous positive airway pressure in transient tachypnea of the newborn: a pilot randomized controlled trial (NCT00556738). *Pediatr Pulmonol.* 2011;46:218–23.
- Friedlich P, Lecart C, Posen R, et al. A randomized trial of nasopharyngeal synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. *J Perinatol.* 1999;19:413.
- Garland JS, Nelson DB, Rice T, Neu J. Increased risk of gastrointestinal perforations in neonates mechanically ventilated with either face mask or nasal prongs. *Pediatrics.* 1985;76:406.
- Khalaf MN, Brodsky N, Hurley J, Bhandari V. A prospective randomized controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. *Pediatrics.* 2001;108:13.
- Khorana M, Paradevisut H, Sangtawesin V, Kanjanapatanakul W, Chotigeat U, Ayuthaya JKN. A randomized trial of non-synchronized nasopharyngeal intermittent mandatory ventilation (nsNIMV) vs nasal continuous positive airway pressure (NCPAP) in the prevention of extubation failure in preterm <1500 grams. *J Med Assoc Thai.* 2008;91 suppl 3:S136.
- Kiciman NM, Andreasson B, Bernstein G, et al. Thoracoabdominal motion in newborns during ventilation delivered by endotracheal tube or nasal prongs. *Pediatr Pulmonol.* 1998;25:175.
- Kishore MSS, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. *Acta Paediatr.* 2009;98:1412.
- Kugelman A, Fefferkorn I, Riskin A, Chistyakov I, Kaufman B, Bader D. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized controlled prospective study. *J Pediatr.* 2007;150:521.
- Kugelman A, Bar A, Riskin A, Chistyakov I, Mor F, Bader D. Nasal respiratory support in premature infants: short-term physiological effects and comfort assessment. *Acta Paediatr.* 2008;97(5):557–61.
- Lemyre B, Davis PG, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. *Cochrane Database Syst Rev.* 2002;1:CD002272.
- Lin CH, Want ST, Lin YJ, Yeh TF. Efficacy of nasal intermittent positive pressure ventilation in treating apnea of prematurity. *Pediatr Pulmonol.* 1998;26:349.
- Llewellyn MA, Tilak KS, Swyer PR. A controlled trial of ventilation using an oro-nasal mask. *Arch Dis Child.* 1970;45:453–9.
- Meneses J, Bhandari V, Alves JG, Herrmann D. Noninvasive ventilation for respiratory distress syndrome: a randomized controlled trial. *Pediatrics.* 2011;127(2):300.
- Owen LS, Morley CJ, Davis PG. Pressure variation during ventilator generated nasal intermittent positive pressure ventilation in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2010;95(5):F359–64.
- Pantalitschka T, Sievers J, Urschitz MS, Herberts T, Reher C, Poets CF. Randomised crossover trial of four nasal respiratory support systems for apnoea of prematurity in very low birth-weight infants. *Arch Dis Child Fetal Neonatal Ed.* 2009;94:F245.
- Reyburn B, Li M, Metcalfe DB, Kroll NJ, et al. Nasal ventilation alters mesenchymal cell turnover and improves alveolarization in preterm lambs. *Am J Respir Crit Care Med.* 2008;178(4):407–18.
- Ryan CA, Finer NN, Peters KL. Nasal intermittent positive pressure ventilation offers no advantages over nasal continuous positive airway pressure in apnea of prematurity. *Am J Dis Child.* 1989;143:1196.
- Squires AJ, Hyndman M. Prevention of nasal injuries secondary to NCPAP application in the ELBW infant. *Neonatal Netw.* 2009;28(1):13–27.
- van der Hoeven M, Brouwer E, Blanco CE. Nasal high frequency ventilation in neonates with moderate respiratory insufficiency. *Arch Dis Child Fetal Neonatal Ed.* 1998;79(1):F61–3.

Part VI
Ventilatory Modes and Modalities

Chapter 28

Positive End-Expiratory Pressure

Sarvin Ghavam and Haresh Kirpalani

I. Definition

- A. Positive end-expiratory pressure (PEEP) is the pressure applied to the airways and lungs during mechanical ventilation to prevent airway and alveolar collapse at the end of expiration.
- B. PEEP is used for infants with respiratory distress syndrome (RDS) or those infants requiring mechanical ventilation in order to help maintain lung volume and alveolar oxygenation.

II. Available evidence

In infants, thus far, evidence exists largely at the level of physiologic measures, rather than rigorous trials with moderate- or long-term, clinically relevant end points.

- A. Avery showed that preventing alveolar collapse at low lung volumes with PEEP conserved surfactant function.
- B. Bonta used individualized levels of PEEP as measured by transmitted esophageal pressures to obtain optimal lung opening, and this enabled him to maximize PaO₂.
- C. In adult ICUs, large trials optimized PEEP using simple incremental grids in acute respiratory distress syndrome (ARDS). For ARDS in adults, individual meta-analysis shows that higher PEEP strategies (versus lower conventional

S. Ghavam, MD

Department of Neonatology, Children's Hospital of Philadelphia,
3401 Civic Center Drive, Philadelphia, PA 19104, USA

H. Kirpalani, BM, MRCP, FRCP, MSc (✉)

The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine,
34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA

e-mail: kirpalanih@email.chop.edu

PEEP strategy) reduced hospital mortality and duration of oxygen support in patients.

- D. A recent Cochrane Review of neonatal studies of PEEP showed insufficient randomized evidence to suggest benefits of “high” vs. “low” levels of PEEP or how to set an appropriate PEEP in neonates.

III. Physiology underlying appropriate use of PEEP

- A. In the first few hours of life, a newborn infant attempts to maintain an open lung by maintaining an end-expiratory lung volume throughout the entire lung and the smaller airways.
- B. Newborn infants initiate PEEP using two mechanisms: First, they increase their rate of ventilation, therefore decreasing the length of time of expiration and alveolar collapse. Secondly, they use the “grunt” at end inspiration: which closes the glottis and prevents loss of functional residual capacity (FRC) before the next breath is initiated. Placing an ETT effectively removes both of these mechanisms.
- C. By raising intra-alveolar pressure, PEEP resists the tendency to develop pulmonary edema, whereby either innate alveolar lung fluid or transudates from high pulmonary blood flow or proinflammatory processes flood the alveolus.
- D. Probably related to this efflux of alveolar fluid and transudates in a sick lung, appropriate PEEP levels in animal studies prevent a proinflammatory state in the lungs.
- E. Because the FRC in premature lungs is close to the airway closing volume, PEEP helps neonates maintain appropriate lung volume.
- F. The chest wall of a premature infant is highly compliant, which has two consequences.
 - 1. It is difficult to stent open the lung, especially during rapid eye movement (REM) sleep.
 - 2. The floppy chest wall raises the work of breathing because of chest wall distortion and “paradoxical” movements of rib cage and abdomen, which add fatigue to an already overworked diaphragm. The diaphragm has a lower efficiency in its attachment to the rib cage than in adults, and the neonatal diaphragm has fewer endurance fibers.
- G. Because the pressure from PEEP is transmitted through the thorax, pressures should be adequate to open closed alveoli, without impeding cardiac function and venous blood return. Fortunately, when the lung is sickest, it is less compliant and thus transmits pressures less to the great veins, being able thus to tolerate higher pressures to be set at the airway.
- H. There is a gradient of “opening” between the superior and inferior parts of a healthy lung, and this is exacerbated during lung injury. It is minimized with appropriate PEEP.

IV. How PEEP helps

- A. PEEP helps maintain open airways and improves lung volume by maintaining FRC at the end of expiration. This helps decrease ventilation–perfusion mismatch and therefore aids in oxygenation.
- B. Improves mean airway pressure in neonates with RDS and stiff lungs.
- C. Overcomes the resistance of the endotracheal tube.
- D. PEEP, therefore, reduces the impact of the compliant chest wall.

V. Indications for PEEP

- A. Always set even a minimal PEEP in any intubated or mechanically ventilated patient. Zero PEEP can cause lung collapse and is deleterious to a neonate’s respiratory status.
- B. Increased work of breathing despite intubation and adequate mechanical ventilation (assessed by blood gases), which maybe manifest as continued tachypnea and retractions.
- C. Decreased lung volume or lung collapse as evidenced by chest radiography findings, which can include “white out-of-the-lung fields,” “haziness,” segmental atelectasis, or inappropriate rib expansion/diaphragmatic placement.
- D. Need for increased oxygen.

VI. How to determine PEEP?

- A. There are no clear neonatal data on how to set PEEP in premature infants.
- B. Setting the best PEEP entails close clinical monitoring of respiratory, gaseous, and cardiovascular parameters outlined below under VII.
- C. Ideally, optimal PEEP would be set by first building a static PV curve and assessing the lower inflection point (LIP), and then setting PEEP 1 cm H₂O above this. Some argue for using the upper inflection point and coming down from that pressure slightly. In either case, both procedures are technically and clinically difficult to perform in clinical practice, even in robust adults. It is also uncertain how many infants with lung disease show a definable inflection point indicating an LIP, with a high interobserver agreement. Finally, but not least, it is clinically difficult to safely construct such a static curve, because at low lung volumes hypoxemia will result and the infant usually needs a skeletal muscle relaxant. To cap it all, it is also unclear whether the dynamic loops available to us now can show this point.
- D. Therefore, many now monitor the improvement of dynamic compliance values as PEEP is adjusted, as obtained from the automated ventilator functions. Anecdotally, this improves as PEEP is increased (recruitment) until there is a flattening of the PV line with consequent fall in compliance (over-recruitment). Alternatively, on machines that measure dynamic compliance, PEEP can be adjusted until the highest compliance is found.
- E. Accepted ranges of PEEP include 4–12 cm H₂O, depending upon the size of infant, severity of lung disease (as indicated by pulmonary compliance, lung volume, oxygen status, and respiratory status of the neonate), and finally blood pressure and peripheral perfusion.

- F. Infants with stiffer lungs (worse RDS) may require higher distending pressures, but there may be detrimental effects from too high a pressure.
- G. Most clinicians begin with PEEP of 4–6 cm H₂O in premature neonates and titrate to 7–8 cm H₂O as needed, based on clinical and radiographic evidence. This is to optimize chest wall expansion and oxygenation.

VII. How to evaluate PEEP?

- A. Monitor clinical status, including respiratory rate, retractions (especially diaphragmatic), and work of breathing. Also monitor the degree to which the chest wall is inflated.
- B. Monitor radiographic evidence of lung inflation - looking for under-inflation (needs higher PEEP to recruit) or over-inflation (air-trapping- needs lowering of PEEP). This, in practice, is the most convenient way to assess adequacy of PEEP as it also allows assessment of the cardiac silhouette for any possible compromise of cardiac output (See E).
- C. Monitor oxygenation status; if increasing oxygen requirements occur, consider increasing PEEP.
- D. Monitor PaCO₂, as hypercapnia (PaCO₂ > 60 torr) may be a sign of overdistention of the lungs. Consider decreasing PEEP in the presence of air trapping and hypercapnia.
- E. Also assess hemodynamic instability with decreasing mean arterial blood pressure as a possible sign of overdistention (high mean airway pressure) and decrease preload to the cardiovascular system. A decrease in PEEP may be warranted. This is also difficult to assess, but current assessments rely on the usually accepted clinical criteria: heart rate with rising tachycardia indicating rate adjustment of cardiac output; temperature of peripheries, or central-peripheral discrepancy. Central venous pressure monitoring might also be helpful, especially as a trend value.
- F. As described above, an ancillary aid is the dynamic compliance value on most ventilators. Beware of inconsistent performance of this parameter, however, depending on what machine is used.

VIII. How is PEEP applied and what to watch?

- A. The ventilator sets PEEP by simply closing an exhalation valve at the required PEEP preset on the ventilator. This is placed on the expiratory limb of the ventilator circuit. Older machines had resistance being spring loaded. Nowadays, the valve is more likely to be electronically set and has relatively short delay times. Springing the valve opposes full emptying of the lung and prevents the lung from full deflation.
- B. Ventilators measure PEEP in two phases; the start value of the measurement corresponds to the set PEEP on the ventilator and the end value is intrinsic PEEP.
- C. Intrinsic PEEP is the actual end-expiratory pressure in the lung. Ideally, this should be at the same level as the set PEEP. However, there is an interaction between the set ventilator parameters and the degree of recoil

of the lung, which decreases as the compliance worsens. This is exemplified on conventional ventilation, where irrespective of the setting, if the inspiratory time (dictating the I:E ratio) is too long or if the respiratory rate is too fast, the lung cannot empty. This is also referred to as inadvertent PEEP. This can be seen in graphic displays as an end-expiratory gas trapping. Too short an expiratory time does not allow for full expiration and “stacking” of ventilator breaths (See “Time Constant,” Chap. 8).

- D. This may become an issue based on the lung compliance and expansion (as seen on chest radiographs) or with babies at risk for air trapping (i.e., meconium aspiration).

IX. Potential hazards

A. Too low PEEP

1. Atelectasis (both segmental and general) based on the amount of PEEP being delivered.
2. Increased oxygen requirement.
3. Tachypnea.
4. Increased work of breathing.

B. Too high PEEP

1. Overdistention of the lungs, with flattening of the diaphragms.
2. Hemodynamic instability, potentially decreased mean arterial blood pressure secondary to decreased venous return.
3. Pneumothorax or air leak syndrome, secondary to poor compliance and high distending pressure in conjunction with surfactant deficiency, common in the premature neonate.

X. Extubation criteria

- A. Most clinicians decrease PEEP with weaning ventilator settings, and consider extubation at PEEP of 5–6 cm H₂O, although a broader range may be acceptable.
- B. As PEEP impacts oxygenation in premature infants, this is a crucial aspect of the weaning process.

Suggested Reading

- Alegroa X. Acute effects of PEEP on tidal volume and respiratory center output during synchronized ventilation in preterm infants. *Pediatr Pulmonol.* 2006;41:759–64.
- Avery ME. Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. *J Appl Physiol.* 1975;38(3):461–6.
- Bamat N, Millar D, Suh S, Kirpalani H. Positive end expiratory pressure for preterm infants requiring CMV for RDS or BPD: a systematic review. *Cochrane Neonatal Database* in press, 2011.
- Bancalari E. Inadvertent positive end-expiratory pressure during mechanical ventilation. *J Pediatr.* 1986;108:567–9.

- Bonta B. Determination of continuous positive airway pressure for the treatment of IRDS by measurement of esophageal pressures. *J Pediatr.* 1977;91(3):449–54.
- Briel M. Higher vs lower positive end expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: syndrome review and meta-analysis. *JAMA.* 2010;303(9):865–73.
- Gattinoni L. Pressure-volume curve of total respiratory system in acute respiratory failure. *Am Rev Respir Dis.* 1987;136:730–6.
- Lachmann B. Open up the lung and keep it open. *Intensive Care Med.* 1992;18:319–21.
- Levy P. A method for studying the static volume-pressure curves of the respiratory system during mechanical ventilation. *J Crit Care.* 1989;4:83–9.
- Marini JJ. Inverse ratio ventilation—Simply an alternative, or something more? *Crit Care Med.* 1995;23:224–8.
- Mehta S. Temporal change, reproducibility, and inter-observer variability in pressure–volume curves in adults with acute lung injury and acute respiratory distress syndrome. *Crit Care Med.* 2003;31:2118–25.
- Monkman S. Positive end-expiratory pressure above the lower inflection point minimized influx of activated neutrophils into lung. *Crit Care Med.* 2004;32(12):2471–5.
- Muscudere JG. Tidal ventilation at low airway pressure can augment lung injury. *Am J Respir Crit Care Med.* 1994;149:1327–34.
- Rider ED. Different ventilation strategies alter surfactant responses in preterm rabbits. *J Appl Physiol.* 1992;73:2089–96.
- Simbruner G. Inadvertent positive end-expiratory pressure in mechanically ventilated newborn infants: Detection and effect on lung mechanics and gas exchange. *J Pediatr.* 1986;108:589–95.
- Stewart TE. Controversies around lung protective mechanical ventilation. *Am J Respir Crit Care Med.* 2002;166:1421–2.
- Wyszogrodski I. Surfactant inactivation by hyperventilation: Conservation by end-expiratory pressure. *J Appl Physiol.* 1975;38:461–6.

Chapter 29

Intermittent Mandatory Ventilation

Steven M. Donn and Sunil K. Sinha

I. Description

A. Definition

1. Intermittent mandatory ventilation (IMV) provides a fixed rate of mechanical ventilation, determined by the clinician, and allows spontaneous breathing between mechanical breaths.
2. This mode may be utilized in the acute care phase (high rates) or the weaning phase (low rates).

B. Characteristics

1. Mandatory breaths occur at fixed intervals determined by the preset breath rate (BR). Total cycle time is the BR (bpm) divided by 60 s/min.
2. With pressure targeting, the mandatory tidal volume (V_T) is determined by the preset pressure limit (PL), flow, and inspiratory time (T_I), as well as the patient's compliance (C_L) and airway resistance (R_{AW}).
3. V_T may not be stable breath to breath, particularly if the patient is breathing asynchronously with the ventilator.
4. The patient may breath spontaneously between mandatory breaths from a flow of gas, with a preset oxygen fraction (FiO_2), provided from the ventilator (continuous and/or demand flow). Spontaneous breaths are

S.M. Donn, MD, FAAP (✉)

Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

S.K. Sinha, MD, PhD, FRCP, FRCPC

Department of Neonatal Medicine, The James Cook University Hospital, University of Durham,
Marton Road, Marton-in-Cleveland, Middlesbrough TS4 3BW, UK
e-mail: sunil.sinha@stees.nhs.uk

supported only by the provided level of positive end-expiratory pressure (PEEP, also known as baseline pressure).

5. The spontaneous BR, V_T , peak flow, and T_1 are determined by the patient.
6. PEEP may be increased to a preset level to enhance the patient's oxygenation.

C. Indications

1. Hypoxemic respiratory failure— $\text{PaO}_2 < 50$ torr (6.7 kPa) while receiving $\text{FiO}_2 \geq 0.5$
2. Hypercapnic respiratory failure— $\text{PaCO}_2 > 60$ torr (8 kPa)
3. Unstable cardiovascular status (bradycardia, hypotension)
4. Impaired respiratory drive (apnea, neurologic impairment)
5. Excessive work of breathing (impaired pulmonary function, airway obstruction)

D. Management of potential complications

1. Overdistension/barotrauma/volutrauma
 - a. If possible, avoid inspiratory pressure (IP) settings above 35 cm H_2O . Wean pressure aggressively.
 - b. The risk of lung injury, as well as intraventricular hemorrhage, in pre-term infants increases when the patient is breathing asynchronously with the ventilator. Consider use of sedation and/or paralytics if synchronized ventilation is not available.
2. Cardiovascular compromise
 - a. The risk increases at mean airway pressures > 15 cm H_2O . Avoid excessive ventilator settings whenever possible.
 - b. Additional medical management of hypotension and/or hypovolemia may be required.
3. Airway complications, including upper airway trauma, endotracheal tube malposition, and tube obstruction from plugging or kinking.
 - a. Endotracheal tubes and ventilator circuits should be firmly secured to avoid excessive movement.
 - b. Lavage and suction should be performed when the physical assessment indicates the need to do so and is most safely accomplished by two people.
4. Oxygen toxicity
 - a. Utilize optimum mean airway pressure and PEEP to improve oxygenation.
 - b. Wean oxygen as quickly as possible.
5. Ventilator-acquired infection
 - a. Infection control policies and procedures should be strictly followed.
 - b. Prophylactic use of antibiotics is a common practice, although of unproven efficacy and potential toxicity.

E. Advantages

1. The clinician-selected rate delivers mechanical breaths at fixed intervals, even if the baby is completely apneic.
2. Useful mode when skeletal muscle relaxants or heavy sedation is required.
3. Easier to avoid inversion of inspiratory:expiratory ratio and gas trapping.

F. Disadvantages

1. May result in significant dyssynchrony between baby and ventilator resulting in wide variability in delivered tidal volumes depending upon whether the baby is breathing *with* the ventilator (large tidal breath), *against* the ventilator (small tidal volume), or somewhere in between.
2. Consequences of dyssynchrony are:
 - a. Inefficient gas exchange
 - b. Gas trapping
 - c. Air leak
 - d. Association with intraventricular hemorrhage

II. Controls, monitors, and alarms

A. Controls

1. Breath rate
 - a. BR adjusts the number of mandatory (i.e., ventilator-controlled breaths) delivered each minute.
 - b. Conventional ventilators typically have a range of zero (CPAP) to 150 breaths per minute (BPM).
 - c. Initial BR is generally between 30 and 60 BPM; however, rates ≥ 60 BPM may be necessary.
2. Inspiratory pressure
 - a. IP adjusts the peak inspiratory pressure applied to the airway during the inspiratory phase. It is the primary determinant of the delivered V_T (i.e., the depth of inspiration).
 - b. Typically, the adjustable range is 3–80 cm H₂O.
 - c. The IP is usually started at the lowest level (e.g., 15–20 cm H₂O) necessary to produce adequate breath sounds and chest excursions and adjusted upward in 1–2 cm H₂O increments.
 - d. If the ventilator system in use has a V_T monitor, IP may be set to achieve a desired V_T based on weight. General rules are 4–6 mL/kg for very low birth weight (VLBW), 5–7 mL/kg for low birth weight (LBW), and 5–8 mL/kg for term infants.
3. Inspiratory time (T_I)
 - a. T_I adjusts the length of time pressure and is applied to the airway during inspiration (i.e., the length of the inspiratory phase).

- b. The adjustable range is typically 0.1–3.0 s.
- c. Initial T_1 generally ranges from 0.3–0.5 s. A shorter T_1 may be required if BR >60 BPM.

4. Flow rate

- a. This control generally has a dual purpose. First, it adjusts the magnitude of flow directed to the airway during the inspiratory phase of each breath. It also determines the flow available for spontaneous breathing between mandatory breaths. Some ventilators automatically adjust the flow available for spontaneous breathing to a value lower than the pre-set inspiratory flow to reduce expiratory resistance.
- b. The range of flow varies among ventilators. The low end is usually 2–3 liters per minute (LPM) with the high end 20–30 LPM, and in some cases up to 40 LPM.
- c. To avoid excessive expiratory resistance, the flow rate should be set to the lowest value that generates the desired IP and produces satisfactory pressure and/or flow waveforms and loops. They are typically 5–8 LPM in preterm infants and up to 10–12 LPM for term infants.

III. Positive end-expiratory pressure (Chap. 28)

- A. PEEP enhances lung volume (FRC) by preventing the collapse of alveoli at end expiration. Increases in PEEP increase mean airway pressure, which correlates with improvement in oxygenation.
- B. The range of PEEP available on most ventilators is 1.0 to 20–25 cm H₂O.
- C. PEEP should be started at moderate levels (4–8 cm H₂O) and increased in 1 cm H₂O increments until the desired effect is achieved. In newborns, PEEP levels higher than 10 cm H₂O are only utilized occasionally.

D. Monitors and alarms.

- 1. The peak inspiratory pressure (PIP) monitor reflects the highest pressure recorded during the inspiratory phase of mandatory breaths. It reflects the IP control setting and, therefore, it usually does not vary breath-to-breath. Some ventilators also have an airway pressure gauge which reflects the dynamic increase and decrease in pressure between the IP and PEEP (ΔP or amplitude).
 - a. The high-pressure alarm, usually set 5–10 cm H₂O above the IP setting, audibly and visually alarms for an increase in airway pressure.
 - b. The low-pressure alarm is generally set 5–10 cm H₂O below the IP. It audibly alarms for a patient circuit leak or disconnection.
 - c. The low PEEP alarm is set 2–3 cm H₂O below the PEEP setting. It also alarms for a patient circuit leak or disconnect.
- 2. The mean airway pressure monitor reflects the average pressure applied over time (i.e., a moving average). This monitor responds to changes in the IP, BR, T_1 , flow, and PEEP settings.

3. In IMV, the BR and T_I monitors reflect the control settings for these parameters. The expiratory time (T_E) and I:E ratio monitors reflect calculated values based on the T_I and BR settings. I:E ratio and T_E are valuable in assessing the risks of gas trapping and inadvertent or auto-PEEP.
4. The apnea alarm reflects decreases in respiratory rate. Often, it is factory preset at 20 s but may be adjustable from 10 s to 2 min on some ventilators.
5. Neonatal ventilators do not always include an oxygen analyzer. However, a stand-alone monitor may be added externally. Most monitors include high and low FiO_2 alarms which are usually set 0.05 above and below the preset level.
6. Most present generation ventilators include V_T and minute volume monitors, either built-in or as external options. Inspiratory/expiratory V_T is the volume (mL) inspired or expired per breath. When both are provided, the degree of airway leak can be assessed. Minute volume is the volume exhaled during a one-minute time frame.
 - a. The V_T monitor is a valuable tool for titrating the IP setting to achieve an optimal V_T (See above).
 - b. The low-minute-volume alarm can alert a significant drop in V_T , BR, or a leak/disconnection in the patient circuit. It may be set 20–25% below the prevailing minute volume.
7. An early sign of failure to wean from mechanical ventilation may be tachypnea. Some ventilator monitoring systems may include a high breath rate alarm or a high-minute-volume alarm to alert the clinician to this situation.
8. Most ventilators include alarms for loss of air and/or oxygen gas pressure, loss of electrical power, and ventilator inoperative conditions. These alarm conditions should be addressed immediately as patient compromise may be highly likely.

IV. Patient management

A. Ventilation

1. The primary controls which adjust the level of ventilation are the amplitude ($\Delta P = IP - PEEP$) and BR.
2. IP should be adjusted to achieve adequate lung inflation and discourage atelectasis. Assessment of bilateral breath sounds, chest excursion, exhaled V_T and chest radiography can guide subsequent adjustments.
3. Once adequate lung inflation has been achieved, BR should be adjusted to maintain $PaCO_2$ and pH within target ranges. Minute ventilation can be very useful to assess this trend.

B. Oxygenation

1. The primary parameters that affect oxygenation are FiO_2 and mean P_{AW} .
2. FiO_2 should be maintained below 0.6, if possible, to avoid an increased risk of oxygen toxicity.

3. Excessive PEEP levels should be avoided to reduce the risk of cardiovascular compromise. However, do not be reluctant to use whatever PEEP is necessary, as long as the patient is adequately monitored.
4. Mean airway pressure correlates with oxygenation. Increases in T_1 may improve oxygenation, without changes in FiO_2 or PEEP, but care should be taken to avoid using an inadequate expiratory time.

C. Weaning (Chap. 68)

1. As the patient's compliance increases, delivered V_T increases. To avoid overinflation, the IP should be decreased in 1–2 cm H_2O decrements for minor adjustments, and 3–5 cm H_2O decrements for moderate adjustments, to a minimum of 10–15 cm H_2O .
2. BR should be decreased in 3–5 BPM decrements for slight adjustments in $PaCO_2$, and 5–10 BPM decrements for moderate adjustments, to a minimum of 5–10 BPM.
3. PEEP should be weaned in 1–2 cm H_2O decrements to a minimum of 3–4 cm H_2O .
4. FiO_2 should be weaned aggressively to <0.4 .
5. Once ventilator parameters have been weaned to minimum values, readiness for extubation may be assessed. Evaluation of respiratory parameters, chest radiography, airway clearance, and hemodynamics can aid the decision process.

Suggested Reading

- Aloan CA, Hill TV. Respiratory care of the newborn. 2nd ed. Philadelphia, PA: Lippincott; 1997.
- Chatburn RL. Fundamentals of mechanical ventilation. A short course in the theory and application of mechanical ventilators. Cleveland Heights, OH: Mandu; 2003.
- Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura; 1998.
- Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal–perinatal medicine: diseases of the fetus and infant. 8th ed. St. Louis: Elsevier/Mosby; 2011. p. 1116–40.
- Goldsmith JP, Karatokin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia, PA: Saunders; 2009.
- Koff PB, Eitzman D, Neu J. Neonatal and pediatric respiratory care. St. Louis: Mosby; 1993.
- Whitaker KB. Comprehensive perinatal and pediatric respiratory care. 3rd ed. Albany, NY: Delmar; 2001.

Chapter 30

Synchronized Intermittent Mandatory Ventilation

Steven M. Donn and Sunil K. Sinha

I. Description

- A. Ventilatory mode in which mechanical breaths are synchronized to the onset of a spontaneous patient breath (if trigger threshold is met) or delivered at a fixed rate if patient effort is inadequate or absent. Spontaneous patient breaths between mechanically assisted breaths are supported by baseline pressure (PEEP) only.
- B. A form of patient-triggered ventilation (PTV).

II. Cycling mechanisms

- A. Time
- B. Flow
- C. Volume (but only if cuffed endotracheal tubes are used, see Chap. 32)

III. Trigger mechanisms

- A. Airway flow change
 - 1. Differential pressure transducer
 - 2. Heated wire anemometer
- B. Airway pressure change
- C. Abdominal impedance
- D. Diaphragmatic activity

S.M. Donn, MD, FAAP (✉)

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

S.K. Sinha, MD, PhD, FRCP, FRCPC

Department of Neonatal Medicine, The James Cook University Hospital, University of Durham,
Marton Road, Marton-in-Cleveland, Middlesbrough TS4 3BW, UK
e-mail: sunil.sinha@stees.nhs.uk

IV. Synchronized intermittent mandatory ventilation breath

- A. In synchronized intermittent mandatory ventilation (SIMV), the breathing time is divided into “breath periods” or “assist windows” based on the selected ventilator rate.
- B. The first time a patient attempts to initiate a breath during an assist window (which begins immediately after a mechanically delivered breath), the ventilator delivers an assisted breath, provided that patient effort exceeds the trigger threshold.
- C. Further attempts to breathe during the same assist window result only in spontaneous breaths, supported only by the baseline pressure.
- D. Mechanical breaths are only delivered if there is insufficient patient effort or apnea during the preceding assist window.
- E. Patient-controlled variables.
 - 1. Spontaneous respiratory rate
 - 2. Inspiratory time (if flow cycled)
- F. Clinician-controlled variables.
 - 1. Peak inspiratory pressure (if pressure targeted)
 - 2. Tidal volume delivery (if volume targeted)
 - 3. Inspiratory time (if time cycled)
 - 4. Flow
 - 5. SIMV rate
- G. Flow cycling.
 - 1. Inspiration is terminated at a percentage of peak flow rather than time.
 - 2. Synchronizes expiratory as well as inspiratory phase, and thus total patient/ventilator synchrony can be achieved for assisted breaths.

V. Spontaneous breath

- A. Supported by baseline pressure (PEEP) only
- B. Work of breathing is higher than for assist/control or with pressure support ventilation
- C. Observation of spontaneous tidal volume is a useful indicator of suitability to wean

VI. Patient management

- A. Indications
 - 1. Works best as a weaning mode, although many clinicians prefer it to assist/control as a primary management mode.
 - 2. Flow triggering especially useful in extremely low-birth-weight infants.
 - 3. Provides partial ventilatory support, as patient can breathe between mechanical breaths.
 - 4. Synchrony can decrease the need for sedatives/paralytics.

B. Initiation

1. Use minimal assist sensitivity.
2. Set SIMV rate at reasonable level to maintain adequate minute ventilation.
3. For flow cycling, termination at 5–10% of peak flow generally works best but must check to see that patient is receiving adequate tidal volume.
4. Other parameters set as for IMV.

C. Weaning

1. Primary weaning parameters include SIMV rate, peak inspiratory pressure (for time or flow cycling), and tidal volume (for volume targeting).
2. If PaCO₂ is too low, it is most likely the result of overventilation. Lower the rate, pressure, or volume depending on lung mechanics.
3. As patient status improves, spontaneous tidal volumes increase, enabling lowering of SIMV rate.
4. Can extubate directly from SIMV or add or switch to pressure support ventilation (PSV).
5. Can also wean by increasing assist sensitivity, thus increasing patient work and therefore tolerance.

VII. Problems

A. Autocycling and false triggering.

1. Leaks anywhere in the system (around ETT, in circuit, etc.) can cause flow- and pressure-triggered devices to misread this as patient effort resulting in delivery of a mechanical breath.
2. Abdominal impedance device may trigger from artifactual motion.

B. Failure to trigger.

1. Assist sensitivity set too high
2. Patient unable to reach trigger threshold
3. Patient fatigue

C. Inadequate inspiratory time (flow cycling) results in inadequate tidal volume delivery. Patient may compensate by breathing rapidly.

Suggested Reading

- Donn SM, Becker MA, Nicks JJ. Special ventilatory techniques I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St. Louis: Elsevier Saunders; 2011. p. 220–34.
- Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. *J Perinatol.* 1994;14:90–4.
- Donn SM, Sinha SK. Controversies in patient-triggered ventilation. *Clin Perinatol.* 1998;25:49–62.
- Sinha SK, Donn SM. Advances in neonatal conventional ventilation. *Arch Dis Child.* 1996; 75:F135–140.

Chapter 31

Assist/Control Ventilation

Steven M. Donn and Sunil K. Sinha

I. Description

- A. Ventilatory mode in which mechanical breaths are either patient (assist) or ventilator (control) initiated
- B. Another form of patient-triggered ventilation (PTV)

II. Cycling mechanisms

- A. Time
- B. Flow
- C. Volume (but only if cuffed endotracheal tubes are used)

III. Trigger mechanisms

- A. Airway flow
 - 1. Heated wire anemometer
 - 2. Differential pressure transducer
- B. Airway pressure
- C. Thoracic impedance
- D. Abdominal impedance
- E. Diaphragmatic activity

S.M. Donn, MD, FAAP (✉)

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

S.K. Sinha, MD, PhD, FRCP, FRCPC

Department of Neonatal Medicine, The James Cook University Hospital,
University of Durham, Marton Road, Marton-in-Cleveland,
Middlesbrough TS4 3BW, UK
e-mail: sunil.sinha@tees.nhs.uk

IV. Assist breath

- A. If patient effort exceeds trigger threshold, mechanical breath is initiated.
 - 1. Trigger delay (response time) is the time from signal detection to rise in proximal airway pressure.
 - 2. Long trigger delay increases work of breathing as patient may complete own inspiratory cycle before receiving ventilatory assistance from the mechanical breath.
- B. Patient-controlled variables.
 - 1. Respiratory rate
 - 2. Inspiratory time (if flow cycled)
- C. Clinician-controlled variables.
 - 1. Peak inspiratory pressure (if pressure targeted)
 - 2. Tidal volume delivery (if volume targeted)
 - 3. Inspiratory time (if time cycled)
 - 4. Flow
 - 5. Control rate
- D. Flow cycling.
 - 1. Inspiration is terminated at a percentage of peak flow rather than time.
 - 2. Fully synchronizes patient and ventilator.
 - 3. Prevents inversion of inspiratory:expiratory ratio and minimizes gas trapping.
 - 4. May result in insufficient inspiratory time and tidal volume delivery.

V. Control breath

- A. Essentially, a backup IMV in case of insufficient patient effort or apnea.
- B. Provides a minimal minute ventilation if baby is unable to trigger the ventilator or fails to breathe.
- C. If the rate set too high, patient may “ride” the ventilator and not breathe spontaneously.
- D. If patient is consistently breathing above the control rate, lowering it has no effect on the mechanical ventilatory rate.

VI. Patient management

- A. Indications
 - 1. Works well for virtually all patients
 - 2. Flow triggering especially useful in extremely low-birth-weight infants
 - 3. Provides full ventilatory support
 - 4. Synchrony can decrease the need for sedatives/paralytics

B. Initiation

1. Use minimal assist sensitivity.
2. Set control rate at reasonable level until patient demonstrates reliable respiratory drive, usually 20–40 breaths/min.
3. For flow cycling, termination at 5–10% of peak flow generally works best, but check to see that patient is receiving adequate tidal volume.
4. Other parameters set as for IMV.

C. Weaning

1. Since reduction in ventilator rate has no impact on minute ventilation if patient breathes above the control rate, primary weaning parameter is peak inspiratory pressure.
2. If PaCO₂ is too low, it is most likely the result of overventilation (too high a peak inspiratory pressure), as infant is unlikely to spontaneously hyperventilate. Lower the pressure.
3. As soon as patient demonstrates reliable respiratory drive, lower the control rate (20–30 bpm).
4. Can extubate directly from assist–control or switch to SIMV or SIMV/PS.
5. Can also wean by increasing assist sensitivity, thus increasing patient work and therefore tolerance.

VII. Problems

A. Autocycling and false triggering.

1. Leaks anywhere in the system (around ETT, in circuit, etc.) can cause flow- and pressure-triggered devices to misread this as patient effort resulting in delivery of a mechanical breath. Setting the assist sensitivity at a level above the measured leak can avoid this.
2. Thoracic impedance triggering may result in mechanical breaths secondary to cardiac impulses rather than respiratory motion.
3. Abdominal impedance device may trigger from artifactual motion.

B. Failure to trigger.

1. Assist sensitivity too high
2. Patient unable to reach trigger threshold
3. Patient fatigue
4. Sedative drugs

C. Inadequate inspiratory time (flow cycling) may result in inadequate tidal volume delivery. Patient may compensate by breathing rapidly.

D. Metabolic acidosis: Baby may attempt to achieve respiratory compensation (alkalosis) by breathing rapidly.

Suggested Reading

- Donn SM, Becker M, Nicks JJ. Special ventilator techniques and modalities I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St Louis: Saunders Elsevier; 2011. p. 220–34.
- Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. *J Perinatol*. 1994;14:90–4.
- Donn SM, Sinha SK. Controversies in patient-triggered ventilation. *Clin Perinatol*. 1998;25:49–62.
- Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database Syst Rev*. 2008;(1). Art. No.: CD000456. DOI: 10.1002/14651858.CD000456.pub3.
- Sinha SK, Donn SM. Advances in neonatal conventional ventilation. *Arch Dis Child*. 1996;75:F135–140.
- Sinha SK, Donn SM. Newer forms of conventional ventilation for preterm newborns. *Acta Paediatrica*. 2008;97:1338–43.

Chapter 32

Volume-Targeted Ventilation

Steven M. Donn and Sunil K. Sinha

I. Description

- A. Form of mechanical ventilation, where tidal volume is the primary target variable and pressure is permitted to fluctuate to deliver this volume.
- B. Although tidal volume may be monitored at the ventilator, measurement at the proximal airway is more accurate and safer for the neonatal patient.
- C. Because uncuffed endotracheal tubes are used in newborns, there may be a variable loss of delivered gas volume from leaks. It is, thus, more appropriate to describe this form of ventilation as volume-controlled, volume-limited, or volume-targeted, rather than volume-cycled ventilation.

II. Modes which can be utilized with volume-targeted ventilation

- A. Intermittent mandatory ventilation (IMV)
- B. Synchronized intermittent mandatory ventilation (SIMV)
 - 1. Alone
 - 2. With pressure support (PSV)
- C. Assist/control (A/C)
- D. Pressure-regulated volume control (PRVC)
- E. Volume-assured pressure support (VAPS)

S.M. Donn, MD, FAAP (✉)

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

S.K. Sinha, MD, PhD, FRCP, FRCPC

Department of Neonatal Medicine, The James Cook University Hospital,
University of Durham, Marton Road, Marton-in-Cleveland, Middlesbrough
TS4 3BW, UK
e-mail: sunil.sinha@tees.nhs.uk

- F. Mandatory minute ventilation (MMV)
- G. Volume guarantee (VG)

III. Characteristics of volume-controlled breaths

- A. Continuous inspiratory flow produces the characteristic “square wave” on the flow waveform.
 - 1. This results in ramping of pressure, with peak pressure and volume delivery occurring at the end of inspiration.
 - 2. This differs from pressure-targeted breaths, which utilize an accelerating, decelerating flow waveform, producing a breath in which peak pressure and peak volume delivery occurs early in inspiration. Thus, there is a fundamental difference.
 - 3. Theoretically, pressure-targeted breaths are advantageous in treating homogeneous lung disease in which there is a need for a high opening pressure, such as early in RDS.
 - 4. Volume-targeted breaths are advantageous in treating heterogeneous lung disease, where slower inflation of the lung should lead to better distribution of gas flow.
- B. May be patient triggered or machine initiated
 - 1. Pressure or flow trigger
 - 2. May be at proximal airway or within ventilator
- C. Flow limited (fixed flow rate)
 - 1. Determines inspiratory time.
 - 2. Square flow waveform; some ventilators allow choice of decelerating flow.
 - 3. Some newer ventilators offer variable flow, but data regarding use in newborns are unavailable.
- D. Dependent variable is pressure
 - 1. Low compliance results in higher pressure delivery.
 - 2. As compliance improves, pressure is auto-weaned.
 - 3. May be influenced by inspiratory flow setting.
- E. Tidal volume is assured.
- F. Maximum alveolar distension depends on end alveolar pressure.

IV. Advantages of volume-controlled ventilation

- A. Consistent tidal volume delivery even in the face of changing compliance
- B. Volume-limited breaths; avoidance of volutrauma
- C. Combination with other modes to facilitate weaning
 - 1. PSV
 - 2. VAPS
 - 3. MMV

V. Clinical limitations

A. Minimal tidal volume delivery

1. Must know that the smallest tidal volume machine is capable of delivering
2. Should not exceed patient's physiologic tidal volume
 - a. <1,000 g: 4–7 mL/kg
 - b. >1,000 g: 5–8 mL/kg
3. Ventilator circuit should be of reasonable rigidity (compliance) so as not to cause excessive compressible volume loss in circuit if pulmonary compliance is low.
4. Smaller patients with smaller ETT (2.5–3.0 mm) may have difficulty triggering (especially if pressure triggered).
5. Flow limitation may result in inadequate inspiratory time in smaller patients.
6. Leaks
 - a. May cause loss in baseline pressure
 - b. May result in autocycling

VI. Clinical indications

- A. Respiratory failure: Virtually, all forms of neonatal respiratory failure have been shown to be amenable to volume-targeted ventilation.
- B. Ventilator-dependent cardiac disease with normal lungs.
- C. Weaning infants recovering from respiratory illness.
- D. Bronchopulmonary dysplasia.

VII. Initiating volume ventilation

A. Select desired mode.

1. A/C or SIMV recommended for acute illness
2. SIMV and/or PSV recommended for weaning

B. Select desired delivered volume to provide V_T .

1. <1,000 g: 4–7 mL/kg.
2. >1,000 g: 5–8 mL/kg.
3. Confirm that patient is receiving appropriate tidal volume.
 - a. Volume monitoring
 - b. Pulmonary graphics
 - (1) Tidal volume waveform
 - (2) Pressure–volume loop

- C. Set flow rate to achieve desired inspiratory time. This can be modified by adding an inspiratory hold to avoid using a flow rate that is inadequate to generate sufficient hysteresis on the pressure–volume loop.

- D. Set mechanical ventilatory rate.
- E. Set trigger sensitivity if using patient-triggered mode.
 1. Generally, use minimal setting unless autocycling.
 2. Assure that patient is able to trigger ventilator.
- F. Some clinicians prefer to set a pressure limit; do not set this too close to peak pressure, or desired tidal volume may not be delivered.
- G. Some ventilators have a leak compensation system. While beneficial in maintaining stable baseline in the presence of a leak, it may increase the work of breathing and possibly expiratory resistance.
- H. Assessment of patient
 1. Adequacy of breath sounds
 2. Adequacy of chest excursions
 3. Patient–ventilator synchrony
 4. Patient comfort
 5. Blood gases
 6. Pulmonary mechanics

VIII. Weaning infants from volume-controlled ventilation

- A. As pulmonary compliance improves, inspiratory pressure is automatically decreased to maintain desired volume delivery.
- B. Adjustments in delivered volume should be made to maintain desired tidal volume delivery.
- C. Adjustment in flow rate may need to be made to maintain same inspiratory time or I:E ratio.
- D. If using A/C:
 1. Decrease control rate (allow patient to assume greater percentage of work of breathing).
 2. May also increase assist sensitivity (trigger).
- E. If using SIMV:
 1. Decrease SIMV rate, but remember that patient receives no support for spontaneous breaths other than positive end-expiratory pressure.
 2. Consider adding pressure support (Chap. 34) or even switching to it completely if the baby has consistently reliable respiratory drive.
- F. Newer modes (VAPS, MMV) may prove even more beneficial for weaning but have limited clinical experience in the newborn at present.

Suggested Reading

- Bandy KP, Nicks JJ, Donn SM. Volume-controlled ventilation for severe neonatal respiratory failure. *Neonatal Intensive Care*. 1992;5:70–3.
- Donn SM. Alternatives to ECMO. *Arch Dis Child*. 1994;70:F81–84.

- Donn SM, Becker MA. Baby in control: neonatal pressure support ventilation. *Neonatal Intensive Care*. 1998a;11:16–20.
- Donn SM, Becker MA. Mandatory minute ventilation: a neonatal mode of the future. *Neonatal Intensive Care*. 1998b;11:22–4.
- Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 8th ed. St. Louis: Elsevier/Mosby; 2011. p. 1116–40.
- Nicks JJ, Becker MA, Donn SM. Neonatal respiratory failure: response to volume ventilation. *J Perinatol*. 1993;13:72–5.
- Sinha SK, Donn SM. Volume- targeted Ventilation. In: Goldsmith JP, Karotkin EH, editors. *Assisted Ventilation of the Neonate*. 5th ed. St Louis: Saunders Elsevier; 2011. p. 186–99.
- Sinha SK, Donn SM, Gavey J, McCarty M. Randomized trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child*. 1997;77:F202–205.
- Tsai WC, Bandy KP, Donn SM. Volume controlled ventilation of the newborn. In: Donn SM, editor. *Neonatal and pediatric pulmonary graphic analysis: principles and clinical applications*. Armonk, NY: Futura; 1998. p. 279–300.
- Sinha SK, Donn SM. Volume controlled ventilatory modes for the newborn: variations on a theme. *Clin Perinatol*. 2001;8:547–60.
- Singh J, Sinha SK, Clark P, et al. Mechanical ventilation of very low birthweight infant; Is volume or pressure a better target variable? *J Pediatr*. 2006;149:308.
- Singh J, Sinha SK, Donn SM. Volume-targeted ventilation of newborn. *Clin Perinatol*. 2007; 34:93–105.
- Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. *Cochrane Database Syst Rev*. 2010;(11). Art. No.: CD003666. DOI: 10.1002/14651858.CD003666.pub3.

Chapter 33

Pressure Control Ventilation

Steven M. Donn

I. Description

- A. Pressure control (PC) was developed in the 1980s for the treatment of ARDS. It is now included in many neonatal ventilators.
- B. Mechanical breaths are delivered at a preset peak inspiratory pressure, with a fixed or variable inspiratory time and variable inspiratory flow, which distinguishes PC from traditional time-cycled, pressure-limited ventilation.
- C. It may be applied as IMV, SIMV (with or without pressure support), or A/C.

II. Features

- A. Constant peak inspiratory pressure.
- B. Variable tidal volume depending on patient lung mechanics.
- C. Square or plateau pressure waveform.
- D. Decelerating flow waveform.
- E. Variable pressure rise time.
 - 1. Rise time refers to the slope of the inspiratory pressure waveform.
 - 2. It is a qualitative number, and it differs from one ventilator to another.
 - 3. If slope is excessive, pressure overshoot may occur. This may be observed as a notch on the inspiratory limb of the pressure–volume loop or a notch at the top of the pressure waveform.
 - 4. If slope is inadequate, there may be inadequate hysteresis on the pressure–volume loop.
- F. High flow rapidly pressurizes ventilator circuit resulting in rapid gas delivery and alveolar filling.

S.M. Donn, MD, FAAP (✉)

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA

e-mail: smdonnmd@med.umich.edu

III. Clinical applications

A. Patients at risk for barotrauma but in need of high peak pressure:

1. RDS
2. BPD
3. MAS

B. Patients with airway obstruction or high airway resistance

IV. Clinician-set parameters

A. Peak inspiratory pressure

B. PEEP

C. Inspiratory time (or cycle termination, if flow cycled)

D. Mode

E. Rate

F. FiO₂

G. Trigger sensitivity

H. Rise time

I. Alarm limits

V. Advantages

A. Variable flow capability to meet patient demand

B. Reduced inspiratory muscle workload

C. Lower peak inspiratory pressures

D. Adjustable inspiratory time

E. Rapid filling of the alveoli

F. Improved gas distribution, V/Q matching, and oxygenation

VI. Disadvantages

A. Delivered tidal volume is variable and depends upon the patient's lung mechanics, including changes in airway resistance and lung compliance.

B. May have adverse effects on tidal volume delivery.

C. Pressure overshoot.

D. Limited data on use in newborns.

VII. Comparison to other pressure-targeted modalities (Table 33.1)

Table 33.1 Comparison of pressure-targeted modalities

Parameter	Pressure limited	Pressure control	Pressure support
Limit	Pressure	Pressure	Pressure
Flow	Continuous, fixed	Variable	Variable
Cycle	Time or flow	Time or flow	Flow (time limited)
Breath type	Mechanical	Mechanical	Spontaneous

Suggested Reading

- Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 8th ed. St. Louis: Elsevier/Mosby; 2011. p. 1116–40.
- Donn SM, Sinha SK. Invasive and noninvasive neonatal mechanical ventilation. *Respir Care*. 2003;48:426–41.
- Donn SM, Sinha SK. Newer techniques of mechanical ventilation: an overview. *Semin Neonatol*. 2002;7:401–8.

Chapter 34

Pressure Support Ventilation

Sunil K. Sinha and Steven M. Donn

I. Description

- A. Ventilatory mode in which spontaneous breaths are partially or fully supported by an inspiratory pressure assist above baseline pressure to decrease the imposed work of breathing created by the narrow lumen endotracheal tube, ventilator circuit, and demand valve, if one is used.
- B. A form of patient-triggered ventilation (PTV); may be used alone in patients with reliable respiratory drive or in conjunction with SIMV.

II. Cycling mechanisms

- A. Time: Inspiratory time limit, chosen by clinician, which cannot be exceeded.
- B. Flow: Termination of inspiratory cycle based on a percentage of peak flow. This varies according to both delivered tidal volume and specific algorithm of the ventilator in use. For most neonatal ventilators, this occurs at 5–10% of peak inspiratory flow.

III. Trigger mechanisms

- A. Airway pressure change (minimum 1.0 cm H₂O)
- B. Airway flow change (minimum 0.1 LPM)

S.K. Sinha, MD, PhD, FRCP, FRCPC (✉)
Department of Neonatal Medicine, The James Cook University Hospital,
University of Durham, Marton Road, Marton-in-Cleveland, Middlesbrough TS4 3BW, UK
e-mail: sunil.sinha@stees.nhs.uk

S.M. Donn, MD, FAAP
Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

IV. Pressure support breath

- A. A spontaneous inspiratory effort which exceeds the trigger threshold initiates delivery of a mechanically generated pressure support breath.
- B. There is a rapid delivery of flow to the patient, which peaks and then decelerates.
- C. The airway pressure rises to the pressure support level, set by the clinician as a value above baseline (PEEP).
- D. When flow cycling criterion is met (decline to the termination level), the breath ends and flow ceases. If this has not occurred by the end of the set inspiratory time limit, the inspiratory phase of the mechanical breath will be stopped.
- E. The amount of flow delivered to the patient during inspiration is variable, depends to a certain extent on respiratory mechanics, and is proportional to patient effort.
- F. Patient-controlled variables:
 1. Respiratory rate
 2. Inspiratory time
 3. Peak inspiratory flow
- G. Clinician-controlled variables:
 1. Pressure support level
 2. Inspiratory time limit
 3. Baseline flow
 4. Baseline pressure (PEEP)
 5. SIMV rate, flow (except with pressure control), inspiratory time, and tidal volume or pressure limit (if SIMV is used)

V. Patient management

- A. Indications
 1. Designed primarily as a weaning mode to enable full or partial unloading of respiratory musculature during mechanical ventilation.
 2. Pressure support is fully synchronized with spontaneous breathing and can decrease the need for sedatives/paralytics.
- B. Initiation
 1. Use minimal assist sensitivity.
 2. The pressure support level can be adjusted to provide either full support (PS_{max}), delivering a full tidal volume breath, or at a lower level to provide partial support. Remember that the pressure support level is the pressure applied above baseline (i.e., a patient receiving 4 cm H₂O PEEP and 16 cm H₂O pressure support actually gets 20 cm H₂O peak inspiratory pressure).
 3. Set the inspiratory time limit for the pressure support breath.

4. Set parameters for the SIMV breaths if they are to be used.
 - a. These can be used analogously to control breaths during assist/control ventilation, providing a “safety net” of background ventilation in the event of inadequate effort (triggering) or apnea.
 - b. If the SIMV rate is set too high, and the majority of minute ventilation is provided by SIMV, the patient may have no impetus to breathe, thus defeating the purpose of pressure support.

C. Weaning

1. Weaning may be accomplished in a variety of ways.
 - a. Decrease the SIMV rate to as low a level as possible, thus increasing spontaneous effort.
 - b. Decrease the pressure support level, thus increasing the percentage of the work of breathing assumed by the patient.
 - c. Consider the use of pressure support alone in patients with a reliable respiratory drive who have no difficulty triggering.
2. Consider extubation when the pressure support level has been reduced to the point, where it delivers about 3–4 mL/kg tidal volume if the patient appears comfortable and is not tachypneic at this level.

VI. Problems

- A. Failure to trigger (may occur with small endotracheal tubes and inadequate patient effort).
- B. Pressure overshoot.
- C. Premature termination.
- D. A common error is using a high SIMV rate with PSV. This interrupts the synchrony of PSV and subjects the patient to possibly unnecessary mandatory breaths. If a high SIMV rate is needed, the baby may not be ready for PSV and might do better in assist/control.

VII. Clinical applications

- A. Weaning mode
- B. Bronchopulmonary dysplasia (BPD)
 1. Infants with BPD exhibit reactive airways with elevated inspiratory resistance.
 2. Pulmonary mechanics in most modes display a flattened inspiratory flow–volume loop.
 3. Variable inspiratory flow during pressure support ventilation enables patient to overcome increased inspiratory resistance and lowers ventilatory work.

VIII. Advantages of pressure support ventilation

- A. Complete patient–ventilator synchrony
- B. Decreased work of breathing compared to other modes
 1. Same tidal volume delivered at lower work of breathing
 2. Larger tidal volume delivered at same work of breathing
- C. Adults treated with pressure support ventilation have described increased comfort and endurance compared to other weaning modes

IX. Additional applications and variations

- A. Volume-assured pressure support (Chap. 39)
 1. Used primarily in adults, but now available for infant use.
 2. Combines features of volume-controlled ventilation and pressure support ventilation.
 3. Clinician determines minimum tidal volume.
 4. As long as spontaneous patient effort results in delivery of desired tidal volume, breath “behaves” like a pressure support breath.
 5. If breath delivers a tidal volume below the desired minimum, it is transitioned to a volume-controlled breath by prolonging inspiration at the minimal set flow and slightly ramping up the pressure, assuring delivery of desired tidal volume.
- B. Mandatory minute ventilation
 1. This mode combines pressure support ventilation with SIMV.
 2. Clinician chooses a minute ventilation rate which the patient is to receive by selecting a desired tidal volume and frequency.
 3. As long as spontaneous breathing results in minute ventilation which exceeds the minimum, all breaths are pressure-support breaths.
 4. If minute ventilation falls below the set minimum, the ventilator will provide sufficient SIMV breaths to allow the patient to “catch up” to the desired level of minute ventilation. This is based on a moving average.

Suggested Reading

Donn SM, Becker MA. Baby in control: neonatal pressure support ventilation. *Neonatal Intensive Care*. 1998a;11:16–20.

Donn SM, Becker MA. Mandatory minute ventilation: a neonatal mode of the future. *Neonatal Intensive Care*. 1998b;11:20–2.

Donn SM, Becker MA, Nicks JJ. Special ventilator techniques and modalities I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH, editors. *Assisted Ventilation of the Neonate*. 5th ed. St Louis: Saunders Elsevier; 2011. p. 220–34.

Donn SM, Sinha SK. Controversies in patient-triggered ventilation. *Clin Perinatol*. 1998;25:49–62.

- Donn SM, Sinha SK. Pressure support ventilation of the newborn. *Acta Neonatologica Japonica*. 1997;33:472–8.
- Gupta S, Sinha SK, Donn SM. The effect of two levels of pressure support ventilation on tidal volume delivery and minute ventilation in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2009;94:F80–3.
- Guthrie SO, Lynn C, LaFleur BJ, et al. A crossover analysis of mandatory minute ventilation compared to synchronized intermittent mandatory ventilation in neonates. *J Perinatol*. 2005;25:643–6.
- Nicks JJ, Becker MA, Donn SM. Bronchopulmonary dysplasia: response to pressure support ventilation. *J Perinatol*. 1994;11:374–6.
- Sinha SK, Donn SM. Advances in neonatal conventional ventilation. *Arch Dis Child*. 1996;75:F135–40.
- Sinha SK, Donn SM. Pressure support ventilation. In: Donn SM, editor. *Neonatal and pediatric pulmonary graphics: principles and clinical applications*. Armonk, NY: Futura; 1998. p. 301–12.
- Sarkar S, Donn SM. In support of Pressure Support. *Clin Perinatol*. 2007;34:117–28.

Chapter 35

Proportional Assist Ventilation

Andreas Schulze

I. Introduction

- A. Patient-triggered ventilation (PTV) attempts to synchronize the upstroke in ventilator pressure with the onset of spontaneous inspiration. Other parameters of the mechanical cycle, such as the peak inspiratory pressure (PIP), pressure rise time, and duration of lung inflation, are preset by the clinician. They are imposed on the infant without adapting to the course of spontaneous inspiratory activity.
- B. In addition to the features of conventional PTV, flow cycling, used in pressure-targeted and pressure support ventilation (PSV), terminates inflation toward the end of spontaneous inspiration. This allows variability in inflation time and prevents inflation from extending into spontaneous expiration, reducing asynchrony between spontaneous inspiratory activity and cycling of the ventilator.
- C. Proportional assist ventilation (PAV) does not couple a more or less preset cycling profile of the ventilator to a single time point event, such as the onset and the end of inspiration. In the PAV modalities, the ventilator is continuously sensitive to the instantaneous respiratory effort, adjusting the assist pressure in a proportionate and ongoing fashion. This may achieve near-perfect synchrony between the ventilator and spontaneous breathing, with relief from disease-related increased mechanical work of breathing.

II. The concept of PAV

- A. PAV servo-controls the applied ventilator pressure, based on continuous input from the patient. This input signal alone controls the instantaneous

A. Schulze, MD, PhD (✉)

Division of Neonatology, Dr. von Hauner Children's Hospital, Munich, Germany

Department of Pediatrics, Klinikum Grosshadern, Ludwig Maximilian University, Marchioninstr. 15, 81377 Munich, Germany

e-mail: andreas.schulze@med.uni-muenchen.de

ventilator pressure, which is adjusted continuously according to the input signal waveform contour, virtually without a time lag.

- B. The input signal is derived from the infant's spontaneous respiratory activity. It ultimately reflects the output of the respiratory center. Therefore, it can theoretically be obtained anywhere along the pathway from the respiratory center to the end organ (i.e., recorded as phrenic nerve activity, diaphragmatic EMG activity), but also as tidal volume and airflow signals from probes inside the airway or from plethysmography.
 - C. The pressure output of the ventilator, being proportional to the input signal in a PAV mode, enhances the effect of the respiratory center activity on ventilation. This implies the following.
 1. The PAV mode increases the amount of ventilation per unit of spontaneous respiratory activity—that is, proportional to the instantaneous magnitude of the effort. In contrast, PTV adds a given amount of tidal volume to the spontaneous breath whenever a breath is detected, regardless of the magnitude of the inspiratory effort and its time course.
 2. The ventilator becomes fully “enslaved,” allowing the infant to control timing, depth, and the entire tidal volume and airflow contours of the breath.
 3. The clinician sets the “gain” of this enhancement.
 - a. The gain is the ratio of applied ventilator pressure per “unit of respiratory center output” (i.e., pressure per input-signal unit).
 - b. The higher the gain, the less mechanical work of breathing needs to be performed by the patient for a given amount of ventilation.
 4. The PAV modality relies on a largely intact functioning of the biologic control of breathing. The mode does not by itself initiate breaths. It cannot reverse a waning respiratory drive.
 - a. During episodes of cessation of spontaneous breathing or hypoventilation, backup conventional mechanical ventilation needs to be started automatically.
 - b. When the infant resumes spontaneous breathing, the ventilator must automatically withdraw backup ventilation.
- III. Ventilator settings for PAV based on airflow and tidal volume signals of spontaneous breathing (respiratory mechanical unloading modes)
- A. The positive end-expiratory pressure (PEEP) level affects the functional residual capacity, as with any other assist modality.
 - B. The gain of the volume-proportional assist (elastic unloading gain, Fig. 35.1) results in the following.
 1. Sets the ratio of delivered ventilator pressure per tidal volume in units of cm H₂O/mL. (The control of the volume-proportional assist is located on the ventilator front panel with a continuous scale).

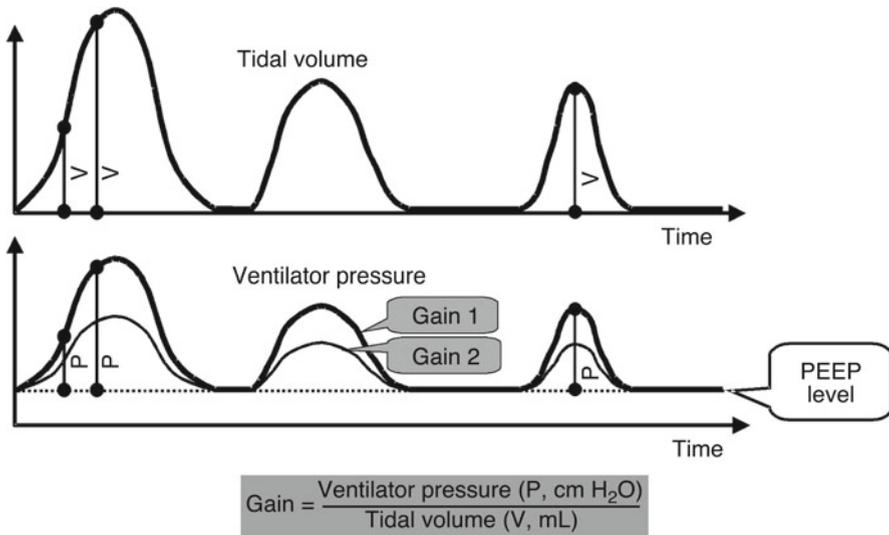


Fig. 35.1 Schematic representation of spontaneous breathing during volume-proportional assist (elastic unloading) at two different settings (gain 1 and gain 2). Vertical lines demonstrate that the gain (ratio of change in ventilator pressure per unit of change in tidal volume) is maintained constant over time while the tidal breathing pattern varies. Gain 2 represents a lower level of the assist

2. Ventilator pressure rises in proportion to the inspired tidal volume and thus specifically opposes the increase in lung elastic recoil pressure that develops during each inspiration.
 3. Volume-proportional assist exerts an elastic unloading effect that specifically reduces elastic work of breathing.
- C. The gain of the flow-proportional assist (resistance unloading gain) (Fig. 35.2) results in the following.
1. Sets the ratio of delivered ventilator pressure per tidal airflow in units of $\text{cm H}_2\text{O/L/s}$. (The control of the flow-proportional assist is located on the ventilator front panel with a continuous scale).
 2. Ventilator pressure increases in proportion to the inspiratory airflow signal and thus specifically opposes airflow-resistive forces.
 3. Flow-proportional assist exerts a resistive unloading effect which reduces resistive work of breathing. If this feature is activated during both inspiration and expiration (full-cycle resistive unloading), it will also facilitate exhalation, shorten the expiratory time constant, and help to avoid inadvertent PEEP in infants with high airway resistance.
- D. Safety limits on ventilator pressure.
- E. Backup conventional ventilation for episodes of hypoventilation or apnea.

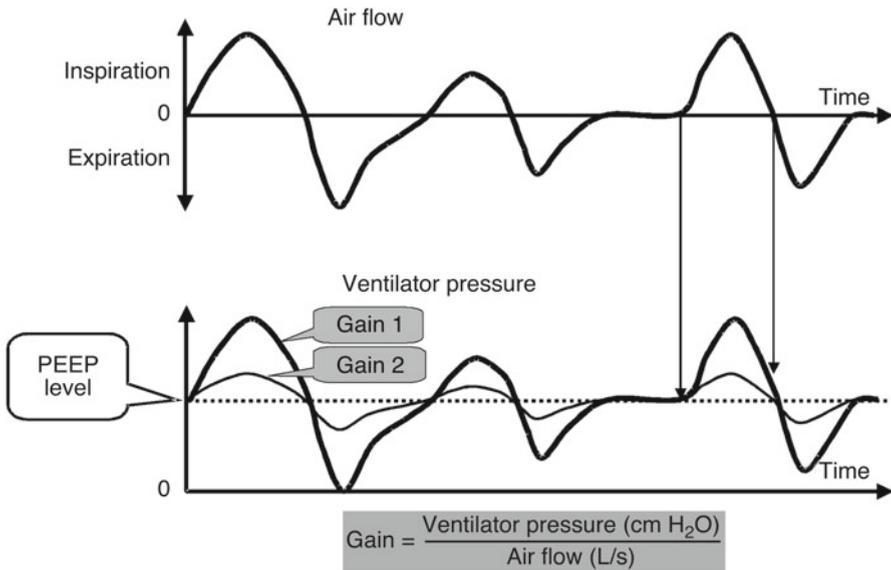


Fig. 35.2 Schematic representation of spontaneous breathing during flow-proportional assist (full-cycle resistive unloading) at two different settings (gain 1 and gain 2). Vertical lines indicate that ventilator pressure changes occur virtually without a time lag to the airflow signal. The gain (ratio of change in ventilator pressure per unit of airflow) is maintained constant over time while the tidal breathing pattern varies. Gain setting 2 represents a lower level of the assist

IV. Patient management

A. Indications

1. Preserved spontaneous breathing activity, but impending respiratory failure from an imbalance between the ability of the respiratory pump and the mechanical workload of breathing.
2. Elastic unloading (volume-proportional assist), primarily for conditions of reduced lung compliance (restrictive disease types).
3. Resistive unloading (flow-proportional assist), primarily for conditions of increased airway resistance (obstructive disease types), including resistance imposed by the endotracheal tube (ETT).
4. Combined elastic and resistive unloading for conditions with combined derangements of lung mechanics. Separate and independent gain settings for the elastic and resistive unloading components allow customization of the ventilatory waveform contour to the relative severity of lung compliance and airway resistance problems.
5. Proportional assist ventilation has not been studied in preterm infants with acute severe pulmonary parenchymal disease before the application of exogenous surfactant, nor air leak syndromes, meconium aspiration syndrome, or other types of severe respiratory disease in the term newborn.

B. Initiation of PAV in infants

1. Set the controls before enabling the modality.
 - a. Set elastic unloading gain and resistive unloading gain to zero and choose the PEEP level as for intermittent mandatory ventilation (IMV).
 - b. Set the upper airway pressure safety limit.
 - c. Choose settings for backup conventional ventilation to provide appropriate full ventilatory support while avoiding hyperventilation.
 - d. PAV can be set up as “pure” PAV, which essentially is modulated CPAP with backup control. It can also be applied in tandem with low-rate IMV or SIMV to mechanically unload spontaneous breathing between the mandatory inflations. In addition, optional settings allow provision of a minimum guaranteed tidal volume during PAV-supported breathing.
2. Start while observing the patient.
 - a. Gradually increase the elastic unloading gain from zero to an appropriate level. Ventilator pressure remains constant at zero gain (CPAP); it is modulated to track the tidal volume signal with elastic unloading gain settings above zero.
 - b. A suitable elastic unloading gain can be identified by clinical criteria. It reduces chest wall distortion and establishes physiologic tidal volumes of about 3–5 mL/kg. Smaller infants need higher gains of elastic unloading (in absolute terms—i.e., in cm H₂O/mL) because tidal volume and compliance relate to body weight. As a general rule, infants <1,000 g usually need about 1 cm H₂O/mL or more of elastic unloading gain while larger infants need less.
 - c. If the gain is turned up above an appropriate level (stronger than current elastic recoil of the lung), ventilator pressure will rise to the set upper pressure limit with each inspiration. The ventilator pressure subsequently is always automatically returned to the PEEP level. Levels of unloading that are too high, thereby, convert the mode into the cycling pattern of PTV—that is, cycling between set PEEP and PIP levels with each onset of spontaneous inspiration. This occurrence identifies an excessive gain and helps to find the range of appropriate gain levels.
 - d. Increase the gain of resistive unloading to compensate at least for the resistance imposed by the ETT. This is about 20–30 cm H₂O/L/s of resistive unloading for a 2.5 mm (internal diameter) ETT. Higher gains may be required when pulmonary resistance is elevated.
 - e. Preterm infants on PAV typically adopt a fast and shallow breathing pattern.

C. Weaning

1. Reduce gain levels gradually with improvement in pulmonary mechanics.
2. Try to be specific in lowering resistive vs. elastic support levels, depending on how pulmonary pathophysiology develops. Compared to other

assist modalities, reduction in ventilator pressure “cost” with proportional assist is likely related to the quality of matching of the unloading settings to the specific type and the degree of lung mechanics derangement.

3. Improvement in pulmonary mechanics can be recognized during PAV when a previously suitable gain turns into overassist with repetitive cycling of airway pressure to the set upper pressure limit. This indicates the possibility of further weaning the assist by reducing the gain.
4. With gains weaned to near-zero levels, the patient has to shoulder the entire work of breathing near the CPAP level and is probably ready to be extubated.

D. Problems

1. ETT leaks

- a. An ETT leak flow mimics inspiratory airflow to a flow sensor mounted at the wye adapter. This may cause the ventilator pressure to increase out of proportion to the inspiratory airflow and/or volume that is truly entering the lung.
- b. Current devices use software algorithms to estimate and adjust for leak flows. This allows PAV to function in infants in the presence of variable leak up to about 20–30% of tidal volume.
- c. Major leaks have effects similar to those of inappropriately high gain settings and preclude the use of PAV that is based on direct airflow measurements.

2. Sensor malfunction

- a. When the flow signal serves as driving input to the closed-loop PAV system, any flow sensor malfunction inevitably leads to a derangement of the applied ventilator pressure pattern.
- b. Distortions of the driving signal and the ventilator pressure waveforms that result from such sensor artifacts can be recognized on the ventilator’s monitor display.

Suggested Reading

- Herber-Jonat S, Rieger-Fackeldey E, Hummler H, Schulze A. Adaptive mechanical backup ventilation for preterm infants on respiratory assist modes. *Intensive Care Med.* 2006;32:302–8.
- Hummler H, Schulze A. New and alternative modes of mechanical ventilation in neonates. *Semin Fetal Neonatal Med.* 2009;14:42–8.
- Musante G, Schulze A, Gerhardt T, et al. Respiratory mechanical unloading decreases thoraco-abdominal asynchrony and chest wall distortion in preterm infants. *Pediatr Res.* 2001; 49:175–80.
- Schulze A, Bancalari E. Proportional assist ventilation in infants. *Clin Perinatol.* 2001;28:561–78.

- Schulze A, Rieger-Fackeldey E, Gerhardt T, Claire N, Everett R, Bancalari E. Randomized cross-over comparison of proportional assist ventilation and patient-triggered ventilation in extremely low birth weight infants with evolving chronic lung disease. *Neonatology*. 2007;92:1–7.
- Schulze A, Gerhardt T, Musante G, et al. Proportional assist ventilation in low birth weight infants with acute respiratory disease. A comparison to assist/control and conventional mechanical ventilation. *J Pediatr*. 1999;135:339–44.
- Schulze A, Schaller P, Töpfer A, et al. Resistive and elastic unloading to assist spontaneous breathing does not change functional residual capacity. *Pediatr Pulmonol*. 1993;16:170–6.
- Younes M. Proportional assist ventilation, a new approach to ventilatory support. *Theory. Am Rev Respir Dis*. 1992;145:114–20.

Part VII
High-Frequency Ventilation

Chapter 36

High-Frequency Ventilation: General Concepts

J. Bert Bunnell

- I. High-frequency ventilation (HFV) and lung protective ventilation
 - A. What is lung protective ventilation?
 1. Open (inflate) the lungs.
 2. Keep the lungs open (do not allow alveolar collapse between breaths).
 3. Ventilate as gently as possible.
 - B. How mechanical ventilation causes lung injury.
 1. Barotrauma: using too much pressure
 2. Volutrauma: using tidal volumes that are too large
 3. Atelectrauma:
 - a. Allowing alveoli to collapse, remain collapsed, or open and collapse with every breath.
 - b. Caused by using too little PEEP (positive end-expiratory pressure) or P_{aw} (mean airway pressure), which are nearly equivalent in their physiologic effects.
 4. Rheotrauma: airway injury caused by shear forces of high gas flow rates
 5. Biotrauma: biochemical and biophysical injury caused by release of inflammatory mediators and cells triggered by all forms of mechanical ventilation
- II. How HFV inherently provides lung protective ventilation.
 - A. Barotrauma:
 1. HFV pressure waveforms quickly attenuate as they advance toward the alveoli, although there is less damping in noncompliant lungs.
 2. Very little pressure amplitude is applied at terminal airways and alveoli.

J.B. Bunnell, ScD (✉)
Bunnell Inc., Department of Bioengineering, University of Utah,
436 Lawndale Drive, Salt Lake City, UT 84115, USA
e-mail: BB2@BUNL.COM

- B. Volutrauma: HFV tidal volumes are 1/5 to 1/10 those of Conventional Mechanical Ventilation (CMV) tidal volumes.
 - C. Atelectrauma: one type of lung injury that is *not* inherently lessened by HFV.
 - 1. One has to manage PEEP and P_{aw} to achieve optimal lung volume.
 - 2. It is safer to use higher PEEP and P_{aw} with HFV compared to CMV. (It is large tidal volumes and pressure amplitudes that cause lung injury when PEEP and P_{aw} is raised.)
 - 3. Raising PEEP and P_{aw} too high can interfere with cardiac output and blood flow through the lungs.
 - 4. Optimizing PEEP and P_{aw} improves blood flow through the lungs as well as maximizing the potential for gas exchange.
 - D. Rheotrauma: no evidence that this type of lung injury has arisen in numerous randomized controlled trials with both HFJV and HFOV.
 - 1. HFJV uses very low overall gas flow rates, but highly accelerated and inadequately humidified inspirations were suspected of causing tracheal injury in the past.
 - 2. HFOV uses much higher overall gas flow rates, but typical inspiratory flow rates are considered to be laminar, which creates a protective boundary layer at airway walls.
 - 3. Active exhalations during HFOV are considered to be turbulent as gas accelerates at every bifurcation when gas from two airways is sucked into one more proximal airway.
 - 4. Parameters and mechanisms for this type of lung injury have yet to be adequately explored.
 - E. Biotrauma:
 - 1. Studies have demonstrated less biotrauma with more gentle forms of assisted breathing, such as CPAP, and HFV is as close to CPAP as one can get with mechanical ventilation.
 - 2. Parameters and mechanisms for this type of lung injury also are yet to be adequately explored.
 - F. If HFV is so inherently lung protective, why are not all patients treated with HFV?
- III. HFV, a “disruptive” technology
- A. Disruptive technologies are not “normal”; they change the way people normally do things, and people are resistant to change.
 - B. HFV is not normal.
 - 1. HFV does not try to mimic normal ventilation.
 - 2. HFV rates are at least 5–10 times normal breathing rates, although comparable rates and examples of enhanced pulmonary gas exchange in nature occur in running and panting animals.

3. HFV tidal volumes are typically smaller than anatomic dead space volume.
 4. Intrapulmonary distribution of fresh gas during HFV is not affected by lung compliance.
- C. People must understand how HFV works physiologically before they can get comfortable with the devices that provide HFV.
- D. Education is the key to embracing the disruptive technology of HFV and optimizing its use.

IV. How does HFV work?

A. Resonant frequency phenomena

1. Forced oscillations experiments revealed that lungs have a natural or “resonant” frequency of 4–8 Hz (1 Hz = 60 cycles per minute) in adult humans.
2. At resonance:
 - a. Gas momentum supplies the energy to overcome lung compliance, and lung recoil supplies the energy to send gas back out of the lungs.
 - b. Timing and energies are perfectly matched to conserve energy.
 - c. Outside force is required *only* to overcome airway resistance.
 - d. Therefore, less pressure is required to move gas in and out of the lungs at resonant frequency.

B. Optimal frequency

1. Optimal frequency produces best ventilation with lowest ΔP (pressure amplitude) and V_T with no gas trapping.
2. Primary determinant of optimal frequency = patient size.
3. Venegas and Fredberg recommend finding and using the “corner frequency” (Fig. 36.1).
 - a. Plot peak pressure or pressure amplitude measured at the carina versus frequency for lungs being ventilated with constant tidal volume.
 - b. Peak pressure falls rapidly with increasing frequency until it reaches a “corner,” where pressure either flattens or begins to rise.
 - c. At this frequency, the lowest pressure is required for ventilation without gas trapping.
 - d. Their theoretical analysis indicates that the smallest baby with the stiffest lungs and high airway resistance has an optimal frequency of 10–12 Hz or 600–720 bpm.
 - e. As compliance improves (increases), optimal frequency decreases. (Thus, anyone larger than the smallest baby would require a frequency <10–12 Hz).
 - f. As airway resistance improves (decreases), optimal frequency increases because it is easier for inspired gas to egress quickly.

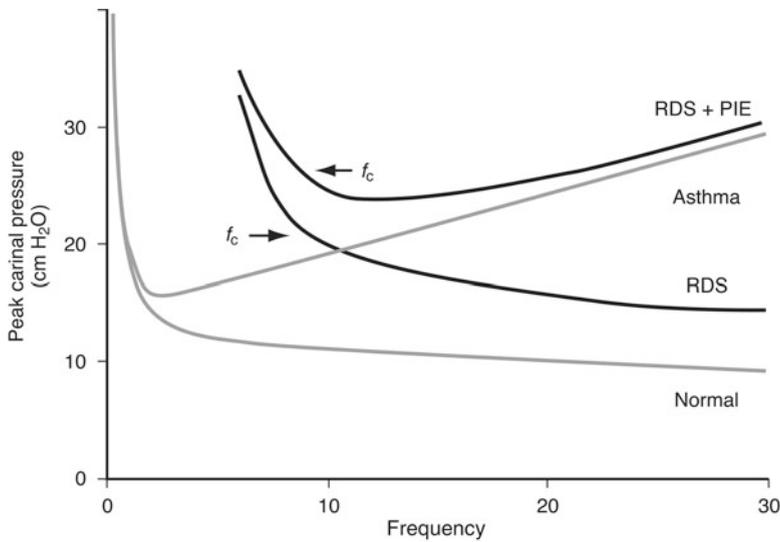


Fig. 36.1 Optimal frequency enables adequate ventilation with the lowest airway pressure, and it is determined by lung size, compliance, and airway resistance. Pressure necessary to achieve adequate ventilation decreases with increasing frequency for normal lungs and lungs with decreased compliance, but gas trapping may result at higher frequencies. Increased airway resistance changes the shape of the curve, lowering the optimal frequency. Lungs with poor airway resistance and hyperinflated by trapped gas, as happens in infants with BPD, have a sharply lower optimal frequency. Note how infants with RDS may be well ventilated at a frequency ~10 Hz, but if their condition deteriorates into PIE or BPD, they may be better ventilated at lower frequencies (these concepts were developed from the theories and numerical analyses of Jose Venegas and Jeff Fredberg. See: Venegas JG, Fredberg JJ. Understanding the pressure cost of high frequency ventilation: why does high-frequency ventilation work? *Crit Care Med.* 1994;22:S49–7)

- g. Since mechanical ventilation of infants triggers inflammation, airway resistance usually worsens the longer an infant is ventilated, and it is wise to use lower frequencies for “sicker” babies.
 - h. Lower frequencies are also indicated when lung volume is optimized, which is essential for adequate oxygenation.
 - i. Therefore, frequencies <10–12 Hz are usually optimal.
 - j. Since HFJV relies on passive exhalation, frequencies a few hertz lower may be required to avoid gas trapping. (The same consideration applies when high pressure amplitudes are used with HFOV).
- C. Flow-streaming, dead space reduction, and direct alveolar ventilation
1. High velocity HFV inspiratory gas spirals into the lungs down the central core of airways, or along one wall of some airways, as it passes bifurcations in short, abrupt bursts.
 - a. The higher the velocity, the sharper the point on the bullet-shaped (parabolic) velocity profile of the in-rushing gas (Fig. 36.2).

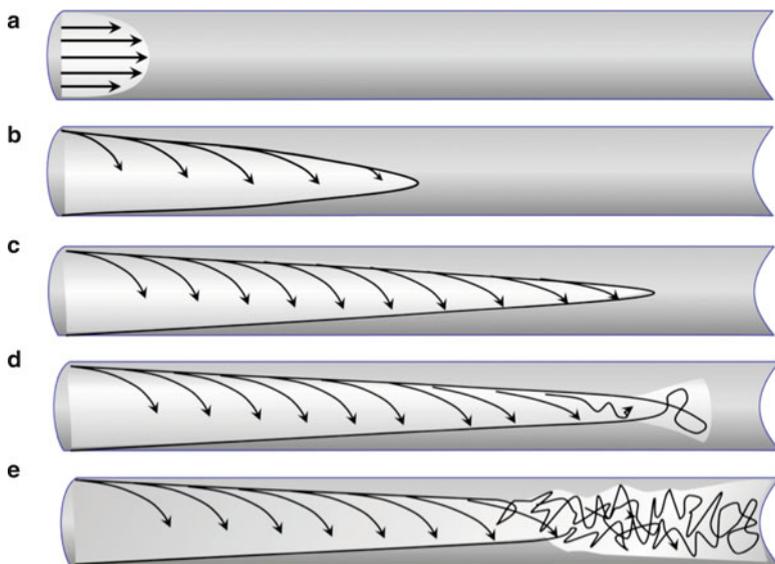


Fig. 36.2 When fluid (liquid or gas) flows into a tube, the velocity profile of the flow is determined by energy and time. (Copyright 2011 Bunnell Inc., Salt Lake City, UT). **(a)** When energy is low, overall flow is relatively slow and laminar with molecules in the center of the tube moving faster than those at the wall, creating a parabolic velocity profile. **(b)** As the fluid moves faster with more energy, the flow begins to spiral with greater velocity in the center of the tube. **(c)** The degree to which flow in the center of the tube outpaces that at its wall is determined by the combination of energy and time or distance. A short, energetic flow pulse (e.g., an HFJV inspiration) will produce a spiral with an exaggerated parabolic velocity profile. **(d)** With either sufficient (i.e., excessive) energy or time, the tip of the moving fluid transitions into turbulence. **(e)** Once turbulence is established, molecular motion is chaotic and the velocity profile of the fluid is flat across the diameter of the tube

- b. If inspiration lasts too long, this high velocity flow will transition into turbulent flow with a flat velocity profile.
 - c. Physiologic or effective dead space volume is reduced, since only portions of the anatomic dead space are used, and gas expired from the last breath is not pushed back into alveoli ahead of the next fresh gas inspiration.
 - d. Fresh gas penetrates some alveoli directly even when $V_T < V_{D,anatomic}$.
2. In HFOV, gas is sucked from many airways into one (the trachea), causing acceleration and a turbulent, *flat* expiratory wave front (velocity profile).
3. The net effect of several HFOV cycles: fresh gas advances down the core of airways while exhaled gas moves out along airway walls (Fig. 36.3).
4. In HFJV, gas flows out passively with lung recoil, seeking the path of least resistance in the annular or “unused” spaces around the highly accelerated inspired gas as illustrated in Fig. 36.2c.

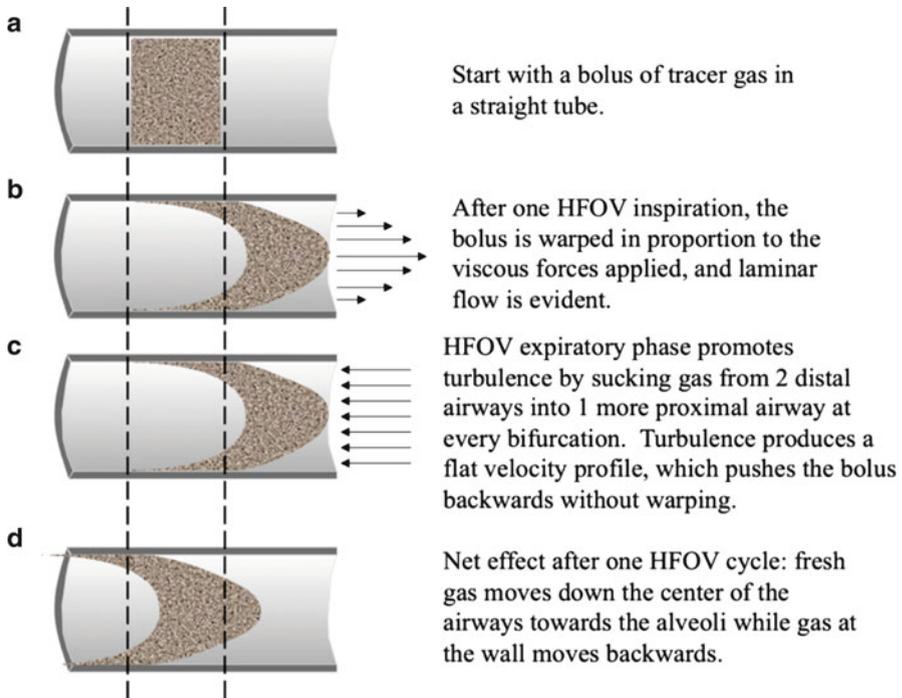


Fig. 36.3 Viscous shear and airway velocity profiles associated with HFOV (modified with permission from Haselton FR, Scherer PW. Bronchial bifurcations and respiratory mass transport. *Science* 1980;208:69. Reprinted with permission from AAAS). (a) Tracer bolus before oscillation. (b) Bolus after one laminar flow inspiratory “push”. (c) Bolus at the beginning of a turbulent expiratory “pull”. (d) Change in tracer bolus after one complete HFOV cycle

D. Increased bulk flow (convection) and enhanced diffusion.

1. The abundant fresh gas of high-frequency inspirations washes expired gas from upper airways.
2. Increased wash out of expired gases increases O₂ and decreases CO₂ partial pressures at the intra-airway/alveolar gas exchange boundary, thereby increasing diffusion.

V. HFV in the NICU

A. There are two basic techniques, HFJV (Jet) and HFOV (Oscillator), plus hybrid devices.

1. HFJV

- a. Inspired gas is injected down the endotracheal tube through a jet nozzle (typical frequency range: 240–660 bpm or 4–11 Hz).
- b. The jet nozzle is built into a special 15-mm ET tube adapter (“LifePort®” ETT adapter, Bunnell Inc.) with two side ports for:

- (1) Gas injection
 - (2) Distal airway pressure monitoring
- c. Spontaneous breathing, concomitant IMV, and HFJV exhalations occur via the main ETT lumen.
2. HFOV
- a. HFOV provides sinusoidal, push–pull, piston-type ventilation from <math><180\text{--}900\text{ bpm}</math> (3–15 Hz).
 - b. Some devices allow I:E or % I-time to be adjusted from 1:1 to approximately 1:2.3.
3. Hybrids (high-frequency positive pressure ventilators, “flow-interrupters,” and combined HFV/IMV devices that provide jet, oscillatory, or positive-pressure ventilation over similar frequency ranges) are also used around the world.
- B. HFV device similarities
1. Small tidal volumes, pressure attenuation, and the need to manage PEEP and P_{aw} for optimal lung volume
 2. Device design: each starts with CMV basics (gas flowing by the patient’s ETT with a valve downstream that may be closed for tidal volume delivery or restricted to provide PEEP), then adds the means to rapidly move gas in and out of the lungs.
 - a. Some devices either work in tandem with or are built into a conventional ventilator. (These approaches are used with HFJV and various hybrids).
 - b. An oscillating diaphragm or piston is the easiest way to move gas in and out rapidly, and this produces oscillatory ventilation.
 - c. Interrupting a source of gas flow can also produce high-frequency inspirations fairly easily, and passive expiration can occur via elastic recoil of the lungs. (This approach is used with HFJV and various hybrids).
 - d. A jet nozzle is used to inject fresh gas directly into an ETT during HFJV.
- C. How HFV devices differ from each other and CMV
1. Gas delivery and inspiration
 - a. HFV produces a train of fresh gas boluses that penetrate through the dead space of the airways without pushing the resident dead space gas ahead of the fresh gas as happens when we breathe normally or are ventilated conventionally.
 - b. Locating the HFV gas delivery source as close to the patient as possible minimizes compressible dead space volume and enhances inspiratory penetration.
 - c. HFJV: sudden, brief inspirations are injected directly into the ETT tube from a jet nozzle that can be embedded in a special ETT adapter (“LifePort”), enabling effective ventilation with tidal volumes in the range of 0.5–1.0 mL/kg body mass.

- (1) Overall gas flow during HFJV is most conservative, requiring ~ 1 L/min for infants vs. up to 20 L/min with HFOV and hybrids.
- (2) Although the inspired gas boluses embody enough energy for the creation of turbulence, there may be insufficient time for it to develop because inspiration is so brief. [Typical inspiratory time (T_I)=0.02 s, or 20 ms.]
- (3) Thus, “transitional” flow (transitional between laminar and turbulent flow) may be created, which is characterized by an exaggerated laminar-type velocity profile, where gas in the center of the airways swirls into the lungs much faster than gas near the airway walls, dramatically reducing physiologic or effective pulmonary dead space volume.

d. HFOV.

- (1) Inspirations are slower than HFJV at frequencies below 15 Hz, producing laminar to transitional flow, where gas in the center of the airways travels toward the alveoli faster than gas near the airway walls.
- (2) Active expirations are faster than the passive expirations of HFJV, producing turbulent flow with blunt velocity profiles as gas from every set of two distal airway branches is sucked into its one adjoining more proximal airway.
- (3) Net effect of HFOV is similar to that of HFJV where effective tidal volumes may be < anatomic dead space volume.

2. Exhalation and gas trapping

- a. Exhalation is passive with HFJV and nonoscillatory hybrids, relying on the elastic recoil of the lungs.
- b. Exhalation is active with HFOV; gas is not only pushed into the lungs on inspiration, but also sucked back out on expiration.
- c. Gas trapping is a primary concern with HFV, and it becomes apparent when PaCO_2 rises and cannot be reduced by increasing airway pressure amplitude.
 - (1) HFJV expiratory waveform is a classic exponential decay to PEEP as patients exhale passively.
 - (a) If HFJV rate is too high, inadvertent PEEP or “auto-PEEP” may occur, which indicates gas trapping.
 - (b) Reducing HFJV rate, which increases T_E when T_I is held constant, alleviates this type of gas trapping.
 - (2) HFOV (e.g., SensorMedics 3100A) expiratory waveform is sinusoidal, lasting twice as long as inspiration when % inspiration time=33 (I:E=1:2).
 - (a) Minimum pressure is below what would be PEEP if exhalation were to occur passively.

- (b) The greater the HFOV pressure amplitude, the lower the minimum pressure excursion.
- (c) If HFOV pressure amplitude is sufficiently large, this minimum pressure waveform excursion may collapse compliant airways, causing “choke points” and gas trapping.
- (d) Raising P_{aw} , which increases intra-airway pressure, may alleviate gas trapping with HFOV.

d. Net effects of passive vs. active expiration are:

- (1) HFJV is usually operated at lower frequencies than HFOV.
- (2) HFOV is usually operated at higher P_{aw} compared to HFJV to maintain the same level of oxygenation.

3. Effective HFV frequency varies with different HFV devices.

- a. Using a frequency too far below or above the corner frequency of the lung may result in unnecessarily large pressure amplitudes in the proximal airways.
- b. HFJV and nonoscillatory hybrid rates are generally lower than HFOV frequencies in order to accommodate passive exhalation.
 - (1) HFJV is similar to CMV: the faster you go, the more CO_2 you eliminate, as long as the rate is not so high as to cause gas trapping.
 - (2) With T_1 typically set as short as possible, rate determines I:E and exhalation time (T_E).
 - (a) For example, I:E changes from 1:4 at 600 bpm (10 Hz) to 1:9 at 300 bpm (5 Hz) when T_1 is 0.02 s.
 - (b) High rates work fine when lungs are small and stiff with short time constants (e.g., RDS in preterm lungs).
 - (c) Rates as low as 240 bpm (4 Hz) where I:E = 1:12 work best with lung disease characterized by long exhalation time constants such as pulmonary interstitial emphysema (PIE), bronchopulmonary dysplasia (BPD), and meconium aspiration syndrome (MAS).
 - (d) See “Pressure Waveforms and Intrapulmonary Gas Distribution” below for further discussion of pulmonary time constants.
- c. HFOV: can be used at higher frequencies (e.g., 15 Hz) because whatever is pushed into the lungs is also sucked back out, although higher frequencies may not be optimal (see “Corner Frequency” above).
 - (1) Tidal volume decreases with increasing HFOV frequency with a set I:E, because of the concomitant decrease in the time allotted for inspiration (see “Inspiratory Times and I:E” below).

- (2) Since ventilation (CO_2 elimination) is proportional to the square of tidal volume (V_T^2) during HFV, ventilation paradoxically decreases with increasing HFOV frequency.
 - (3) Raising HFOV frequency may therefore require an increase in pressure amplitude to maintain appropriate ventilation.
 - (4) Pressure amplitude oscillates around the mean pressure, and if the negative excursion of pressure amplitude during expiration goes too low, airways may collapse and cause gas trapping.
- d. Lowering HFOV frequency increases delivered tidal volume, which may improve gas exchange, enable reduction in pressure amplitude, and alleviate gas trapping, as long as frequency does not go too far below the corner frequency.
4. Inspiratory times and I:E
- a. HFJV: Rate and T_I settings determine I:E.
 - (1) HFJV rate and T_I are typically adjustable from 240 to 660 bpm and 0.020–0.034 s, respectively.
 - (2) I:E is therefore adjustable from 1:2 to 1:12 depending on rate and T_I settings.
 - b. HFOV: % T_I is used, or I:E is set directly at 1:1 to 1:2.3.
 - (1) % T_I is the percent of the breath cycle allotted to inspiration.
 - (2) T_I and frequency are inversely related, so when % T_I is fixed at 33% establishing I:E=1:2, and frequency is changed, T_I and T_E change proportionally in the opposite direction.
 - (3) 1:2 is almost universally used for reasons that may be mostly historical—a reaction to early problems when inadequate P_{aw} led to gas trapping.
 - (4) HFOV at I:E=1:2 lengthens exhalation time, reducing the negative excursion of the pressure waveform that can cause airway collapse.
5. Pressure waveforms and intrapulmonary gas distribution
- a. HFV provides ventilation that favors lung disorders with short time constants, such as RDS, where lung compliance is low (“stiff lungs”).
 - (1) Gas can flow in and out of such lungs very quickly in either direction.
 - (2) The diffuse, homogeneous nature of RDS is compatible with both HFOV’s sinusoidal and HFJV’s more “spiked” and complex airway pressure waveform.
 - b. Intrapulmonary distribution of HFV is determined primarily by airway resistance because of the high velocity of its inspiratory flow.

- (1) HFJV inspiratory airway pressure rises sharply from PEEP and ends abruptly (spikes) at the end of inspiration, which is usually 0.020 s.
 - (2) HFOV inspiratory airway pressure rises from its P_{aw} and returns to its P_{aw} within the inspiratory portion of the breath cycle (it is rounded), which is longer than that of HFJV at all HFOV rates <15 Hz.
 - (3) The faster the inspiration, the less gas will penetrate inflamed and restricted peripheral airways like those found in PIE.
 - (a) The concept of pulmonary time constants, which are a measure of how quickly the lungs can inflate or deflate, helps explain this phenomenon.
 - (b) Time constants are calculated by multiplying airway resistance and lung compliance.
 - (c) When lung compliance is low (as with RDS in the preterm baby), the time constant is short, and thus it is possible to ventilate preterm babies at high rates with a short T_1 and small tidal volume.
 - (d) When airway resistance is high, as is the case with asthma in adults and PIE in infants, the time constant is long, meaning it takes more time for inspirations to reach the alveoli and for expiration to be completed.
 - (e) This concept may explain why HFJV works well for PIE: it automatically reduces ventilation of the long time constant-injured areas of the lungs in favor of the short time constant-healthier areas of the lungs. (Less gas reaches damaged bronchioles and alveoli downstream from narrowed airways, while more gas is delivered through more patent airways to healthier areas of the lungs with better perfusion).
- c. HFJV waveforms embody greater frequency content (i.e., energy content at several multiples or harmonics of the primary frequency), which makes it helpful in treating nonhomogeneous lung disorders.
- (1) HFJV intrapulmonary distribution is ideal for MAS, BPD, and RDS compromised by PIE.
 - (2) Operating HFJV at lower rates [e.g., 240 bpm (4 Hz)] enables I:E with longer exhalation times (I:E = 1:12), enabling trapped interstitial gas more time to diffuse from the lungs.

6. Spontaneous breathing

- a. Gas flow used during HFJV is extremely low (~1 L/min in infants), so gas for spontaneous breathing is supplied by tandem CMV. (Hybrids supply gas for spontaneous breathing in a similar manner).
- b. Information concerning spontaneous breathing by infants during HFOV is lacking.

VI. Alveolar recruitment and maintenance of lung volume during HFV

- A. The most important and challenging goal of lung protective ventilation with HFV: full alveolar recruitment, as indicated by chest radiography and ability to reduce F_1O_2 to <0.30 .
- B. Focus on P_{aw} first.
 1. HFJV: maintain current P_{aw} when starting HFJV unless it is very high (>15 cm H_2O) or switching from HFOV to HFJV.
 - a. If starting from CMV, raise PEEP by ~ 2 cm H_2O to maintain P_{aw} .
 - b. If starting from HFOV, either maintain P_{aw} or reduce it by $1-2$ cm H_2O .
 2. HFOV: raise P_{aw} by $2-5$ cm H_2O when starting from either CMV or HFJV.
- C. Optimize P_{aw} .
 1. P_{aw} during HFOV will typically be at least 2 cm H_2O higher than that required by CMV or HFJV to maintain the same oxygenation.
 2. Use chest radiographs in conjunction with pulse oximetry to assess either atelectasis and need for more P_{aw} , or hyperinflation and indication for less P_{aw} .
 3. Increased P_{aw} may impede pulmonary blood flow and cardiac output; thus, one must maintain a balance between adequate lung volume and right ventricle afterload.
 4. For HFJV, one can use CMV at 5 bpm to determine if PEEP is adequate once SpO_2 is stable, and F_1O_2 is adjusted so that SpO_2 is close to 90% .
 - a. Make certain that CMV PIP is set high enough to cause adequate chest rise.
 - b. Switch from 5 bpm CMV to CPAP or as close to 0 bpm as possible without causing apnea alarms on the CMV (i.e., use minimal CMV rate, PIP, and T_1).
 - c. If SpO_2 remains stable, PEEP is adequate and CMV breaths are not needed. (Continue with CMV in CPAP mode or at minimal rate, PIP, and T_1).
 - d. If SpO_2 falls, increase PEEP by $1-2$ cm H_2O and reinstitute CMV at 5 bpm for a few minutes until SpO_2 returns to baseline ($\sim 90\%$).
 - e. Repeat switch to CPAP or minimal CMV with higher PEEP until HFJV can continue with CPAP or minimized CMV with SpO_2 stabilized near 90% with reduced F_1O_2 .
 - f. If $F_1O_2 > 0.30$, determine if further alveolar recruitment is indicated.
 5. For HFOV, use pulse oximetry and chest radiography to assess lung inflation to find and maintain optimal P_{aw} .
 6. Lung inflation is typically assessed using the top margin of the dome of the right hemidiaphragm and its location in relation to ribs on chest radiograph. Optimal lung inflation is achieved when this margin

is between the bottom of the eighth or ninth rib and no more than midway between the ninth and tenth ribs.

7. Recommendations for achieving optimal lung inflation during HFOV using this technique:
 - a. Below the 11th rib, decrease frequency first in 2 Hz decrements until 10 Hz is reached, then decrease P_{aw} by 20%.
 - b. Between the 10th and 11th rib, decrease frequency first in 2 Hz decrements until 10 Hz is reached, then decrease P_{aw} by 10%.
 - c. Between 8 and 9.5 ribs, no change.
 - d. Above the eighth rib, increase P_{aw} by 10%.
 - e. Above the seventh rib, increase P_{aw} by 20%.
8. Assuming acceptable lung inflation during HFOV:
 - a. $F_{I}O_2 > 0.40$, increase P_{aw} in 1 cm H_2O increments until $F_{I}O_2$ can no longer be decreased.
 - b. $F_{I}O_2$ 0.30–0.40, may increase P_{aw} or make no change, depending on lung inflation.
 - c. $F_{I}O_2 < 0.30$, decrease P_{aw} in 1 cm H_2O decrements until $F_{I}O_2$ needs to be increased.
 - d. If $F_{I}O_2$ requires an increase of 0.2, evaluate lung inflation.

VII. Who HFV helps and why

A. HFV is “very gentle.”

1. It has proven effective in preventing lung injury in preterm infants.
 - a. HFV should begin as soon as exogenous surfactant and nasal CPAP/CMV appear to be inadequate, although early use is controversial because of a higher incidence of cerebral injury (IVH, PVL) in some observations and studies.
 - b. Strategies of implementation are key to avoiding such injuries.
 - (1) Most important: avoid hyperventilation by careful monitoring of $PaCO_2$ (transcutaneous continuous monitoring is recommended).
 - (2) Full lung recruitment and maintenance of appropriate lung volume is also key.
 - c. HFV may enhance delivery of exogenous surfactant.
2. HFJV has proven effective in treating lung injury and air leaks such as PIE.
 - a. Implementation at the first sign of air leaks is key.
 - b. Strategy is straightforward:
 - (1) Do not try to minimize P_{aw} ; it should be managed to maintain adequate lung volume.
 - (2) Minimize the use of CMV and manual ventilation.

- (3) If interstitial gas is evident, use lower rates and I:E with prolonged T_E to enable diffusion of gas from affected areas.
3. Although HFOV studies have focused on preventing rather than treating lung injury, inherent lung protective ventilation features of HFOV support its use in preference to CMV.
- B. Combining unique characteristics of HFV offers a broad range of therapeutic capabilities.
 1. Every HFV device offers effective use of high-frequency and small V_T within the limits of its design.
 2. Clinicians must learn individual device controls that enable separate management of ventilation and oxygenation, when it is appropriate to increase or decrease P_{aw} , and how to effectively use concomitant CMV breaths, if available, for alveolar recruitment.
- C. HFV devices can ventilate patients that are impossible to ventilate any other way.
 1. Severe congenital diaphragmatic hernia patients, where small HFV V_T and high P_{aw} can preserve what little lung is available for ventilation.
 2. Upper airway leaks and fistulas where HFJV “shoots” inspired gas right past disruptions, enabling downstream ventilation and airway injuries to heal.
 3. Cardiac surgery patients.
 - a. HFJV can facilitate cardiac output at relatively low P_{aw} .
 - b. Surgical repair can be accomplished while on HFJV, providing improved access to the heart and major vessels.
 - c. Chest may be closed postsurgery without adverse effects on cardiac output.
 4. Obstructive lung disorders, such as airway stenosis and aspiration pneumonia, where HFV may facilitate removal of excess secretions and improve ventilation/perfusion matching.
 5. Patients with conditions where HFV may facilitate delivery or improve the benefits of using specialty gases such as nitric oxide or helium (e.g., PPHN or status asthmaticus).
 6. BPD and pulmonary hyperinflation/gas trapping.
 - a. Success follows proper strategy and patience (average time to extubation was 7 days in a retrospective study of 10 patients treated with HFJV)
 - b. Strategy
 - (1) No CMV breaths.
 - (2) Moderate PEEP (~8 cm H_2O) to maintain airway patency.
 - (3) Lower rates and I:E with prolonged T_E to enable diffusion of gas from affected areas (e.g., 240 bpm with I:E = 1:12).

VIII. How to maximize the benefits and minimize the risks of HFV.

- A. Learn when to start HFV without hesitation when indicated by pathophysiology, experience, and worsening patient condition.
- B. Match ventilator strategy to pathophysiology and the availability of an appropriate device.
 - 1. Using appropriate ventilator strategies for specific lung disorders is more important than which ventilator you use, but learn the limitations of the devices you have available.
 - 2. HFJV limitations.
 - a. Passive exhalation
 - (1) Adjust rate for patient size (larger patients require lower rates).
 - (2) Pay attention to lung time constants: more compliant lungs require lower rates.
 - b. Be ready to suction right after initiation of HFJV.
 - (1) HFJV facilitates mucociliary clearance; be ready to take advantage of it.
 - (2) Only suction when indicated; otherwise, you will unnecessarily collapse alveoli.
 - 3. HFOV limitations.
 - a. Active exhalation
 - (1) Must increase P_{aw} to avoid gas trapping.
 - (2) Select HFOV patients who will benefit from higher P_{aw} (e.g., RDS).
 - b. May not work well with nonhomogeneous lung disorders.
 - c. Watch out for mucus impaction.
 - 4. Hybrids, combined HFV and CMV, including HFJV.
 - a. Compressible volume of conventional-style circuits limits ventilator power and effectiveness.
 - b. Concomitant CMV must be managed appropriately.
 - (1) Increase CMV rate to actively recruit collapsed alveoli (~5 bpm).
 - (2) Decrease CMV (to CPAP if possible) when atelectasis resolves.
 - (3) Cease CMV (i.e., use CPAP) when air leaks are present.
- C. Find and use optimal PEEP/ P_{aw} , paying particular attention to whether you need to recruit more lung volume or you need to stabilize the volume already available.
- D. Recruit collapsed alveoli by *temporarily* increasing concomitant CMV rate with HFJV or P_{aw} with HFOV.

1. If recruitment is successful as indicated by improved oxygenation, CMV rate should be reduced and PEEP must be optimized with HFJV.
 2. $P_{\bar{a}w}$ should be optimized with HFOV to support open alveoli without compromising cardiac output.
- E. Keep $PaCO_2$ in proper range by careful monitoring. (Transcutaneous CO_2 monitoring is strongly recommended).
- F. Adjust HFV settings rationally as patient's condition changes.
1. In general, do not drop PEEP or $P_{\bar{a}w}$ when $F_I O_2$ is still >0.30 .
 2. Do not stop prematurely.
 - a. If you get an unacceptable blood gas, reassess and adjust strategy.
 - b. If you get a normal or better blood gas, wean appropriately.
 - c. Weaning to conventional ventilation may not be needed; you can extubate directly to nasal CPAP.

IX. Conclusions

- A. HFV is not for every patient, but it can provide incredible benefits if the appropriate device is used on the appropriate patient in the appropriate way at the appropriate time.
- B. Let common sense and solid knowledge of pulmonary pathophysiology and respiratory therapy be your guides.

Suggested Reading

- Bandy DP, Donn SM, Nicks JJ, Naglie RA. A comparison of proximal and distal high-frequency jet ventilation in an animal model. *Pediatr Pulmonol.* 1986;2:225–9.
- Boros SJ, Mammel MC, Coleman JM, et al. A comparison of high-frequency oscillatory ventilation and high-frequency jet ventilation in cats with normal lungs. *Pediatr Pulmonol.* 1989;7:35–41.
- Boynton BR, Villanueva D, Hammond MD, et al. Effect of mean airway pressure on gas exchange during high-frequency oscillatory ventilation. *J Appl Physiol.* 1991;70:701–7.
- Clark RH. High-frequency ventilation. *J Pediatr.* 1994;124:661–70.
- Donn SM, Zak LK, Bozynski MEA, et al. Use of high-frequency jet ventilation in the management of congenital tracheoesophageal fistula associated with respiratory distress syndrome. *J Pediatr Surg.* 1990;25:1219–21.
- Harris TR, Bunnell JB. High-frequency jet ventilation in clinical neonatology. In: Pomerance JJ, Richardson CJ, editors. *Neonatology for the clinician.* Norwalk, CT: Appleton & Lange; 1993. p. 311–24.
- Haselton FR, Scherer PW. Bronchial bifurcations and respiratory mass transport. *Science.* 1980;208:69–71.
- Henderson Y, Chillingworth FP, Whitney JL. The respiratory dead space. *Am J Physiol.* 1915;38:1–19.
- Keszler M, Durand DJ. Neonatal high-frequency ventilation. Past, present, and future. *Clin Perinatol.* 2001;28:579–607.
- Kocis KC, Meliones JN, Dekeon MK, Callow LB, et al. High-frequency jet ventilation for respiratory failure after congenital heart surgery. *Circulation.* 1992;86(Suppl II):II-127–32.

- Musk GC, Polglase GR, Bunnell JB, McLean CJ, Nitsos I, Song Y, Pillow JJ. High positive end-expiratory pressure during high frequency jet ventilation improves oxygenation and ventilation in preterm lambs. *Pediatr Res.* 2011;69:319–24.
- Perez Fontan JJ, Heldt GP, Gregory GA. Mean airway pressure and mean alveolar pressure during high-frequency jet ventilation in rabbits. *J Appl Physiol.* 1986;61:456–63.
- Slutsky AS. Lung injury caused by mechanical ventilation. *Chest.* 1999;116(1 Suppl):9S–15.
- Slutsky AS. Mechanisms affecting gas transport during high-frequency oscillation. *Crit Care Med.* 1984;12:713–7.
- Venegas JG, Fredberg JJ. Understanding the pressure cost of high frequency ventilation: why does high-frequency ventilation work? *Crit Care Med.* 1994;22:S49–57.

Chapter 37

High-Frequency Jet Ventilation

Martin Keszler

I. Indications

- A. *Late rescue treatment:* High-frequency jet ventilation (HFJV) has been used extensively for the treatment of refractory respiratory failure unresponsive to conventional mechanical ventilation (CMV). Air leak syndrome has been the most commonly treated underlying disorder, but infants with pulmonary hypoplasia secondary to diaphragmatic hernia, respiratory distress syndrome (RDS), meconium aspiration syndrome, and pneumonia are also treated routinely using HFJV with considerable success in the rescue mode.
- B. *Early rescue treatment:* HFJV has documented efficacy and is used extensively in the treatment of moderate to severe RDS, pulmonary interstitial emphysema (PIE), large leaks through a bronchopleural fistula (intractable pneumothorax) or tracheoesophageal fistula, abdominal distention with poor chest wall compliance, congenital diaphragmatic hernia, and in patients with meconium aspiration syndrome with or without pulmonary hypertension.
- C. *Prophylactic use:* Despite evidence of effectiveness of HFJV in lowering the incidence of bronchopulmonary dysplasia (BPD) in one large multi-center study, first-line treatment of infants with RDS at high risk for developing BPD is not widely practiced.

II. Benefits of HFJV

- A. Lower pressure amplitude (Δ Pressure = peak inspiratory pressure [PIP] – positive end-expiratory pressure, PEEP), compared to conventional ventilation
- B. Very effective CO₂ elimination
- C. Flexibility to use both low and high mean airway pressure (P_{aw}) as indicated
- D. More rapid resolution of air leaks
- E. Decrease in airflow through points of airway disruption

M. Keszler, MD (✉)

Department of Pediatrics, Women and Infants' Hospital of Rhode Island, Brown University,
101 Dudley Street, Providence, RI 02905, USA

e-mail: mkeszler@wihri.org

- F. Ability to use high PEEP safely
- G. Effective recruitment and maintenance of lung volume with background sigh
- H. Improved hemodynamics because of less interference with venous return
- I. Mobilization of secretions and aspirated material
- J. Decreased risk of BPD

III. Possible complications of HFJV

- A. Mucosal damage to the trachea and large bronchi was reported in some early studies when inadequate humidification was used. This is no longer a problem.
- B. Increased incidence of periventricular leukomalacia and intraventricular hemorrhage (IVH) reported in one study, likely related to inadvertent hyperventilation or rapid change in PaCO_2 . Similar findings were seen in some oscillatory ventilation studies and with conventional hyperventilation. Risk of inadvertent hyperventilation can be minimized by using transcutaneous PCO_2 monitoring, especially when initiating HFJV.
- C. Air trapping is possible if an inappropriately high ventilator rate is used. This is a phenomenon that can occur with all ventilators.

IV. Clinical use

A. Patient selection

1. Risks and benefits should be carefully considered before initiating HFJV.
2. Early, rather than late, initiation is preferable in most situations.
3. Patient selection should be based on clinical experience and published evidence of efficacy.

B. Basic control of gas exchange

1. Oxygenation is determined by FiO_2 and $\text{P}\bar{\text{a}}\text{w}$ (increased $\text{P}\bar{\text{a}}\text{w}$ = improved oxygenation).
2. $\text{P}\bar{\text{a}}\text{w}$ is determined by PIP, PEEP, and inspiratory time with PEEP being by far the most important. Because of the extremely short T_I , the $\text{P}\bar{\text{a}}\text{w}$ is only slightly above PEEP.
3. Ventilation (CO_2 elimination) is primarily controlled by pressure amplitude ($\Delta P = \text{PIP} - \text{PEEP}$), which determines the delivered tidal volume (V_T). In HFJV, CO_2 elimination is proportional to V_T^2 ; therefore, even small changes in V_T can result in large swings in PaCO_2 . PIP should be increased by 1–2 cm H_2O to lower PaCO_2 and lowered by 1–2 cm H_2O to increase PaCO_2 .
4. When lung volume is optimized, compliance may improve dramatically and this can lead to a rapid drop in PaCO_2 . Close observation of the chest wall movement and aggressive lowering of PIP may be needed to avoid dangerously low PaCO_2 . Transcutaneous CO_2 monitoring is recommended to minimize this risk.
5. Rate has a relatively minor effect on ventilation. Usual range is 300–500 breaths/min, depending on size of baby and time constants. A rate that is too fast may increase PaCO_2 because of gas trapping.

6. Unlike with HFOV, a change in ventilator rate does not change the V_T , unless the rate change eliminates or causes gas trapping.
7. T_I should almost always remain at the lowest possible value of 0.02 s.
8. Background IMV rate of 2–5 breaths/min may be superimposed on the HFJV pulses to recruit/maintain lung volume (periodic sigh). The PIP should be slightly lower than the HFJV PIP or so as not to interrupt the jet ventilator. T_I of the sigh breaths should be about 0.5 s. Background IMV should be omitted in the presence of overexpansion or air leak.
9. Note that sighs recruit lung volume but adequate P_{aw} (PEEP) is needed to maintain it. Higher PEEP is needed with HFJV than with CMV, because of the very short T_I .
10. Weaning from HFJV is accomplished primarily by weaning PIP, leaving rate unchanged, except as dictated by changes in time constants (see below).
11. Recognize that decreasing ΔP by lowering PIP also lowers P_{aw} and thus affects oxygenation. This problem can be avoided by increasing PEEP to compensate.

C. Important principles of clinical application

1. The standard 15 mm endotracheal tube (ETT) adapter needs to be replaced with the Bunnell Life Port® adapter prior to initiating HFJV. The jet and pressure monitoring lines should be initially capped, then connected to the jet circuit with the ventilator in STANDBY mode.
2. The tip of the ETT should not be too close to the carina—optimally at least 1 cm above—to avoid inadvertently directing the jet stream preferentially down one or the other main bronchus.
3. The ETT should be cut to the shortest practical length to avoid bending and kinking, the patient circuit should be supported so as to keep the tube straight.
4. The baby's head must be kept in the midline and slightly extended with a shoulder roll, to keep the ETT as straight as possible with the bevel in the midline and to optimize penetration of the jet stream down the airways. Allowing the head to be turned to the side results in the jet stream hitting the wall of the trachea, because the ETT enters the trachea at an angle. This may result in mucosal damage and is certain to reduce the efficiency of gas exchange.

D. Matching ventilator strategy to disease pathophysiology

1. Choosing appropriate ventilator strategy is critical—a wrong strategy may lead to lack of response and/or complications.
2. Ventilator settings should be selected according to each patient's specific needs.
3. The underlying disease, postnatal age, and patient size must all be considered in choosing an appropriate strategy and settings.

E. Low pressure strategy

1. This approach may be appropriate when air leak is a major problem (e.g., PIE, pneumothorax), and the imperative is to reduce peak and mean airway pressures in an effort to resolve the air leak.
2. PIP should be set 10–15% below current levels on CMV.
3. PEEP should be 5–6 cm H₂O, depending on severity of air leak and coexisting lung disease (may need to be higher if severe atelectasis coexists with PIE).
4. Remember that oxygenation is related to P_{āw} and that it may deteriorate with the drop in PIP and short T_I. Marginal PaO₂ may have to be accepted and higher FiO₂ is often needed.
5. Permissive hypercapnia is usually appropriate.
6. Use of the low pressure strategy should be limited to infants with severe diffuse PIE and lung overexpansion; less severe or more localized PIE is best treated with an intermediate pressure strategy to avoid atelectasis.
7. T_I should be kept at 0.02 s.
8. Background IMV should be omitted in most cases of air leak, especially if the lungs are overexpanded and severe PIE is present.
9. Optimal HFJV rate depends on an estimation of the patient's time constants (usual range 360–420 breaths/min) to allow adequate expiratory time.
10. If marginal oxygenation prevents further decrease in PIP but PaCO₂ is low, decrease the pressure amplitude by increasing PEEP to avoid hypocapnia and to maintain oxygenation.
11. If diffuse atelectasis develops and oxygenation is inadequate, an increase in P_{āw}, usually by increasing PEEP is indicated, provided ventilation is adequate. The background IMV may be (re)started at this time.
12. If ventilation is also inadequate, PIP should be increased as well.
13. As air leak resolves and atelectasis becomes the dominant problem transition to the optimal volume strategy. (See below)

F. Optimal volume strategy

1. This strategy is appropriate in most situations, especially in RDS.
2. The goal is to optimize lung volume, thereby improving V/Q matching and to avoid the recruitment/derecruitment cycle typical of conventional large V_T ventilation.
3. When switching from CMV, P_{āw} should be increased by 10–15% by increasing PEEP.
4. The following rule of thumb can be used for initial PEEP settings:
 - a. Set PEEP at 6–7 cm H₂O if FiO₂ is <0.30
 - b. Set PEEP at 7–8 cm H₂O if FiO₂ is 0.30–0.50
 - c. Set PEEP at 9–12 cm H₂O if FiO₂ is >0.50
5. PIP should initially remain the same as on CMV. If starting HFJV without prior CMV, choose a pressure that results in adequate chest wall movement.

6. Background sigh rate is set at 5/min with T_1 of 0.3–0.5 s and PIP set 1–2 cm H_2O below the jet PIP.
 7. Rate of 420–500 breath/min with T_1 of 0.02 s is appropriate early in the course of RDS, because time constants are short. Later, as compliance improves, rate should be lowered to no more than 420 bpm to avoid gas trapping.
 8. Optimization of lung volume is reflected by marked improvement in oxygenation. If the initial settings do not allow weaning of FiO_2 to <0.35 , PEEP should be increased further.
 9. When adequate lung volume recruitment has been achieved, as evidenced by improved oxygenation, turn the background IMV rate down to 2/min and observe for possible deterioration of oxygenation. If oxygenation remains good, the PEEP is adequate. If oxygenation is deteriorating, return to a rate of 5/min to rerecruit lung volume and increase PEEP by 1–2 cm H_2O . Repeat the process, if necessary. When oxygenation remains stable with background rate of 2/min, leave the settings there.
 10. Background IMV may be omitted once stable lung volume is reached. However, note that the randomized clinical trials were done using background sighs.
 11. The background sigh breath rate or pressure should *not* be increased as a primary means of increasing P_{aw} . This is more safely accomplished by raising PEEP. Remember that the large V_T of conventional ventilation is the very thing you are trying to avoid.
 12. Once lung volume is optimized, compliance may improve rapidly. This will be reflected in improved chest wall movement and CO_2 elimination. *PIP must be lowered promptly to avoid hypocapnia.* Follow $PaCO_2$ closely and use transcutaneous CO_2 monitoring if available.
 13. The decreased PIP will lower P_{aw} as well, which is appropriate, because the recruited lungs are now more compliant and require less distending pressure to maintain recruitment (LaPlace's law).
 14. If the FiO_2 is ≤ 0.30 – 0.35 , the P_{aw} (PEEP) may need to be lowered further to avoid overexpansion.
 15. Periodic chest radiographs are helpful in verifying adequate lung expansion or detecting overexpansion. The goal is $8\frac{1}{2}$ to 9 rib expansion.
- G. Treatment of meconium aspiration syndrome (MAS) and persistent pulmonary hypertension of the newborn (PPHN).
1. MAS is a heterogeneous disorder and evolves rapidly over time. The effectiveness of HFJV in this syndrome is variable, ranging from poor to dramatic.
 2. Very early on, when large airways are obstructed with particulate meconium, HFJV may be ineffective as the jet stream is broken up by the obstructing debris. This can usually be corrected by effective suctioning of the airway.

3. On the other hand, HFJV provides a sort of internal vibration that helps to mobilize secretions/aspirated material. The expiratory flow along the periphery of the large airways brings the secretions proximally. Be ready to suction when initiating HFJV, as large amounts of meconium may be refluxed.
4. When the surfactant inactivation or inflammatory effect predominates, HFJV is usually quite effective and the high volume strategy is appropriate. However, beware of overexpansion and gas trapping. Remember: larger infants with airway obstruction have long time constants and need slower rates. Typical range is 240–360 breaths/min (4–6 Hz).
5. If there is evidence of overexpansion, the correct intervention is to lower the rate and allow more expiratory time, thus eliminating dynamic PEEP, rather than lowering the set PEEP. Adequate PEEP is needed to maintain airway patency and lung volume.
6. Although HFJV is an effective and relatively gentle means of hyperventilation, it is no longer recommended to treat PPHN with respiratory alkalosis. Avoid extremes of PaCO₂ and pH, which are easily achieved with HFJV, but are associated with an increased risk of intracranial hemorrhage and periventricular leukomalacia.

H. Miscellaneous conditions responsive to HFJV

1. When diaphragmatic excursion is impaired by increased intra-abdominal pressure, the small V_T of HFJV with sufficiently high PEEP to apply counter-pressure on the diaphragm and maintain lung volume is advantageous. Babies with acute abdominal distention from necrotizing enterocolitis or similar conditions and those postrepair of gastroschisis, diaphragmatic hernia, or omphalocele often respond dramatically with improved gas exchange and hemodynamics. Inadvertent hypocapnia may occur unless great care is taken to monitor chest wall movement and blood gases closely.
2. Infants with airway disruption, such as intractable pneumothorax with constant large flow through chest tubes, tracheoesophageal fistula, or tracheal tear, respond with improved gas exchange and decreased flow through the point of airway disruption. This is because the jet stream moves down the center of the airway with virtually no lateral pressure on the airway wall. The gas that does escape is probably expiratory gas. A strategy intermediate between the optimal and low-pressure strategy is probably best in these situations. *Each patient must be individually assessed regarding appropriate strategy.*
3. Infants with lung hypoplasia appear to benefit from the gentler ventilation and smaller V_T possible with HFJV. Because of the decreased number of alveoli in hypoplastic lungs, each lung unit must accept a larger than normal V_T with conventional ventilation, thus leading to volutrauma. Permissive hypercapnia is usually tolerated, but occasionally infants with PPHN need to have their PaCO₂ lowered into the high 30s before

PPHN will respond to iNO. An intermediate approach between the optimal volume and low pressure strategy works best. Beware of overexpansion of the lungs, which will exacerbate pulmonary hypertension.

4. Limited clinical experience and small studies suggest that HFJV may be useful in extremely immature preterm infants with evolving or established BPD. These infants have distended, “floppy” airways and are very prone to gas trapping, as the airways collapse during expiration. HFJV may benefit these infants by splinting these airways open with fairly high PEEP (7–9 cm H₂O), and allowing more efficient gas exchange and more even aeration of the lungs, in part because HFJV breaths are less affected by variation in regional impedance.

I. Weaning from HFJV

1. Weaning is accomplished by lowering FiO₂ first and PEEP second, once the FiO₂ is ≤ 0.30 .
2. PIP is lowered in response to low/normal PaCO₂ or excessive chest wall movement. Remember to compensate for decreasing PIP by increasing the PEEP, if necessary, to maintain P_{aw}.
3. Ventilator rate is not decreased as a means of weaning. However, if initially higher than 420/min, it may need to be lowered to accommodate lengthening time constants because of increasing compliance and/or increasing airway resistance as RDS evolves into early BPD.
4. Infants can be weaned from HFJV directly to CPAP. This is usually possible, once PIP is ≤ 10 –12 cm H₂O and PEEP ≤ 6 cm H₂O.
5. Alternately, once the pressure is ≤ 16 –20 cm H₂O and PEEP ≤ 7 cm H₂O, the infant can be switched to conventional ventilation. Usually, a 10% higher ΔP is needed after the change to maintain ventilation. PEEP may be lowered by 1 cm H₂O to maintain constant P_{aw}.

Suggested Reading

- Donn SM, Zak LK, Bozynski MEA, et al. Use of high-frequency jet ventilation in the management of congenital tracheo-esophageal fistula associated with respiratory distress syndrome. *J Pediatr Surg.* 1990;25:1219–22.
- Engle WA, Yoder MC, et al. Controlled prospective randomized comparison of HFJV and CV in neonates with respiratory failure and persistent pulmonary hypertension. *J Perinatol.* 1997;17:3–9.
- Gonzalez F, Harris T, Black P, et al. Decreased gas flow through pneumothoraces in neonates receiving high-frequency jet versus conventional ventilation. *J Pediatr.* 1987;110:464–6.
- Harris TR, Bunnell JB. High-frequency jet ventilation in clinical neonatology. In: Pomerance JJ, Richardson CJ, editors. *Neonatology for the clinician.* Norwalk, CT: Appleton & Lange; 1993. p. 311–24.
- Keszler M. High-frequency ventilation: evidence-based practice and specific clinical indications. *NeoReviews.* 2006;7(5):e234–49.

- Keszler M, Donn S, Bucciarelli R, et al. Multi-center controlled trial of high-frequency jet ventilation and conventional ventilation in newborn infants with pulmonary interstitial emphysema. *J Pediatr*. 1991;119:85–93.
- Keszler M, Durand D. High-frequency ventilation: past, present, and future. *Clin Perinatol*. 2001;28:579–607.
- Keszler M, Modanlou HD, Brudno DS, et al. Multi-center controlled clinical trial of high frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. *Pediatrics*. 1997;100:593–9.
- Sugiura M, Nakabayashi H, Vaclavik S, Froese AB. Lung volume maintenance during high frequency jet ventilation improves physiological and biochemical outcome of lavaged rabbit lung. *Physiologist*. 1990;33:A123.
- Wiswell TE, Graziani LJ, Kornhauser MS, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics*. 1996a;98:918–24.
- Wiswell TE, Graziani LJ, Kornhauser MS, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics*. 1996;98:1035–43.

Chapter 38

High-Frequency Oscillatory Ventilation

Reese H. Clark

I. Introduction

- A. Definition—High-frequency oscillatory ventilation (HFOV) is a rapid rate, low tidal volume form of mechanical ventilation. HFOV uses a constant distending pressure (mean airway pressure) with pressure oscillations around the mean pressure. The ventilatory rates range from 300 to 900 cycles per minute. Tidal volumes are often less than the dead space so HFOV relies on alternative mechanisms of gas exchange to promote carbon dioxide removal from the lung.
- B. Reasons for the development of HFOV:
 1. To improve gas exchange in patients with severe respiratory failure
 2. To reduce ventilator-induced lung injury
 - a. Prevention of volutrauma. HFOV dramatically reduces the tidal volume needed to maintain ventilation (normocapnia). During HFOV, the lung can be held close to mean lung volume. There is minimal change in lung volume with each delivered breath. Visually, this translates to chest wall vibration that is barely perceptible. By contrast, during conventional mechanical ventilation (CMV), the lung is cycled from low to high volume with each breath, such that chest rise and fall is easily visible.
 - b. Reduced exposure to inspired oxygen. HFOV improves the uniformity of lung inflation, reduces intrapulmonary shunt, and improves oxygenation. The need for supplemental oxygen is reduced and exposure to oxygen-free radicals is decreased.
 - c. Prevention of atelectrauma (open-lung approach). In healthy infants and children, lung volumes, both end-inspiratory and end-expiratory,

R.H. Clark, MD (✉)

Pediatrix Medical Group, Department of Pediatrics, Greenville Memorial Hospital,
701 Grove Road, Greenville, SC 29605, USA
e-mail: reese_clark@pediatrix.com

change rapidly. At the end of a normal exhalation, the chest wall interacts with the lung to define functional residual capacity (lung volume at the end of expiration of a normal tidal volume breath). In neonates with retained lung fluid, lung disease, or lung injury, functional residual capacity is decreased, and portions of the lung, generally the dependent areas, are collapsed. Alveolar units are prone to collapse in patients with lung disease in which there is inadequate or dysfunctional surfactant. The breath-to-breath cycle of recruitment and subsequent “derecruitment” of these units causes lung injury. This mechanism of injury explains the observation that recruitment of lung volume and normalization of functional residual capacity protects the lung against ventilator-induced lung injury and also reduces the need for high levels of inspired oxygen. A goal of respiratory support is to open these areas and to normalize end-expiratory lung volume (i.e., functional residual capacity). HFOV does this by reducing changes in lung volume and promoting lung recruitment. Strategies that promote lung recruitment and reduce tidal volume act synergistically to reduce lung injury.

3. To decrease pulmonary morbidity in patients who require assisted ventilation
4. To provide a method of assisted ventilation that allows severe pulmonary air leaks to heal

II. Differences between HFOV and CMV

A.	Parameter	CMV	HFOV
1.	Rate (breaths per minute)	0–150	180–1,500
2.	Tidal volume (mL/kg)	4–20	0.1–5
3.	Alveolar pressure (cm H ₂ O)	5–50	0.1–20
4.	End-expiratory lung volume	Low	High

B. Advantages of HFOV

1. Improves ventilation at lower pressure and volume swings in the lung.
2. Safer way of using “super” PEEP (positive end-expiratory pressure). The lung can be inflated to higher mean volumes without having to use high peak airway pressures to maintain ventilation (carbon dioxide removal).
3. Produces more uniform lung inflation.
4. Reduces air leak.

C. Disadvantages of HFOV

1. As with CMV, there is potential for gas trapping and the development of inadvertent PEEP. The time for exhalation during HFOV is very short. Gas delivered to the lung during the inspiratory cycle may become trapped in the lung. This “trapped” gas can cause overinflation of the lung and lung injury (stretch injury or air leak). The propensity for gas trapping is dependent on the high-frequency device being used.

Devices that facilitate exhalation are less likely to cause gas trapping than devices that depend on the passive recoil of the chest and lung.

2. Defining optimal mean lung volume is difficult, yet crucial, to the safe use of HFOV.
 - a. Increasing lung volume results in decreasing venous return, which can be severe enough to compromise cardiac output. Lung overinflation can also cause acute lung injury, especially if cardiac output is compromised.
 - b. Under-inflation of the lung is equally dangerous. Collapsed lungs are difficult to recruit, and recruitment of collapsed lungs can be associated with significant lung injury. Atelectasis is associated with increased pulmonary vascular resistance, increased intra- and extra-pulmonary shunts and life threatening hypoxemia.

III. Types of HFOV

- A. Diaphragm HFOV with variable fractional inspiratory time. The SensorMedics 3100A oscillatory ventilator (Chap. 48) is the only HFOV device approved for use in newborns in the USA. It is an electronically controlled diaphragm that produces pressure oscillation in the patient circuit. Adjusting the power, frequency or fractional inspiratory time to the diaphragm driver controls the airway pressure amplitude. The mean airway pressure is set independently from the pressure oscillations. Adjusting the bias flow or the outlet resistance in the patient circuit controls mean airway pressure.
- B. Piston HFOV with a fixed fractional inspiratory time. These types of HFOV devices have used a 1:1 inspiratory-to-expiratory (I:E) ratio. In healthy adult rabbits, the use of a 1:1 I:E ratio has been shown to be associated with gas trapping and inadvertent PEEP. Newer devices allow for 1:2 and 1:1 I:E ratios. The Hummingbird is the best example of this type of HFOV.
- C. Hybrid devices employ a Venturi to generate negative pressure during the expiratory cycle.

IV. Calculations of minute ventilation (i.e., how much carbon dioxide is removed from the lung)

- A. For conventional ventilation and normal breathing: $\text{Rate} \times V_T$
- B. For HFOV: $\text{Rate}^{(0.5-1)} \times V_T^{(1.5-2)}$
 1. This equation predicts that factors effecting tidal volume delivery have a larger impact on ventilation during HFOV than they do for CMV. Changes in endotracheal tube size, lung compliance, airway resistance, and chest wall rigidity all impact delivery of “tidal volume.”
 2. It is also important to remember that the impedance of the respiratory system increases with frequency. During HFOV, as frequency is increased, tidal volume delivery and minute ventilation may decrease.
 3. Some devices, such as the SensorMedics 3100A, have lower V_T output at higher frequencies. This can be compensated by increasing the power setting.

C. Theory for improved ventilation during HFOV

1. Enhanced molecular diffusion.
2. Enhanced convection (Pendelluft effect)—regional differences in time constants for inflation and deflation cause gas to recirculate among lung units and improve gas exchange.
3. Taylor dispersion—augmented diffusion occurs because of turbulent air currents that result from interaction between axial velocity and the radial concentration gradient in the airways; and molecular diffusion.
4. Asymmetric velocity profiles—convective gas transport is enhanced by asymmetry between inspiratory and expiratory velocity profiles that occur at branch points in the airways.
5. Reduced dependence on bulk convection.

D. Oxygenation

1. Directly related to the degree of lung inflation (lung surface area).
2. Directly related to amount of inspired oxygen (FiO_2).
3. Both over- and underinflation of the lung can lead to decreased venous return, increased pulmonary vascular resistance, and compromised cardiac output.

E. Physiologically targeted strategies of HFOV

1. Poor lung inflation. HFOV has its most dramatic effects in infants whose primary pathophysiology is decreased lung inflation. When used with continuous distending pressure (CDP) directed at recruiting lung volume, and followed by careful weaning of the CDP once lung inflation is improved and FiO_2 is decreased, HFOV reduces lung injury and improves oxygenation. This approach exploits the concept of pressure–volume hysteresis, assuming the lung is not too injured and still has some recruitable volume. By using a CDP that is higher than the lung opening pressure (and usually greater than that which is generally accepted during CV), HFOV recruits collapsed lung units. Once open, these lung units can be maintained open at a mean airway pressure lower than that used for lung recruitment.
2. Pulmonary hypertension. HFOV can be effective in patients with pulmonary hypertension, if the process leading to pulmonary hypertension is poor lung inflation and regional hypoxia and hypercarbia. Improving lung inflation improves ventilation–perfusion matching and gas exchange, thereby relaxing the pulmonary vascular bed and decreasing pulmonary arterial pressure. HFOV is not as effective in patients with airway obstruction or in patients with poor cardiac output, especially from myocardial dysfunction. Airway obstruction attenuates the pressure signal as it is propagated across the airways to the alveoli. This attenuation decreases the alveolar ventilation and reduces ventilator efficiency. In patients with poor cardiac output, the constant high end expiratory

pressure decreases venous return and adds to further impair cardiac output.

3. Reported indications for HFOV. Numerous clinical reports of uncontrolled trials of the use of HFOV as a rescue technique have been published. The absolute indications and contraindications remain to be established by carefully controlled clinical trials. The following list represents reported indications for rescue HFOV:
 - a. Persistent air leak (e.g., bronchopleural fistula, pulmonary interstitial emphysema)
 - b. Persistent neonatal respiratory failure associated with:
 - (1) Respiratory distress syndrome (RDS)
 - (2) Pneumonia
 - (3) Adult respiratory distress syndrome (ARDS)
 - (4) Meconium aspiration syndrome (MAS)
 - (5) Lung hypoplasia syndromes
 - (6) Congenital diaphragmatic hernia (CDH)
 - (7) Hydrops fetalis
 - (8) Potter's variant
 - c. Tracheoesophageal fistula in patients who are unable to undergo surgical correction quickly (e.g., premature infants)
 - d. Primary pulmonary hypertension, which is responsive to reversal of atelectasis
4. Reported contraindications
 - a. Airway disease associated with gas trapping. Most authors agree that HFOV is not effective in patients with airway obstruction. The use of HFOV in patients with airway disease can accentuate problems with gas trapping.
 - b. Uncorrected shock. Appropriate use of HFOV increases mean lung volume. As lung volume increases, right atrial volume will decrease. These changes impede venous return. Reduced venous return may amplify problems with hypotension unless preload is increased through aggressive treatment of shock and its causes. These problems are identical to the problems seen with increasing levels of positive end-expiratory pressure during conventional forms of mechanical ventilation.

F. Specific reports and summary of results of clinical trials

1. Respiratory distress syndrome (RDS)

The largest prospective study involving HFOV was reported by the HIFI Study Group. Of 673 preterm infants weighing between 750 and 2,000 g, 346 were assigned to receive CV and 327 to receive HFOV. No infant received surfactant. The incidence of bronchopulmonary dysplasia (BPD) was nearly identical in the two groups. HFOV did not reduce

mortality or the level of ventilatory support during the first 28 days. HFOV was associated with an increased incidence of pneumoperitoneum of pulmonary origin, grades 3 and 4 intracranial hemorrhage, and periventricular leukomalacia. These results suggested that fixed ratio HFOV, as used in this trial, did not offer any advantage over CMV, and it might be associated with undesirable side effects.

2. In a much smaller study ($n=98$), also in non-surfactant-treated infants, Clark et al. showed that HFOV could be used to reduce the incidence of chronic lung disease in premature infants with RDS without increasing the incidence of intraventricular hemorrhage (IVH). The HFOV strategy used in this study was designed to recruit lung volume. The average CDP used during HFOV was 2–3 cm H₂O higher than the mean Paw used during CMV.
3. In a multicenter trial ($n=176$), the HIFO study group showed that rescue HFOV could be used to reduce the incidence of air leak syndromes in infants with established severe lung disease. There was a slight increase in incidence of grades 3 and 4 IVH in those infants treated with HFOV.
4. Gerstmann et al. did the first study in which all infants received surfactant. The purpose of this study was to compare the hospital course and clinical outcome of preterm infants with RDS treated with surfactant and managed with HFOV or CMV as their primary mode of ventilatory support. A total of 125 infants ≤ 35 weeks' gestation with a/A < 0.5 were studied. HFOV was used in a strategy to promote lung recruitment and maintain lung volume. Patients randomized to HFOV demonstrated the following significant findings compared with CMV-treated patients: less vasopressor support, less surfactant redosing, improved oxygenation, sustained during the first 7 days, less prolonged supplemental oxygen or ventilator support; reduced treatment failures, more survivors without BPD at 30 days; less need for continuous supplemental oxygen at discharge, lower frequency of necrotizing enterocolitis, fewer abnormal hearing tests, and decreased hospital costs. In pulmonary follow-up at 6 years of age, infants randomized to HFOV had normal lung volume measurements, whereas those randomized to CMV had larger than normal residual volume and decreased vital capacity.
5. Using the Infant Star HFOV and a volume recruitment strategy, Thome et al. were unable to reproduce the results reported by Gerstmann (HFOV) or Keszler (HFJV).
6. The two largest clinical studies show conflicting results.
 - a. Courtney et al. studied 500 infants. Those randomly assigned to HFOV were successfully extubated earlier than infants assigned to synchronized intermittent mandatory ventilation (SIMV). Of infants assigned to HFOV, 56% were alive without need for supplemental oxygen at 36 weeks of postmenstrual age, compared to 47% of those receiving SIMV. There was no difference between the groups in the risk of IVH, cystic PVL, or other complications.

- b. Johnson et al. studied 400 infants who were assigned to HFOV and 397 who were assigned to CMV. The composite primary outcome (death or CLD diagnosed at 36 weeks of postmenstrual age) occurred in 66% of the infants assigned to receive HFOV and 68% of those in the CMV group. There were also no significant differences between the groups in a range of other secondary outcome measures, including serious brain injury and air leak.
7. Meta-analysis by Cools et al. assessed the effectiveness of elective HFOV versus conventional ventilation in premature patients with RDS. They performed a systematic review and meta-analysis of individual patients' data from 3,229 participants in ten randomized controlled trials, with the primary outcomes of death or BPD at 36 weeks' postmenstrual age, death or severe adverse neurological event, or any of these outcomes. For infants ventilated with HFOV, the relative risk of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age was 0.95 (95% CI 0.88–1.03), of death or severe adverse neurological event 1.00 (0.88–1.13), or any of these outcomes 0.98 (0.91–1.05). No subgroup of infants (e.g., gestational age, birth weight for gestation, initial lung disease severity, or exposure to antenatal corticosteroids) benefited more or less from HFOV. Ventilator type or ventilation strategy did not change the overall treatment effect.

G. Current status

1. Animal studies show that HFOV reduces lung injury, promotes more uniform lung inflation, improves gas exchange, and prolongs the effectiveness of exogenous surfactant in experimental models of acute lung injury.
2. Clinical studies show that the results are strategy-specific. When used with a strategy designed to optimize and maintain lung inflation, HFOV can be used safely to reduce the occurrence of BPD. However, technology is ever changing and the debate over the best surfactant and the gentlest mode of ventilation continues.

H. Air leak syndromes

1. Pulmonary interstitial emphysema (PIE).
 - a. Clark et al. showed that HFOV improved gas exchange in premature infants with severe respiratory failure and PIE. Compared to previously reported data involving CMV, HFOV also appeared to improve survival. Similar results have been reported with HFJV.
 - b. Current status: PIE remains a serious complication of assisted ventilation. The introduction of surfactant has reduced the incidence of PIE, but has not eliminated the disease process. HFOV improves gas exchange and appears to improve the outcome of patients with PIE. However, affected infants are at high risk for long-term pulmonary and neurological morbidity.

2. Pneumothorax

- a. Blum-Hoffman et al. showed that HFOV was effective in improving oxygenation and ventilation in patients with air leak syndromes. Carter et al. reported similar results.
- b. Current status: Both HFJV and HFOV appear to improve gas exchange and allow for more rapid resolution of pneumothoraces.

3. Extracorporeal membrane oxygenation (ECMO) candidates

- a. Paranka et al. demonstrated that 50% of the ECMO-eligible patients could be rescued with HFOV alone. The outcome of patients rescued with HFOV was as good as for those who went on ECMO. Patients with CDH (30%) and MAS (50%) were not as likely to respond to HFOV as were patients with pneumonia (85%) and/or RDS (90%).
- b. Vaucher et al., using a different type of HFOV and a different clinical strategy, did not demonstrate results as encouraging. Patients who met criteria and were treated with ECMO had less BPD than infants who were “rescued” with alternate therapies. Walsh-Sukys presented similar findings. Both these studies show that prolonged use of HFOV or CMV to avoid ECMO may increase the risk for development of BPD.
- c. Kinsella et al. reported that treatment with HFOV and inhaled nitric oxide was more effective than either therapy alone in the management of babies with lung disease and PPHN. This finding was particularly true for infants with RDS or MAS.
- d. Current status: Results achieved with HFOV are likely to be device- and strategy-specific. The relative roles surfactant, inhaled nitric oxide, liquid ventilation, HFOV, and ECMO play in the management of term infants with severe respiratory failure have not yet been determined.

I. Reported complications of HFOV

1. Adverse cardiopulmonary interactions. It is essential to maintain the balance between adequate lung volume and cardiac preload. During HFOV, lung volume is nearly constant. Failure to maintain adequate preload and/or optimal lung volume can result in progressive hypotension and hypoxemia.
2. Mucostasis.
 - a. The HFOV I:E setting effects mucus clearance from the lung. Mucus can build up in the airways during HFOV. When weaned from HFOV and returned to CMV, some patients will rapidly mobilize these secretions. Airways can become occluded and frequent suctioning may be required during the 24- to 48-h period following HFOV. Airway trauma associated with suctioning should be avoided by passing the suction catheter only one centimeter below the endotracheal tube. While mucostasis is an uncommon complication of HFOV, it can be life threatening.

- b. Premature patients with RDS who were treated with HFOV may actually require less suctioning.
 - c. Management of airway secretions must be individualized. Try to avoid suctioning unless clinically indicated (increasing PaCO₂, visible airway secretions, or decreasing oxygen saturation).
3. Gas trapping—see above.
 4. IVH and PVL. Recent meta-analysis suggest that the association between HFOV and poor neurologic outcome is more related to how HFOV is used than whether it is used. HFOV can cause rapid reduction in PaCO₂, which can cause sudden changes in cerebral blood flow. To use HFOV safely, acute changes in ventilation, especially overventilation (i.e., hypocapnia and alkalosis), must be avoided.

J. General and disease-specific recommendations

1. Atelectasis with diffuse radioopacification of the lung (RDS or pneumonia)
 - a. The CDP required to optimize lung inflation is higher than that which is usually achieved on CMV. Mean airway pressure can be increased in 1–2 cm H₂O increments until PaO₂ improves or the chest radiograph shows normal inflation. Evidence of overinflation or signs of cardiac compromise should be avoided. Radiographic signs of overinflation include “extra clear” lung fields, a small heart, flattened diaphragms, and more than nine posterior ribs of lung inflation. Signs of cardiac compromise include increased heart rate, decreased blood pressure, poor peripheral perfusion, and metabolic acidosis.
 - b. Mean airway pressures used in the management of uncomplicated RDS in premature infants are generally lower than those used to treat term newborns. The severity of the lung disease, the age at start of HFOV, the use of surfactant, and the presence of infection will all influence the amount of pressure that is required. CDPs commonly reported are:
 - (1) For infants < 1 kg, 5–18 cm H₂O
 - (2) For infants 1–2 kg, 6–20 cm H₂O
 - (3) For infants > 2 kg 10–25 cm H₂O
 - c. Frequency is generally held constant at 8–15 Hz. Most clinical data report the use of 10 Hz. In infants who are < 1 kg, extreme caution must be taken to avoid hyperventilation and alkalosis. If PaCO₂ is low and the pressure amplitude is less than 20 cm H₂O, the frequency may need to be increased in order to decrease minute ventilation and allow the PaCO₂ to rise to a normal range. Also, if small changes in power settings result in large changes in PaCO₂, ventilation control will be improved by increasing the frequency to 15 Hz.

2. Meconium aspiration syndrome
 - a. Some of these patients present with diffuse lung injury with limited pulmonary hypertension and minimal airway obstruction. These patients respond as described above.
 - b. By contrast, some newborns with MAS have severe airway obstruction and PPHN. These infants are not as responsive to HFOV.
 - c. During the initiation of HFOV in patients with MAS, a chest radiograph should be obtained to assess lung inflation and to rule out evidence of gas trapping. Lowering the frequency and increasing CDP may reduce gas trapping from narrowed airways.
 - d. Patients who have poor lung inflation, minimal improvement in gas exchange during HFOV, and clinical evidence of pulmonary hypertension, are more likely to respond to a combination of HFOV and inhaled nitric oxide than to either therapy alone.
3. Lung hypoplasia syndromes
 - a. Similar to patients with MAS, the patients most likely to respond to HFOV are those in whom the primary pathophysiologic process is poor lung inflation.
 - b. Patients whose lung volumes have been optimized on HFOV, as evidenced by clear lung fields but who still have severe pulmonary hypertension, are less likely to respond to HFOV alone.
 - c. Patients with both poor lung inflation and pulmonary hypertension may be best treated with a combination of HFOV and inhaled nitric oxide.
4. Air leak syndrome
 - a. Patients who have severe persistent air leak (such as PIE or recurrent pneumothoraces) require a different approach. The goal of assisted ventilatory support must be to allow the air leak to resolve. If the air leak is unilateral, placing the involved lung in the dependent position will increase the resistance to gas flow to this lung and promote atelectasis. Both lung collapse and decreased ventilation of the dependent lung will promote air leak resolution.
 - b. In addition to dependent positioning, using a strategy of HFOV that emphasizes decreasing mean airway pressure over decreasing FiO_2 will help allow air leak resolution.
5. Idiopathic PPHN with normal lung inflation. These patients are easy to ventilate on low levels of conventional support. HFOV is not as effective in these patients and can be associated with the development of life-threatening hypoxemia, if the balance between preload and lung volume is not carefully addressed.

Suggested Reading

- Blum-Hoffmann E, Kopotic RJ, Mannino FL. High-frequency oscillatory ventilation combined with intermittent mandatory ventilation in critically ill neonates: 3 years of experience. *Eur J Pediatr.* 1988;147(4):392–8.
- Clark RH, Gerstmann DR, Null Jr DM, Delemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. *Pediatrics.* 1992;89(1):5–12.
- Clark RH, Gerstmann DR, Jobe AH, Moffitt ST, Slutsky AS, Yoder BA. Lung injury in neonates: causes, strategies for prevention, and long-term consequences. *J Pediatr.* 2001;139(4):478–86.
- Clark RH, Gerstmann DR, Null DM, et al. Pulmonary interstitial emphysema treated by high-frequency oscillatory ventilation. *Crit Care Med.* 1986;14(11):926–30.
- Cools F, Askie LM, Offringa M, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet.* 2010;375(9731):2082–91.
- Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med.* 2002;347(9):643–52.
- Gerstmann DR, Minton SD, Stoddard RA, et al. The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics.* 1996;98(6 Pt 1):1044–57.
- Gerstmann DR, Wood K, Miller A, et al. Childhood outcome after early high-frequency oscillatory ventilation for neonatal respiratory distress syndrome. *Pediatrics.* 2001;108(3):617–23.
- The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med.* 1989;320(2):88–93.
- HiFO Study Group. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. *J Pediatr.* 1993;122((4):609–19.
- Johnson AH, Peacock JL, Greenough A, et al. High-Frequency Oscillatory Ventilation for the Prevention of Chronic Lung Disease of Prematurity. *N Engl J Med.* 2002;347(9):633–42.
- Keszler M, Donn SM, Spitzer AR. High-frequency jet ventilation in respiratory distress syndrome. *J Pediatr.* 1991a;119(2):340–1.
- Keszler M, Donn SM, Bucciarelli RL, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. *J Pediatr.* 1991b;119(1 Pt 1):85–93.
- Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr.* 1997;131(1 Pt 1):55–62.
- Paranka MS, Clark RH, Yoder BA, Null Jr DM. Predictors of failure of high-frequency oscillatory ventilation in term infants with severe respiratory failure. *Pediatrics.* 1995;95(3):400–4.
- Thome U, Kossel H, Lipowsky G, et al. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. *J Pediatr.* 1999;135(1):39–46.
- Vaucher YE, Dudell GG, Bejar R, Gist K. Predictors of early childhood outcome in candidates for extracorporeal membrane oxygenation. *J Pediatr.* 1996;128(1):109–17.

Part VIII
Commonly Used Neonatal Ventilators

Chapter 39

VIP Bird Gold Ventilator

Michael A. Becker and Steven M. Donn

I. Introduction

The Bird VIP Gold ventilator (CareFusion, San Diego, CA) provides both neonatal and pediatric ventilation. The ventilator breaths are synchronized in all modes. Continuous tidal volume, graphic monitoring of waveforms and mechanics are also available.

II. Monitoring

A. Internal

1. AC power
2. External DC power
3. Patient effort
4. Demand flow (pressure limited modality only)
5. Peak inspiratory pressure (PIP)
6. Mean airway pressure (P_{aw})
7. Positive end expiratory pressure (PEEP)
8. Rate (total breath rate)
9. Inspiratory time
10. I:E ratio

M.A. Becker, RRT (✉)

Department of Critical Care Support Services, C.S. Mott Children's Hospital,
University of Michigan Health System, 200 E Hospital Drive, Ann Arbor,
MI 48109, USA
e-mail: mabecker@med.umich.edu

S.M. Donn, MD, FAAP

Division of Neonatal–Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

11. Tidal volume (I=inspiratory or E=expiratory)
12. Expiratory minute volume
13. Airway pressure monometer (aneroid gauge)

B. Bird graphic monitor

1. Waveforms (2 of the 3 displayed at the same time)
 - a. Flow
 - b. Volume
 - c. Pressure
2. Mechanics
 - a. Pressure–volume loop
 - b. Flow–volume loop
3. Trends (24-h trend monitoring)
4. Pulmonary mechanics calculations
 - a. Compliance and C_{20}/C ratio
 - b. Resistance

III. Alarms

A. Alarms/limits

1. Blender input gas alarm
2. High breath rate alarm
3. High pressure alarm
4. High/prolonged pressure alarm
5. High tidal volume
6. Low inlet gas pressure alarm
7. Low minute volume alarm
8. Low PEEP/CPAP pressure alarm
9. Low peak pressure alarm
10. Pressure support/VAPS time limit

IV. Nomenclature

A. Pressure vs. volume ventilation

1. Pressure ventilation
 - a. The pressure is controlled.
 - b. The volume delivery varies with changes in compliance.
 - c. There are three pressure modalities: time-cycled, pressure-limited (TCPL), pressure control (PC), and pressure support (PS).
2. Volume ventilation
 - a. The volume delivery is controlled.
 - b. The pressure varies with changes in compliance.

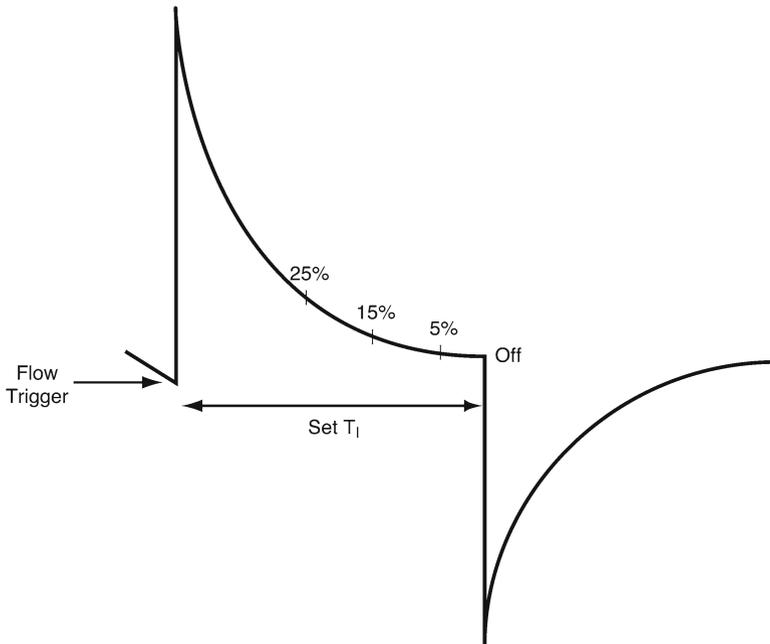


Fig. 39.1 Termination sensitivity[®] or expiratory trigger. Inspiration is initiated by a change of flow at the airway. When the lungs have inflated, flow decreases at the proximal airway, which results in the breath being terminated. The point of termination is clinician-adjustable, and represents a percentage of peak inspiratory flow. Thus, a 5% termination sensitivity setting means that the breath will be terminated when airway flow has decreased to 5% of peak flow (i.e., there has been a 95% decay of the curve). T_i = inspiratory time

B. Assist/control vs. SIMV/PS

1. Assist/control (A/C)

- a. A set number of control breaths are delivered in the event of apnea or failure to trigger.
- b. If the patient triggers the ventilator with a spontaneous effort, an assist breath is delivered.

2. SIMV/PS

- a. A set number of control breaths are delivered.
- b. If the patient's spontaneous effort triggers the ventilator above the set control rate, the additional breaths will be supported by a pressure-limited breath called pressure support (PS).

C. Flow-cycling (Fig. 39.1)

1. Use of "termination sensitivity" (or expiratory trigger) enables the baby to end mechanical inspiration nearly synchronously with his/her own spontaneous breathing.

2. Inspiration ends at a percentage (almost always 5%) of the peak inspiratory flow rate rather than the set inspiratory time, and if properly set, this occurs before the set T_I .
3. Flow-cycling prevents inversion of the I:E ratio during rapid breathing and greatly reduces gas trapping which could occur in A/C at a fixed T_I , because T_E is shortened the faster the baby breathes.
4. In rare instances, the baby may “choose” a T_I that is too short to provide an adequate V_T . Switch to time-cycling.

V. Modalities of ventilation

A. Time-cycled, pressure-limited (TC/PL)

1. Continuous flow.
2. Mechanical breaths are pressure-limited and may either be time-cycled or synchronized to the patient's own respiratory effort by flow-cycling, changes that are detected by a proximal flow sensor (pneumotachograph).
3. The pressure is controlled and the volume varies with lung compliance.

B. Pressure control (PC)

1. A pressure limited breath is delivered at a variable flow rate.
2. It accelerates to peak flow and then decelerates.
3. The endotracheal tube resistance and the patient compliance determine the flow rate, which can also be modulated with “Rise Time” (see below).

C. Pressure support (PS)

1. A pressure-limited breath that is patient-triggered. The patient has primary control of the inspiratory time and flow.
2. The inspiratory flow may be modified with Rise Time, an adjustment that affects the flow and pressure waveforms. The setting of 1 is the steepest rise. The breath will be given quickly. The setting of 7 will give the breath more slowly and may be very helpful in the management of infants with high resistance disease or small endotracheal tubes.

D. Volume-controlled (targeted) ventilation

1. A preset volume is delivered with each breath.
 - a. The volume is constant and pressure varies depending upon the patient's lung compliance.
 - b. The breaths are triggered by a flow change at the flow sensor, indicating the patient is making a respiratory effort.
 - c. The minimum tidal volume leaving the ventilator is 10 mL.
2. Because cuffed endotracheal tubes are not used in newborns, there is usually some leakage of delivered volume. It is more appropriate to refer to this as volume-controlled or volume-limited ventilation, and not volume-cycled ventilation.

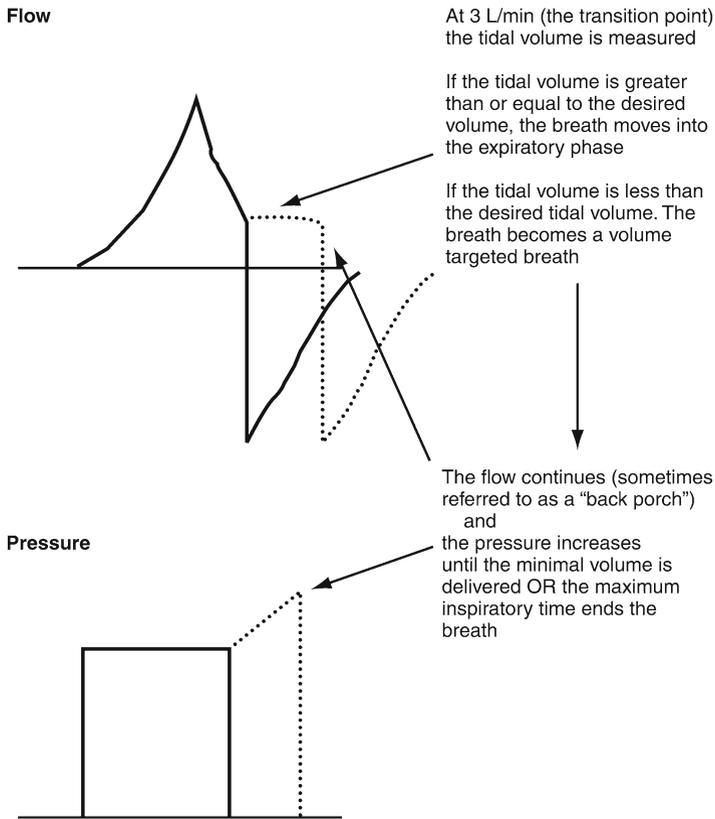


Fig. 39.2 Suggested algorithm for setting up volume assured pressure support (VAPS)

E. Volume-assured pressure support (VAPS) (Fig. 39.2)

1. VAPS begins as a variable flow (decelerating waveform), pressure limited breath (a pressure support type breath).
2. A minimal volume target is set.
3. At a selected transition point, generally set at 3 LPM (the lowest setting, it gives the pressure support breath the maximum time to deliver the minimal tidal volume), the tidal volume is measured.
4. If the volume target is met, the breath will flow-cycle and move into the expiratory phase.
5. If the volume is not met, the breath converts from a pressure support breath to a volume-targeted breath. The flow continues, the inspiratory time extends and the pressure increases slightly until the minimal target volume is achieved or the maximum inspiratory time limit ends the breath. This mode will deliver either patient-triggered breaths or a control rate if the patient has no effort.

F. Continuous positive airway pressure (CPAP)

1. Continuous gas flow through the circuit with expiratory resistance to provide the desired pressure.
2. May be oxygen-enriched.
3. No additional volume or pressure boost is provided.

VI. Management

A. Ventilator management

1. Ventilation (PaCO_2). Carbon dioxide removal is related to the minute ventilation (MV). $\text{MV} = \text{tidal volume } (V_T) \times \text{respiratory rate}$. Measured inspiratory tidal volumes should be 4–8 mL/kg to avoid overinflation. Normal $\text{MV} = 240\text{--}360 \text{ mL/kg/min}$
 - a. Pressure-targeted
 - (1) V_T is adjusted by the change in pressure or ΔP (PIP–PEEP).
 - (2) Compliance and resistance will affect the delivered tidal volume.
 - b. Volume-targeted
 - (1) The inspiratory tidal volume delivered to the patient is determined by the set tidal volume minus the volume that is compressed in the ventilator circuit (and any leak).
 - (2) The compressed volume varies with the pressure that is generated within the circuit and patient compliance.
 - (3) Always monitor the measured inspiratory and expiratory volumes to determine the leak volume.
2. Oxygenation (PaO_2). Correlated directly to $\text{P}\bar{\text{a}}\text{w}$ (mean airway pressure) and FiO_2
 - a. Increases in PIP, inspiratory time, PEEP, and rate all contribute to higher $\text{P}\bar{\text{a}}\text{w}$ and an increase oxygenation.
 - b. FiO_2 .

VII. Weaning and extubation (Chap. 68)

- A. Weaning the ventilator. Our weaning strategies encourage the patient to breath above the set respiratory rate. This is done by decreasing the rate to the point where the patient breaths spontaneously.
 1. Pressure modes
 - a. Weaning in A/C
 - (1) It is possible to wean in either A/C or SIMV/PS.
 - (2) As compliance improves the patient requires less pressure to deliver the appropriate desired inspiratory tidal volume.

b. Weaning in SIMV/PS

- (1) Set the mandatory (SIMV) breath as $\Delta P = (\text{PIP} - \text{PEEP})$ to deliver inspiratory tidal volume of 4–8 mL/kg.
- (2) The pressure support (PS) level should be set at the same (PS_{max}) or slightly lower pressure, delivering approximately an inspiratory tidal volume of 4–8 mL/kg.
- (3) Decrease the rate of the control breaths until all the breaths are PS breaths (a low SIMV rate of 6–10/min may be used as a safeguard).
- (4) Extubate from a rate of zero and a minimal PS level ($\text{PS}_{\text{min}} = 3\text{--}4 \text{ mL/kg } V_T$).

2. Volume modes

a. Weaning in A/C

- (1) Weaning in volume A/C is difficult.
- (2) Decrease the rate until the patient begins spontaneous respirations.
- (3) At rates of $\leq 20\text{--}40$, change to SIMV/PS to continue weaning.

b. Weaning in SIMV/PS

- (1) Set the volume parameter to deliver a measured inspiratory tidal volume of 5–6 mL/kg.
- (2) The pressure support (PS) should be set at the same (PS_{max}) or slightly lower pressure that is being generated by the volume breath, delivering an inspiratory tidal volume of approximately 4–6 mL/kg.
- (3) Decrease the rate of the control breaths until all the breaths are PS breaths (a low SIMV rate of 6–10/min may be used as a safeguard).
- (4) Extubate from a rate of zero and a minimal PS level ($\text{PS}_{\text{min}} = 3\text{--}4 \text{ mL/kg } V_T$).

3. VAPS

a. Weaning in A/C

- (1) VAPS A/C is generally not considered a weaning mode.
- (2) As compliance improves, the PIP may be decreased. Review waveforms for the occurrence of transitional breaths (a switch to volume-targeted breaths).

b. Weaning in SIMV/PS

- (1) Decrease the rate of the control breaths until all the breaths are PS breaths.
- (2) Extubate from a rate of zero and a minimal PS level.

B. Extubation. When to extubate has always been a subjective decision. We have attempted to make it more objective with the initiation of a minute ventilation trial.

1. Record the total minute ventilation (MV) measured by the proximal flow sensor. Do not change the respiratory support.
2. Change the ventilator mode to SIMV (CPAP), rate of zero and no pressure support. Use the TCPL mode because in this mode the patient can breathe spontaneously from the continuous flow provided by the ventilator.
3. After 10 min, record the spontaneously generated MV.
4. If spontaneous MV is $\geq 50\%$ of the mechanically delivered MV, extubate the baby.

Suggested Reading

- Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura; 1998.
- Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. *J Perinatol.* 1994;14:90–4.
- Donn SM, Sinha SK. Controversies in patient-triggered ventilation. *Clin Perinatol.* 1998;25:49–61.
- Donn SM, Sinha SK. Neonatal ventilation – aspects of weaning and extubation: physiological considerations. *Perinatology.* 1999;1:317–24.
- Donn SM, Sinha SK. Newer modes of mechanical ventilation for the neonate. *Curr Opin Pediatr.* 2001;13:99–103.
- Gillespie LM, White SD, Sinha SK, Donn SM. Usefulness of the minute ventilation test in predicting successful extubation in newborn infants: a randomized controlled trial. *J Perinatol.* 2003;23:205–7.
- Goldsmith JP, Karotkin EH, editors. Assisted Ventilation of the Neonate. 54th ed. St. Louis: Elsevier Saunders; 2011.
- Nicks JJ, Becker MA, Donn SM. Bronchopulmonary dysplasia: response to pressure support ventilation. *J Perinatol.* 1994;14:495–7.
- Sinha SK, Donn SM. Advances in neonatal conventional ventilation. *Arch Dis Child.* 1996;75:F135–40.
- Sinha SK, Donn SM. Neonatal ventilation – aspects of weaning and extubation: clinical aspects. *Perinatology.* 2000a;2:1–10.
- Sinha SK, Donn SM. Weaning infants from mechanical ventilation: art or science? *Arch Dis Child.* 2000b;83:F64–70.
- Sinha SK, Donn SM. Newer modes of neonatal ventilation. *International J Intensive Care.* 2000c;7:109–15.
- Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura; 2000d.
- Sinha SK, Donn SM. Volume controlled ventilatory modes for the newborn: variations on a theme. *Clin Perinatol.* 2001;8:547–60.
- Sinha SK, Donn SM, Gavey J, McCarty M. Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child.* 1997;77:F202–5.
- Sinha SK, Nicks JJ, Donn SM. Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. *Arch Dis Child.* 1996;75:F213–8.
- Wilson Jr BJ, Becker MA, Linton ME, Donn SM. Spontaneous minute ventilation predicts readiness for extubation in mechanically ventilated preterm infants. *J Perinatol.* 1998;18:436–9.
- Wiswell TE, Donn SM, eds. Surfactant and mechanical ventilation. *Clin Perinatol.* 2007; 34:1–217.

Chapter 40

AVEA Ventilator

Michael A. Becker and Steven M. Donn

I. Introduction

The AVEA ventilator (CareFusion, San Diego CA), a single platform device, is designed to meet the needs for ventilator support in the neonatal, pediatric, and adult patient populations. Each population has unique options of available modes and modalities of ventilation. This review focuses only upon the neonatal applications.

II. Description

Both volume- and pressure-targeted ventilation are available for the neonatal population. A proximal flow sensor is used to provide flow-triggered synchronization of all ventilator breaths as well as proximal volume measurements.

III. Additional features

A. Artificial airway compensation (AAC).

1. When activated the ventilator automatically calculates the drop in pressure through the endotracheal tube and adds that amount of pressure to the system.
2. It takes into consideration flow, gas composition, tube diameter and length, as well as the pharyngeal curve.

B. Leak compensation: the flow control valve (FCV) and the exhalation valve work together to compensate for baseline leaks.

M.A. Becker, RRT (✉)

Department of Critical Care Support Services, C.S. Mott Children's Hospital,
University of Michigan Health System, 200 E Hospital Drive, Ann Arbor, MI 48109, USA
e-mail: mabecker@med.umich.edu

S.M. Donn, MD, FAAP

Division of Neonatal–Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

- C. Circuit compliance compensation: not active for neonatal patients.
- D. Heliox delivery: by connecting an 80/20 mixture mixture of heliox via the smart connector technology, the ventilator is not only able to deliver an accurate heliox concentration but also measure accurate tidal volume delivery.
- E. An adjustable FiO_2 concentration when either the *increase oxygen* or *suction* button is activated. In the infant mode, the default is an increase in FiO_2 of 20% (from the set FiO_2). It may be adjusted from 0–79%.
- F. Internal battery and compressor: automatically activated backup for the loss of electricity or air gas source.

IV. Monitoring

- A. Internal
- B. Graphic monitoring
 - 1. Waveforms.
 - a. Flow
 - b. Volume
 - c. Pressure
 - 2. Mechanics.
 - a. Pressure–volume loop
 - b. Flow–volume loop
 - 3. Trends: 24-h trending of over 50 monitored respiratory parameters.
 - 4. Pulmonary mechanics calculations: at present, only dynamic compliance can be calculated for neonatal patients.

V. Alarms/limits

- A. High rate (bpm)
- B. Low V_{TE} (mL)
- C. High V_{TE} (mL)
- D. Low V_{E} (L)
- E. High V_{E} (L)
- F. Low P_{peak} (cm H_2O)
- G. High P_{peak} (cm H_2O)
- H. Low PEEP (cm H_2O)
- I. Apnea interval (seconds)

VI. Nomenclature

- A. Pressure versus volume ventilation
 - 1. Pressure-targeted ventilation
 - a. The pressure is controlled.
 - b. Volume varies with changes in pulmonary compliance and airway resistance.

2. Volume-targeted ventilation

- a. The volume delivered from the ventilator is controlled.
- b. The pressure varies with changes in pulmonary compliance and airway resistance.

B. Modes

1. Assist/control (A/C)

- a. A preset number of control breaths are delivered.
- b. If the patient triggers the ventilator with a spontaneous effort another breath of the same type is delivered.

2. SIMV/PS

- a. Generally considered to be a weaning mode of ventilation.
- b. A preset number of control breaths are delivered.
- c. If the patient's spontaneous effort triggers the ventilator above the set control rate, the additional breaths will be supported by a pressure-limited breath called pressure support (PS).

C. Flow-cycling

1. Use of flow cycling (the expiratory trigger) enables the baby to end mechanical inspiration nearly synchronously with spontaneous breathing.
2. Inspiration ends at a percentage (adjustable from 5–45%) of the peak inspiratory flow rate rather than the set inspiratory time. If properly set, flow-cycling should end inspiration before the set inspiratory time (T_I).
3. Flow-cycling helps to prevent inversion of the I:E ratio during rapid breathing and greatly reduces the risk of gas trapping.
4. Flow-cycling enables complete synchronization between the baby and ventilator.
 - a. The baby initiates the mechanical breaths (inspiratory trigger).
 - b. The baby terminates the mechanical breaths (expiratory trigger).
5. In rare instances, the baby may “choose” a T_I that is too short to provide an adequate V_T . In this case, it may be appropriate to use time-cycling.

VII. Modalities of ventilation

A. Pressure modalities

1. There are three pressure modalities available for the neonatal population.
 - a. Time-cycled pressure-limited (TCPL)
 - b. Pressure control (PC)
 - c. Pressure support (PS)
 - d. CPAP

2. Time-cycled, pressure-limited (TCPL)
 - a. Flow is *continuous*.
 - b. Mechanical breaths are pressure limited and synchronized to the patients' own respiratory effort by flow changes, detected by a proximal flow sensor (hot wire anemometer).
 - c. The pressure is controlled and the volume varies with lung compliance.
 3. Pressure control (PC)
 - a. A pressure-limited breath is delivered at a *variable* flow rate.
 - b. The flow wave form shows rapid acceleration followed by rapid deceleration.
 - c. The endotracheal tube resistance and the patient compliance determine the inspiratory flow rate, which may also be modulated by the "Rise Time" setting (see below).
 4. Pressure support (PS)
 - a. A pressure-limited breath that is patient-triggered. The patient has primary control of the inspiratory time (which may be limited) and flow.
 - b. The inspiratory flow can be modified by adjusting the Rise Time parameter. The Rise Time settings are qualitative, ranging from 1 to 9. The setting of 1 is the steepest acceleration of flow; the breath will be delivered quickly. The Rise Time setting of 9 will deliver the breath with a slower acceleration of flow. The proper Rise Time may help to avoid pressure overshoot or inadequate hysteresis.
 5. Continuous positive airway pressure (CPAP) is also available and is achieved by continuous gas flow through the circuit with expiratory resistance to provide the desired pressure.
 - a. May be oxygen-enriched.
 - b. No additional volume or pressure boost is provided.
- B. Volume modality (volume control; volume-targeted)
1. A preset volume is delivered with each breath. May be very useful in attempting to control ventilation in the treatment of patients with changing compliance.
 2. The volume is controlled at the ventilator. In the monitoring area, this value is referred to as volume delivered.
 3. The volume leaving the machine is constant and the pressure will vary dependent upon the patient's lung compliance and airway resistance. However, there will be a significant compression (loss) of volume within

the ventilator circuit when lung compliance is poor. This is referred to as compressible volume loss.

4. The set volume, flow rate, and inspiratory pause parameters determine the inspiratory time.

VIII. Management

A. Ventilator management: With the newer generation ventilators, combine three assessments to enable determination of the best strategy: physical patient assessment, monitoring of measured values, and graphic assessment to enable individual strategies based upon pathophysiology and the interaction of the baby and the ventilator.

1. Ventilation (PaCO_2). Carbon dioxide removal is related to the minute ventilation (MV). $\text{MV} = V_T \times \text{respiratory rate}$. Measured inspiratory tidal volumes should be 4–7 mL/kg to avoid overinflation. The normal $\text{MV} = 240\text{--}360$ mL/kg/min. This calculation is based on expiratory tidal volume (V_{TE}) and will be affected by endotracheal tube leaks.

a. Pressure modalities

- (1) The V_T is adjusted by setting the inspiratory pressure (IP) in TCPL/PC and Pressure control ventilation. This pressure is above the level of PEEP; the difference between peak pressure and PEEP is also referred to as ΔP or amplitude.
- (2) Compliance and resistance will affect the delivered tidal volume.

b. Volume-targeted

- (1) The inspiratory tidal volume (V_{TI}) delivered to the patient is determined by the set tidal volume minus the volume that is compressed in the ventilator circuit.
- (2) The compressible volume loss varies with the pressure that is generated within the circuit, which in turn is a reflection of compliance.
- (3) Always monitor both the inspiratory and expiratory tidal volumes (or percentage leak) to determine the volume of leak. This is important because of the use uncuffed endotracheal tubes in neonates.

2. Oxygenation (PaO_2) correlates directly with mean airway pressure ($\text{P}\bar{a}\text{w}$) and FiO_2 .

- a. Increases in peak inspiratory pressure (PIP), inspiratory time, positive end expiratory pressure (PEEP) and rate all contribute to increases in $\text{P}\bar{a}\text{w}$. Increased $\text{P}\bar{a}\text{w}$ increases oxygenation by increasing pulmonary surface area.
- b. FiO_2 increases will also increase oxygenation unless there is a diffusion barrier or ventilation–perfusion mismatch.

IX. Weaning and extubation (see also Chap. 68)

A. Weaning the ventilator: Typical weaning strategies encourage the patient to breath above the set (control or mandatory) respiratory rate. This is done by decreasing the rate to the point where the patient breaths spontaneously and triggers most, if not all, of the breaths.

1. Pressure

a. Weaning in assist control (A/C)

- (1) Adjust IP to maintain the measured inspiratory tidal volumes between 4–7 mL/kg.
- (2) As the patient's compliance improves, the required IP will decrease.

b. Weaning in SIMV/PS

- (1) Adjust IP of the mandatory TCPL or PC breaths to keep the measured inspiratory tidal volumes between 4–7 mL/kg.
- (2) The IP of the PS breath can be adjusted to deliver either a full tidal volume breath (called PS_{max}) or at a lower level to provide a partially supported breath. At the lowest level, PS_{min} , the delivered V_T matches the imposed work of breathing created by the endotracheal tube and ventilator circuit.
- (3) If the SIMV rate is set too high, it may interfere with spontaneous breathing and offset the advantages of PS.

2. Volume

a. Weaning in A/C

- (1) Weaning directly to extubation is difficult to accomplish in the volume assist-control mode
- (2) Changing to SIMV/PS is recommended

b. Weaning in SIMV/PS

- (1) Decrease the rate of volume control breaths and supplement the minute ventilation by additional PS breaths.
- (2) Wean the control rate and adjust the PS IP to provide a reasonable V_T .
- (3) Once the PS IP has been weaned to a level which provides a 3–4 mL/kg V_T , the baby is usually able to be extubated.

Suggested Reading

Donn SM, Becker MA, Nicks JJ. Special ventilatory techniques I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St. Louis: Elsevier Saunders; 2011. p. 220–34. http://www.carefusion.com/pdf/Respiratory/Ventilation/AVEA_brochure.pdf.

Chapter 41

Bear Cub 750_{PSV}

Joanne Nicks

I. Description

- A. The Bear Cub 750_{PSV} Infant Ventilator (CareFusion, San Diego, CA) is pneumatically powered with 30–80 psig air and oxygen, and is electronically controlled.
- B. Designed to ventilate newborn, infant, and pediatric patients weighing between 500 g and 30 kg.
- C. Provides a range of modes, controls, monitors, and alarms appropriate for the targeted patient population.
- D. An optional flow sensor may be placed at the proximal airway to provide synchronized mandatory breaths and volume monitoring.

II. Breath types and modes of ventilation

A. Breath types

1. The changeover from expiration to inspiration may be time-triggered based on the rate setting or flow-triggered based on the Assist Sensitivity setting. Flow-triggering requires that the flow sensor be properly installed.
2. Mandatory breaths are pressure-limited; however, the peak inspiratory pressure may be less than the inspiratory pressure setting if the Volume Limit function is activated.
3. The changeover from inspiration to expiration may be time-cycled based on the inspiratory time setting or flow-cycled based on a fixed termination at 10% of peak inspiratory flow. If the Volume Limit function is activated, mandatory breaths may be volume-cycled. When a breath is flow-cycled or volume limited, the actual inspiratory time may be less than the set T_I .

J. Nicks, RRT, AAS (✉)
Pediatric Respiratory Care, C.S. Mott Children's Hospital,
1540 East Hospital Dr. SPC 4208, Ann Arbor, MI 48109, USA
e-mail: jnicks@med.umich.edu

B. Modes and modalities

1. Assist/control. The patient may trigger mandatory breaths in excess of the preset rate provided the Assist Sensitivity threshold is met (flow sensor must be installed). As a result, the mandatory breaths are synchronized with the patient's breathing pattern.
2. Flow-cycled assist/control. A pressure-limited breath is delivered at a preset inspiratory pressure based on the mandatory set rate, or with each patient effort that meets the Assist Sensitivity threshold. Delivered breaths may be flow-cycled when the inspiratory flow falls to 10% of the peak flow rate, or time-cycled at the preset inspiratory time, whichever occurs first.
3. SIMV. In this mode, a combination of mandatory breaths and spontaneous breaths is possible. Based on "assist windows," mandatory breaths are delivered in synchrony with the patient's breathing pattern at the preset rate (flow sensor required). In between mandatory breaths, the patient may breathe spontaneously from the preset Base Flow (but receives only PEEP).
4. IMV. Mandatory breaths are delivered at preset intervals based on the rate setting without regard for the patient's breathing pattern. The patient may breathe spontaneously in between mandatory breaths as in SIMV.
5. Flow-cycled SIMV. A pressure limited breath is delivered at a preset inspiratory pressure based on the mandatory set rate, in synchrony with the infant's spontaneous effort. These breaths may be flow-cycled when the inspiratory flow falls to 10% of the peak flow rate, or time-cycled at the preset inspiratory time limit, whichever occurs first. In between mandatory breaths, the infant may breathe spontaneously.
6. SIMV/PSV. A mandatory pressure-limited breath is delivered to the patient at a preset inspiratory pressure and time-cycled at the preset inspiratory time limit, synchronized to patient effort. Any spontaneous efforts recognized by the ventilator (i.e., exceeding the Assist Sensitivity threshold) between mandatory breaths will be supported at the preset inspiratory pressure and may be flow-cycled when the inspiratory flow falls to 10% of the peak flow rate, or time-cycled at the preset inspiratory time limit, whichever occurs first.
7. PSV. All spontaneous efforts that reach the Assist Sensitivity threshold will be supported by the preset inspiratory pressure and may be flow-cycled when the inspiratory flow falls to 10% of the peak flow rate, or time-cycled at the preset inspiratory time limit, whichever occurs first. There is no mandatory rate. If the patient is apneic for the duration of the apnea alarm setting, the ventilator will deliver a backup mandatory breath at the preset pressure and inspiratory time limit. If no patient initiated breaths are taken during a time out period based on the set ventilator rate or 10 s, which ever is less, another backup breath will be delivered. This sequence will continue until a breath is recognized. An apnea alarm will be reported throughout this sequence.

8. CPAP. The patient breathes spontaneously at a constant airway pressure determined by the PEEP setting. When a flow sensor is installed, spontaneous breaths are monitored by the ventilator. If the patient is apneic for the duration of the apnea alarm setting, the ventilator will deliver a backup mandatory breath at the preset pressure and inspiratory time. If no patient initiated breaths are taken during a time out period based on the set ventilator rate or 10 s, which ever is less, another backup breath will be delivered. This sequence will continue until a breath is recognized. An apnea alarm will be reported throughout this sequence.

III. Controls

A. Ventilation

1. PEEP/CPAP: 0–30 cm H₂O—sets the level of baseline pressure.
2. Inspiratory pressure: 0–72 cm H₂O—the primary determinant of delivered tidal volume.
3. Rate: 1–150 BPM—sets the number of mandatory breaths in SIMV and IMV, and the minimum number of mandatory breaths in assist/control.
4. Inspiratory time: 0.1–3.0 s—determines the maximum length of the inspiratory phase of mandatory breaths.
5. Inspiratory flow: 1–30 LPM—sets the flow delivered by the ventilator during the inspiratory phase of a mandatory breath.
6. Base flow: 1–30 LPM—sets the flow available to the patient for spontaneous breathing.
7. Volume Limit: 5–300 mL The preset inspiratory pressure generally determines the delivered volume. A dramatic improvement in patient compliance may result in excessive tidal volume delivery unless the inspiratory pressure is adjusted accordingly. The Volume Limit function allows the clinician to set a maximum tidal volume to be delivered. If the preset inspiratory tidal volume should be reached prior to achieving the preset inspiratory pressure, the ventilator will terminate inspiration and cycle into the expiratory phase.

B. Oxygenation: FiO₂: 0.21–1.0

C. Other

1. Assist sensitivity: 0.2–5.0 LPM—sets the amount of flow which the patient must generate at the proximal airway flow sensor to trigger a mandatory breath in assist/control and SIMV or a pressure support breath. It also sets the threshold for monitoring the patient's total breath rate in CPAP.
2. Overpressure relief valve: 15–75 cm H₂O—a mechanical valve that provides a secondary protection against excessive airway pressure. Recommended setting is 15 cm H₂O above the inspiratory pressure setting.
3. Manual breath: push button control which delivers one mandatory breath according to the preset control settings.

IV. Monitors

A. Timing

1. Breath rate: reflects the total breath rate in assist/control, SIMV, pressure support and CPAP (flow sensor required), and the mandatory rate in IMV
2. Patient initiated: indicates the patient has exceeded the Assist Sensitivity requirement for breath delivery, triggering a mechanical or spontaneous breath
3. Inspiratory time: displays T_I of both mandatory and spontaneous breaths
4. Expiratory time: displays T_E of mandatory breath only (i.e., time elapsed from the end of one mandatory breath to the beginning of the next)
5. I:E Ratio: reflects the calculated relationship between the duration of inspiration to the duration of expiration for mandatory breaths only

B. Pressure

1. Peak inspiratory pressure: displays the maximum pressure reached during each pressure breath
2. Mean airway pressure: reflects the average pressure applied to the proximal airway over time
3. PEEP: indicates the PEEP/CPAP measured at the proximal airway

C. Volume (requires properly installed flow sensor)

1. Minute volume: displays the measured exhaled minute volume from all breath types (i.e., mandatory and spontaneous).
2. Inspiratory tidal volume: displays the inspired tidal volume measured at the proximal airway for both mandatory and spontaneous breaths.
3. Exhaled tidal volume: displays the expired tidal volume measured at the proximal airway for both mandatory and spontaneous breaths.
4. % Leak—reflects the calculated difference between inspiratory and exhaled tidal volume. Helpful in assessing the need for re-intubation with a larger endotracheal tube.

V. Alerts and alarms

- A. Low PEEP/CPAP: will be activated if the measured proximal pressure falls below the set value for a minimum of 250 ms. Low PEEP/CPAP must be set within 10 cm H₂O of the PEEP setting or a prolonged inspiratory pressure alarm will sound.
- B. High breath rate: will activate whenever the monitored value for breath rate exceeds the alarm setting.
- C. Low minute volume: will activate when the monitored minute volume falls below the set threshold (flow sensor must be attached).
- D. High pressure limit: will activate when the proximal pressure exceeds the set threshold. Breath will be immediately terminated.

- E. Low inspiratory pressure: automatically set by the ventilator based on the following algorithm:

$$0.25 \left[\begin{array}{c} \square \\ \square \end{array} \right] \text{High pressure limit} \left[\begin{array}{c} \square \\ \square \end{array} \right] \frac{\text{Low PEEP} \left[\begin{array}{c} \square \\ \square \end{array} \right]}{\text{CPAP}} + \frac{\text{Low PEEP} \left[\begin{array}{c} \square \\ \square \end{array} \right]}{\text{CPAP}}.$$

- F. Apnea: indicates that no breath has been initiated/detected in the preset time interval (e.g., 5, 10, 20, or 30 s).

VI. Optional features

- A. Graphics monitor: pressure, flow, and volume waveforms
- B. Computer connection: RS-232
- C. Analog connection: pressure, flow, and breath phase

Suggested Reading

Instruction Manual for Bear Cub 750_{PSV} Infant Ventilator. Palm Springs, CA, Bear Medical Systems, Inc., 1998.

Chapter 42

Newport Wave

Robert L. Chatburn and Teresa A. Volsko

I. Classification

- A. The Wave ventilator (Newport Medical Instruments, Newport Beach, CA) is a pressure or flow controller that may be pressure-, time-, or manually triggered; pressure- or flow-targeted; and pressure-, flow-, or time-cycled.
- B. It has an optional compressor, an internal air–oxygen blender, and a gas outlet port that will power a nebulizer during inspiration.

II. Input

- A. The Wave uses 100–110 V AC at 60 Hz to power the control circuitry.
- B. The pneumatic circuit operates on external compressed gas sources (i.e., air and oxygen) at 40–70 psig.
- C. The operator may input the mode of ventilation; pressure-triggering, inspiratory pressure target, and pressure-cycling thresholds (for high pressure alarm); PEEP/CPAP; peak inspiratory flow rate; inspiratory time; ventilatory frequency; bias flow; and FiO_2 .

III. Control scheme

A. Control variables

1. The Wave controls inspiratory pressure for all spontaneous breaths and for mandatory breaths whenever the peak pressure is preset using the PRESSURE CONTROL knob.
2. For all other mandatory breaths, the Wave controls inspiratory flow.

R.L. Chatburn, MHHS, RRT-NPS, FAARC (✉)
Cleveland Clinic, Respiratory Institute, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: CHATBUR@ccf.org

T.A. Volsko, MHHS, RRT, FAARC
Respiratory Care and Polysomnography Programs, Youngstown State University,
One Perkins Square, Youngstown, OH 44308-1062, USA

B. Phase variables

1. Trigger variables

- a. Inspiration is pressure-triggered when pressure in the patient circuit reaches the SENSITIVITY setting. The threshold for triggering a mandatory breath is adjustable from 0.1 to 5 cm H₂O below the baseline pressure.
- b. A mandatory breath may also be manually triggered.

2. Target variables

- a. Inspiration is pressure-targeted during ASSIST/CONTROL and SIMV modes whenever the PRESSURE CONTROL setting (0–80 cm H₂O) is lower than the natural peak inspiratory pressure (PIP) that would result from the FLOW and INSPIRATORY TIME settings along with the patient's lung impedance. Inspiratory pressure may also be limited by a mechanical pressure relief valve, adjustable from 0 to 120 H₂O, although the primary purpose of this valve is as a safety pop-off.
- b. If the PRESSURE CONTROL setting is high enough so that there is no pressure limit (or if it is set to off), inspiration is flow-targeted. Inspiratory flow rate may be set from 1 to 100 L/min.
- c. An inspiratory pause may be set. The pause setting is adjustable at 0, 10, 20, or 30% of the ventilatory period using a switch on the back of the machine.

3. Cycle variables

- a. Inspiration may be pressure-cycled when the high inspiratory pressure alarm threshold is violated. It may be set over a range of 5–120 cm H₂O.
- b. Inspiration cannot be volume-cycled because the Wave main flow control system does not measure instantaneous volume. Using the INSP. TIME and FLOW controls, this ventilator is capable of delivering tidal volumes of 5–2,000 mL.
- c. Spontaneous breaths are flow-cycled when using PRESSURE SUPPORT. Actually, there is a complex mathematical control equation used for flow-cycling in this mode that includes peak flow, delivered flow, and elapsed inspiratory time. Cycling flows range from <5 to 100% of peak flow. Secondary pressure- and time-cycling thresholds are automatically set as backups to the primary flow-cycling threshold.
- d. Inspiration is normally time-cycled according to the INSPIRATORY TIME setting (adjustable from 0.1 to 3.0 s).

4. Baseline variables

- a. Baseline pressure may be adjusted from 0 to 45 cm H₂O using the PEEP/CPAP dial.

- b. Baseline continuous flow, or “bias flow,” may be set from 0 to 30 L/min. It is controlled through feedback from the proximal airway pressure. Flow is delivered at the set rate in between breaths when proximal pressure is very close to the set baseline pressure. It is reduced or turned off at pressures above baseline.

C. Modes

1. Assist/control

During continuous mechanical ventilation, inspiration is pressure-triggered (depending on the presence of spontaneous breathing efforts and the sensitivity setting) or time-triggered (according to the the RESPIRATORY RATE setting), and may be pressure- or flow-targeted, and is time-cycled.

2. SIMV

- a. In SIMV, mandatory breaths are pressure-triggered (depending on the presence of spontaneous breathing efforts and the sensitivity setting) or time-triggered (according to the frequency setting), may be pressure- or flow-targeted, and are time-cycled. A mandatory breath is pressure triggered the first time a spontaneous breathing effort is detected in each ventilatory period (the ventilatory period is equal to the reciprocal of the RESPIRATORY RATE). If a breathing effort is not detected during a given ventilatory period, a mandatory breath will be delivered at the beginning of the next period. The ventilator will continue to deliver mandatory breaths according to the RESPIRATORY RATE setting until a spontaneous breath is detected, and the sequence of events repeats itself.
- b. Spontaneous inspirations between mandatory breaths are supported only by the baseline pressure (i.e., PEEP/CPAP) . The tidal volume spontaneous breaths produce may be augmented by the application of pressure support. The PRESSURE SUPPORT setting adjusts the inspiratory pressure delivered to the patient, which is measured relative to baseline pressure.

3. SPONTANEOUS

Inspiration is pressure-controlled in the SPONTANEOUS mode at the set PEEP/CPAP level. A PRESSURE SUPPORT level may also be set. The slope or rise time of pressure during PRESSURE SUPPORT is automatically controlled using “predictive learning logic” software to maintain optimal patient synchronization.

D. Control subsystems

1. Control circuit

- a. The Wave uses pneumatic and electronic control components.
- b. Triggering and cycling signals arise from the inspiratory time and ventilatory frequency settings as well as signals from the airway pressure transducer and flow sensors.

- c. Output control signals from two pressure transducers (one monitors airway pressure and one monitors pressure in the exhalation valve) and two redundant flow transducers (monitoring the output of the master flow control valve) are used to control flow.
 - d. The exhalation manifold is controlled pneumatically.
2. Drive mechanism
 - a. The Wave uses either external compressed gas (for air and oxygen) or an electric motor and compressor (for air) in conjunction with a pressure regulator. Gas from supply lines is fed to an internal air-oxygen blender.
 - b. Mixed gas leaves the blender at 28 psig and enters a rigid-walled vessel (the “accumulator”). The flow control system is driven by the pressure from the accumulator, reducing the instantaneous flow demand required of the blending system. This action allows a wide range of peak flow settings, significantly increases the peak spontaneous flow capability above the mandatory flow target, reduces the flow required of the compressed gas supply, and improves response time. The accumulator also acts as a mixing chamber, which helps to stabilize the delivered oxygen concentration within a given breath. An optional Flush Valve assembly allows for instantaneous dumping of the accumulator to enable immediate FiO_2 changes when necessary.
 3. Output control valves
 - a. All gas flow to the patient is regulated by the main flow control valve, which is a proportional solenoid valve.
 - b. An electromagnetic poppet valve switches between two sources of a pneumatic signal to the exhalation valve. One source comes from the output of the master flow control valve and keeps a diaphragm-type exhalation manifold closed during assisted breaths. The other source is a pressure regulator that generates an adjustable pressure signal to control baseline pressure (i.e., PEEP/CPAP).
 - c. The microprocessor coordinates the activity of both valves such that the exhalation valve closes as the flow control valve begins to deliver flow to the patient circuit.

IV. Output

A. Waveforms

1. The Wave delivers a rectangular flow waveform when set for volume control, that is, if the natural PIP is below the setting of the PRESSURE CONTROL knob or if this knob is set to “off.”
2. If PIP is limited using the PRESSURE CONTROL knob, a variety of pressure waveforms can be achieved, ranging from rectangular to triangular depending on the respiratory system mechanics and the inspiratory flow rate.

B. Displays

1. In addition to the various control settings, the Wave displays include visual alarm indicators (LEDs) and digital display of set tidal volume (calculated based on flow and inspiratory time settings); measured inspiratory tidal volume and minute volume; ventilatory rate; peak, mean, and baseline airway pressures; and peak inspiratory flow.
2. An electronic pressure gauge provides airway pressure measurement over the range of 0–120 cm H₂O.
3. The Wave is usually sold with the Compass, which incorporates a heated, filtered exhalation system and provides monitoring of expiratory tidal volume and minute volume, I:E ratio, FiO₂, and expiratory flow.

V. Alarms

A. Input power alarms. An audible alarm is activated if the electrical power is interrupted if the air or oxygen supply falls below 32 psig.

B. Control circuit alarms

1. A visual INSPIRATORY TIME TOO LONG alarm is activated if the inspiratory time and ventilatory rate settings result in an I:E ratio greater than the pre-set maximum. There are two selectable maximum ratios: 1:1 and 3:1.
2. When the inspiratory time is set such that the pre-set maximum I:E ratio is violated, the ventilator will override the inspiratory time setting to restrict the I:E to the pre-set value.
3. Audible and visual VENTILATOR INOPERATIVE alarms are activated when malfunction of the integrated circuit or ventilator occurs.
4. The two pressure and two flow sensors are automatically re-zeroed at regular intervals during use. If the drift between the pressure or flow sensors is large, the visual display flashes automatically.

C. Output alarms

1. A low-pressure alarm is adjustable from 1 to 118 cm H₂O, and a high-pressure alarm is adjustable from 3 to 120 cm H₂O.
2. High and low minute volume alarms are adjustable from 1 to 50 and 0 to 49 L/min, respectively (or 0.1 to 5 and 0 to 4.9 L/min).
3. The Compass offers high and low expiratory minute volume as well as high and low FiO₂ alarms.

VI. Unique clinical features

- A. The Wave is a ventilator that is useful in acute (or critical care) and subacute care settings.
- B. It can ventilate a wide range of patients from neonates to adults.

Suggested Reading

- Cairo JM, Pilbeam SP. Mosby's respiratory care equipment. 8th ed. St. Louis: Mosby Elsevier; 2010.
- Chatburn RL. Classification of ventilator modes: update and proposal for implementation. *Respir Care*. 2007;52(3):301–23.
- Chatburn RL. Classification of mechanical ventilators. In: Tobin MJ, editor. *Principles and practice of mechanical ventilation*. 2nd ed. New York: McGraw-Hill; 2006. p. 37–52.
- Chatburn RL. Computer control of mechanical ventilation. *Respir Care*. 2004;49:507–15.
- Chatburn RL. *Fundamentals of mechanical ventilation*. Cleveland Heights: Mandu; 2003.
- Chatburn RL, Primiano Jr FP. A new system for understanding modes of mechanical ventilation. *Respir Care*. 2001;46:604–21.
- Chatburn RL. Principles and practice of neonatal and pediatric mechanical ventilation. *Respir Care*. 1991;36:569–95.
- Chatburn RL. Understanding mechanical ventilators. *Expert Rev Respir Med*. 2010;4(6): 809–819.
- Goldsmith JP, Karotkin EH, editors. *Assisted ventilation of the neonate*. 5th ed. Philadelphia: Elsevier/Saunders; 2011.
- MacIntyre NR, Branson RD. *Mechanical ventilation*. 2nd ed. St. Louis: Saunders Elsevier; 2009.
- Pilbeam PP, Cairo JM. *Mechanical ventilation. Physiology and clinical applications*. St. Louis: Mosby Elsevier; 2006.

Chapter 43

Newport e360

Cyndy Miller

I. Introduction

The e360 ventilator (Newport Medical, Costa Mesa, CA) supplies invasive or noninvasive ventilatory support and monitoring for infant, pediatric, and adult patients.

II. Description of unique features

- A. Circuit Check ensures that intelligent breath management functions are calibrated to the installed breathing circuit system.
- B. Quick Setup (Worldwide [WW] Version) makes set up easier for new patients.
- C. Pressure or flow triggering are available for all breaths.
- D. Automatic Leak Compensation can provide more reliable triggering in spite of variable airway leaks, without the user having to readjust the flow trigger setting.
- E. Slope Rise adjustment (including an AUTO setting for WW version) ensures that breath delivery meets patient comfort needs.
- F. FlexCycle function automatically manages the flow cycling off threshold for each individual pressure support and volume target pressure support breath to avoid early or late cycling off, despite changing patient mechanics.
- G. Breath choices include those with pressure, volume, and adaptive target schemes.
- H. Monitored tidal volume (mL or mL/kg) for tracking of volume goals.
 - I. Event History log (.csv files) and screen images (.bmp files) can be saved to the internal drive and downloaded to a flash drive via USB port for viewing on a PC.

C. Miller, RRT, AS/AA (✉)
Department of Clinical Education, Newport Medical Instruments,
1620 Sunflower Avenue, Costa Mesa, CA 92626, USA
e-mail: CMiller@nmitkb.com

III. Input

A. Power: Choose one.

1. AC: 100–240 V AC, 250 V AC, max, 50/60 Hz ($\pm 10\%$).
2. Internal battery (up to 60 min).
3. External Battery: 10 V DC to 14 V DC.

B. Source gas:

1. Mixed gas delivery: Air and O₂; 30–90 psig, 50 psig nominal.
2. 0.21 or 1.00 FiO₂ gas delivery: Air or O₂; 30–90 psig, 50 psig nominal.
3. Use optional air compressor as primary air gas supply or as a pressure-switched backup air supply.

IV. Control scheme

A. Control variables

1. Inspiratory pressure set point

- a. Pressure limit ($>$ ambient) setting determines destination gauge pressure maintained for pressure control (PC) and biphasic pressure release ventilation (BPRV) mandatory breaths. Flow delivery is servo controlled (allows free inhalation).
- b. Pressure support ($>$ PEEP) setting determines the delta pressure that is maintained for pressure support (PS) spontaneous breaths. Flow delivery is servo controlled (allows free inhalation).
- c. Exhalation valve pressure is also servo controlled during biphasic pressure release mandatory breaths (allows free exhalation).

2. Adaptive dual control pressure/volume

- a. Pressure limit setting determines *maximum* destination gauge pressure maintained for volume target pressure control (VTPC) and volume target pressure support (VTPS) breaths. Minimum destination gauge pressure is PEEP +5 cm H₂O. Goal is delivery of set tidal volume at the lowest pressure. Flow delivery is servo controlled (allows free inhalation).
- b. Delivered tidal volume for one VTPC breath determines destination pressure selected for the subsequent VTPC breath and delivered tidal volume for one VTPS breath determines delta pressure selected for the subsequent VTPS breath.

3. Inspiratory flow (volume) set point

- a. Flow or t_{Insp} , tidal volume, and flow waveform (square or descending ramp) settings determine the flow profile that is directly controlled for all volume controlled (VC) breaths.
- b. Common nomenclature refers to these breaths as being volume controlled.

B. Phase variables

1. Trigger

a. Flow:

- (1) All modes and breath types
- (2) Range: 0.1–2 L/min
- (3) Automatically compensated for changes in bias flow/leak compensation flow

b. Pressure:

- (1) All modes and breath types
- (2) Range: 0–5 cm H₂O below baseline pressure.

c. Ventilator/time:

- (1) A/CMV, SIMV, and backup ventilation.
- (2) Occurs if the flow or pressure trigger is not activated in the patient triggering time window

d. Operator/manual:

- (1) All modes and breath types
- (2) Manually triggered and cycled by the operator

2. Target variables: Newport breath type naming applies the term “target” to the second control variable when using the adaptive control scheme (as in VTPC), but this text describes the target variables according to Chatburn’s method.

a. Pressure:

- (1) PC breaths
- (2) BPRV (open exhalation valve ON) breaths
- (3) VTPC (volume target ON) breaths
- (4) All spontaneous breaths

b. Volume: VC breaths

3. Cycle variables

a. Volume: VC breaths

b. Time

- (1) PC breaths
- (2) VTPC breath
- (3) BPRV breaths
- (4) PS and VTPS breaths (if flow or pressure cycling off thresholds are not met before 1.2 s for Ped/Infant patient category and 2 s for adult patient category).

- c. Flow: PS and VTPS breaths [if inspiratory flow decays to the Exp Thresh (expiratory threshold) setting before the pressure or time cycling threshold is met]. Exp (flow) Threshold is operator adjustable from 5 to 55% of peak flow or it may be set to AUTO. AUTO activates FlexCycle, which manages the Expiratory Threshold setting automatically between 5 and 55% (breath by breath).
- d. Pressure: PS and VTPS breaths (if inspiratory pressure reaches a predetermined threshold above the target pressure level before the flow or time cycling thresholds are met).

4. Baseline variables

- a. Pressure (PEEP/CPAP control) 0 (ambient) to 45 cm H₂O
- b. (Bias) Flow
 - (1) Automatic regulation and intercoupling with the flow trigger setting eliminates operator readjustment when leak changes.
 - (2) Leak compensation ON: 3–8 L/min for Ped/Infant patient selection; 3–15 L/min for Adult patient selection.
 - (3) Leak compensation OFF: 3 L/min.
 - (4) NIV ON: 3–25 L/min, regardless of patient type or leak compensation On/Off setting.

V. Operator-set controls

A. Control input

- 1. Two graphical user interfaces, membrane buttons and a rotary adjustment knob.
- 2. Servo-controlled feedback system automatically reconciles differences between the measured and target values during all phases of breath delivery.
- 3. Operator inputs settings via touch–turn–accept method or the toggle–accept method.

B. Control management: The operator selected mode and mandatory breath type determine:

- 1. Spontaneous breath type available in SIMV and SPONT modes
- 2. Which operator settings are relevant to breath management

C. Operator initiated maneuvers

- 1. Inspiratory hold
- 2. Expiratory hold
- 3. $P_{0.1}$
- 4. Negative inspiratory force
- 5. Pressure volume maneuver (WW version) (for creating a quasi-static PV curve)

D. Modes

1. A/CMV (AKA A/C, Assist Control or CMV) delivers only mandatory breaths. Breath types: PC, VC, VT_{PC}, and BPRV.
2. SIMV delivers both mandatory and spontaneous breaths if the patient breathes at a rate above the set Resp Rate and delivers only mandatory breaths if the patient does not breathe at a rate above the set Resp Rate.
3. SPONTANEOUS delivers only spontaneous breaths. Spontaneous breath types include PS (when VC, PC, BPRV mandatory breath types are selected) and VT_{PS} (when VT_{PC} mandatory breath type is selected).

E. Mandatory breath types

1. VC—achieves the tidal volume setting.
2. PC—sustains the pressure limit setting above ambient for the duration of the t_{Insp} setting.
3. VT_{PC}—sustains the lowest pressure between 5 cm H₂O above baseline and the pressure limit setting above ambient that is predicted to achieve the set tidal volume for the duration of the t_{Insp} setting.
4. BPRV—sustains the pressure limit setting above ambient for the duration of the t_{Insp} setting. Open Exh is ON.

F. Spontaneous breath types

1. PS—sustains the pressure support setting above PEEP until the flow, pressure or time cycling off threshold is met.
2. VT_{PS}—sustains the lowest pressure between 5 cm H₂O above baseline and the pressure limit setting above ambient that is predicted to achieve the set tidal volume until the flow, pressure, or time cycling off threshold is met.

G. Mode/breath type logic: The mode/breath type logic is summarized in Table 43.1, using Chatburn's Universal Mode Translator Version 2.

VI. Control subsystems

A. Inhalation system

1. Includes: Gas pathway and regulation, To Patient port, the emergency intake valve, the emergency relief valve and the oxygen sensor (access sensor using a flathead screwdriver).
2. The inspiratory manifold is autoclaveable.
3. Install a fresh filter on the To Patient port for each patient.

B. Exhalation system

1. Includes the From Patient port, exhalation valve and flow sensor.
2. From Patient port and exhalation valve can be autoclaved and the exhalation flow sensor can be disinfected in alcohol or gas sterilized.
3. Keep a clean, dry filter on the From Patient port while ventilating.
4. Optional: install the filter heater to keep the filter dry in spite of high humidity in exhaled gas and increase filter use time.

Table 43.1 Universal mode translator V2.0

Manufacturer	Model	Manufacturer's mode name	Class	Family	Genus						Species				Variety		
					Primary breath			Secondary breath			Target scheme	Trigger	Within breath target	Cycle	Operational logic	Between breath target	Volume
Target scheme	Trigger	Sync	Within breath target	Sync	Cycle	Sync	Target scheme	Trigger	Within breath target	Cycle							
Newport	e360	Volume target pressure control A/CMV (assist control)	Pressure	CMV	Adaptive	Variable Time/ press/flow	Yes	Insp press	Insp only	Variable Time	No	N/A	Variable N/A	Variable N/A	Variable N/A	Between breath target Volume	Operational logic Between-breath target tidal volume preset and inspiratory pressure adjusted to meet target
Newport	e360	Volume target pressure control SIMV (synchronized intermittent mandatory ventilation)	Pressure	IMV	Adaptive	Time/ press/flow	Yes	Insp press	Insp only	Time	No	Adaptive	Press and flow	Insp press	Press/ flow/ time	Volume	Between-breath target tidal volume preset and inspiratory pressure adjusted to meet target
Newport	e360	Volume target pressure support (SPONT)	Pressure	CSV	Adaptive	Press/flow	Yes	Insp press	Insp only	Press/ flow/ time	Yes	N/A	N/A	N/A	N/A	Volume	Between-breath target tidal volume preset and inspiratory pressure adjusted to meet target

Newport	e360	Pressure control A/CMV (assist control)	Pressure	CMV	Set-point	Time/press/flow	Yes	Insp press	Insp only	Time	No	N/A	N/A	N/A	N/A		
Newport	e360	Pressure control SIMV (synchronized intermittent mandatory ventilation)	Pressure	IMV	Set-point	Time	Yes	Insp press	Insp only	Time	No	Set-point	Press & flow	Insp press	Press/flow/time	N/A	
Newport	e360	Biphasic pressure release A/CMV (assist control)	Pressure	CMV	Set-point	Time/press/flow	Yes	Insp press	Insp/exp	Time	No	N/A	N/A	N/A	N/A	Pressure control with open exhalation valve for free breathing	
Newport	e360	Biphasic pressure release SIMV (Synchronized intermittent mandatory ventilation)	Pressure	IMV	Set-point	Time/press/flow	Yes	Insp press	Insp/exp	Time	No	Set-point	Press and flow	Insp press	Press/flow/time	N/A	Pressure control with open exhalation valve for free breathing
Newport	e360	Volume control A/CMV (assist control)	Volume	CMV	Set-point	Time/press/flow	Yes	Volume/flow	No	Volume	No	N/A	N/A	N/A	N/A		

(continued)

Table 43.1 (continued)

Manufacturer	Model	Manufacturer's mode name	Class	Family	Genus						Species				Variety			
					Primary breath			Secondary breath			Target scheme	Trigger	Within breath target	Cycle	Within breath target	Cycle	Between breath target	Operational logic
					Target scheme	Trigger	Sync	Variable	Sync	Variable								
Newport	e360	Volume control SIMV (synchronized intermittent mandatory ventilation)	Volume	Breath sequence	IMV	Set-point	Time	Yes	Volume/flow	No	Volume	No	Set-point	Press and flow	Insp press	Press/flow/time	N/A	N/A
Newport	e360	Pressure support (SPONT)	Pressure	CSV	Set-point	Press/flow	Yes	Insp press	Insp only	Press/flow/time	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Reproduced with permission from Mandu Press Ltd

VII. Output

A. Flow waveforms

1. Mandatory VC breaths: rectangular (square) or descending ramp (operator selectable) flow waveform.
2. All other breaths: decelerating flow waveform with flow regulated to maintain the intended pressure profile.

B. Displays

1. Graphics.
 - a. Scalar waveforms: Pressure, volume, and flow-time (manual/auto-scale)
 - b. Loops: Volume pressure and flow volume (manual/auto-scale)
 - c. Slow inflation pressure volume loop (curve) (WW Version)
 - d. Airway opening pressure gauge
2. Trends: Expiratory tidal volume (VTE), expiratory tidal volume % variance (leak) (VTE% Var), expiratory minute volume (MVE), peak pressure (Ppeak), mean pressure (Pmean), PEEP/CPAP, total respiratory rate (RRtot), and rapid shallow breathing index (RSBI).
3. Event history log (1,000 color-coded events).
4. Monitored values: FiO₂, Ppeak, Pplat, Pmean, PEEP/CPAP, Total PEEP (PEEPtot), inspiratory minute volume (MVI), MVE, MVE spont, inspiratory tidal volume (VTI), VTE, VTE% Var, Insp flow, Exp flow, inspiratory time (*t* Insp), time constant, I:E ratio (set and monitored), RRtot, RR spont, RSBI, dynamic effective compliance (Cdyn effective), static compliance (Cstat), inspiratory resistance (RI), expiratory resistance (RE), imposed work of breathing (WOBim), occlusion pressure (P_{0,1}), and negative inspiratory force (NIF).

VIII. Alarms

A. Audible and visual alarms

1. There are adjustable alarms for high/low minute volume, high rate, apnea, high/low airway opening pressure, and disconnect.
2. There are automatically set alarms for high/low FiO₂, Insp time too short/long, set inverse ratio >4:1, high/low and sustained high baseline (PEEP), volume target not met and backup ventilation (BUV) in response to a low minute volume alarm (BUV automatically resets when minute volume reaches 10% above low alarm limit).
3. Alarm Features include a 2-min alarm silence, an alarm indicator reset, alarm loudness selector (1–10), alarm tone selector (1, 2, or 3) suction disconnect function which presilences alarms for 2 min, suspends ventilation after a planned disconnect, and senses reconnection to resume ventilation.

Electronic Ports/Connections include remote alarm/nurse call, external battery, com1, VGA, external alarm silence, RS232, and USB (upload software and download images and event logs).

Suggested Reading

Newport e360 Ventilator Operating Manual, Newport Medical, Costa Mesa, CA. e360 elearning program on the Newport website: <http://newportnmi.com/educationlogin-e360.asp>.

Chapter 44

Dräger Babylog VN500 Infant and Pediatric Ventilator

Donald M. Null, Jr.

I. Description

- A. The Babylog VN500 Ventilator (Dräger, Inc., Luebeck, Germany) replaces the Babylog 8000 Plus. It is a time-cycled, volume constant, pressure controlled, continuous flow ventilator that is designed for both Neonatal and Pediatric patients. Admission of a new patient requires the user to select either a neonatal or pediatric setting, which then determines the ventilator start-up settings.
- B. The unit comprises the following:
 - 1. Infinity C500 control and display unit (Medical Cockpit)
 - 2. Babylog VN500 Ventilation unit
 - 3. GS500 gas supply
 - 4. Trolley 2 (cart for all components)
- C. Main ventilator functions and monitor systems
 - 1. The cockpit contains the specific information and operating steps for the Babylog VN500. It allows for selecting the patient category, ventilation mode, therapy controls, alarms, and monitoring. The ventilation unit indicates inspiratory and expiratory phases via a bar display along with inspired oxygen concentration and minute volume.
 - 2. The therapy bar contains the controls for the active ventilation mode. Changes are made by touching the control. The color turns yellow and the unit of the parameter to be adjusted is displayed. Turning the knob adjusts the parameter and depressing it confirms the value and the color turns green.

D.M. Null, Jr., MD (✉)
Primary Children's Medial Center, Newborn Intensive Care Unit,
100 North Mario Capecchi Drive, Salt Lake City, UT 84113, USA
e-mail: Donald.Null@HSC.UTAH.EDU

II. Peak flow and volume measurement

A. Parameters are measured with a heated-wire anemometer.

1. A neonatal or pediatric flow sensor is used.
2. The sensor may be integrated in the wye (wye sensor) or into a separate sensor adapter between the wye and the endotracheal tube (ETT) connector (ISO sensor).
3. These sensors are slightly different in their flow responses. Therefore, for optimal measurement results, the sensor type needs to be selected in one of the ventilator menus.
4. Both inspiratory and expiratory volumes are displayed along with calculated leak.
5. Minute volume is measured and can be used to assess effect of weaning ventilator support.

B. Trigger function

1. Spontaneous breathing is detected using a flow measurement.
2. Trigger sensitivity may be set from 0.2 to 5 L/min.

III. Additional features

A. Automatic leak compensation

1. Determines difference between measured flow on the inspiratory and expiratory sides.
2. Leak compensation takes in to account airway pressures.
3. If leakage is above the flow trigger threshold, the user must increase this to avoid autotriggering.

B. Automatic tube compensation

1. Controls airway pressure at tracheal level.
2. The tube type and its internal diameter must be entered.
3. Support is calculated by the equation:

$$\Delta P_{aw} = \text{comp.} \cdot K_{\text{tube}} \cdot \text{Flow}^2$$

Comp = degree of compensation entered (0–100%)

K_{tube} = tube coefficient (found in table in user manual)

Flow = patient flow

C. O₂ change for suctioning

1. O₂ is increased one to twofold as configured from current O₂ concentration.
2. When O₂ enrichment is started, it ventilates patient for a maximum of 180 seconds. When the device is disconnected for suctioning, acoustic alarms are suppressed. After reconnecting the device, increased FiO₂ continues for 120 s.

3. Internal battery

- a. Automatically switches on without interruption if main power supply fails.
- b. An alarm message is displayed: *Internal Battery Activated*.
- c. Approximately 2 min before expiration of battery operating time, an alarm message appears: *Internal Battery Low*.

IV. Monitoring

A. Internal

B. Displays

1. Curves
2. Graphic trends
3. Numeric trends
4. Loops
5. Alarm history
6. Logbook: records changes, events, and alarms in chronological order
7. Numeric parameters
8. Preconfigured lists for measured values and set values
9. Customized lists for measured values and set values
10. C20/C ratio
11. Smart pulmonary view
 - a. Compliance
 - b. Resistance

V. Alarms

A. Alarm/limits automatic

1. Airway pressure high (cm H₂O)
2. Airway pressure low (cm H₂O)
3. V_T low
4. PEEP high (cm H₂O)
5. PEEP low (cm H₂O)
6. Pressure limited
7. Volume measurement inaccurate
8. V_T not reached
9. Pressure limited (ATC/PPS)
10. Pressure limited (volume guarantee modality)
11. Disconnection
12. Leakage
13. Airway obstructed
14. FiO₂ high
15. FiO₂ low
16. CO₂ sensor

B. Alarm limits settable

1. MV high
2. MV low
3. PAW high
4. RR high
5. Tapn (apnea alarm time)
6. EtCO₂ high
7. EtCO₂ low

C. Nurse call provides high priority alarms to go to central station

VI. Nomenclature

A. Pressure versus volume ventilation

1. Pressure-targeted ventilation.
 - a. Pressure is controlled.
 - b. Volume varies with change in pulmonary compliance and airway resistance.
2. Volume-targeted ventilation
 - a. The volume delivered from the ventilator is controlled.
 - b. The pressure varies with change in pulmonary compliance and airway resistance.

B. Modes

1. Assist/control (A/C)
 - a. All spontaneous breaths are assisted.
 - b. A minimum number of assisted breaths is set.
2. SIMV/PS
 - a. Preset number of supported breaths.
 - b. If patient's breath rate exceeds the preset rate, the additional breaths will be supported with pressure support.
3. Flow-Cycling: In PS, VS, and PPS modes, inspiration is terminated when inspiratory flow decelerates to 15% of the peak flow.

VII. Ventilation modes

- A. PC–CMV (pressure control–continuous mandatory ventilation)
Peak pressure is set along with T_i , which determines duration of breaths. Breaths are time-cycled and not patient triggered. Spontaneous breathing can take place between controlled breaths.
- B. PC–SIMV (pressure control–synchronized intermittent mandatory ventilation)
Peak pressure is set along with T_i which determines duration of breaths. Respiratory rate is set and the patient can trigger the mechanical breaths.

The respiratory rate per minute that is set is prevented from increasing if the patient's respiratory rate is greater by a refractory period built in.

- C. Pressure support

During spontaneous breathing, all patient breaths meeting trigger criteria will be supported. Pressure support is flow-cycled, as above.
- D. PC–A/C (pressure control–assist control)

Peak pressure is set and duration of breaths is set by T_1 . All inspiratory efforts meeting trigger criteria initiate a synchronized breath. A minimum number of breaths are controlled by setting the respiratory rate (RR).
- E. PC–PSV (pressure control–pressure support ventilation)

All patient breaths are supported with the level set by P_{Insp} . A minimum RR can be set, which will start if too few patient-triggered breaths occur. The maximum inspiratory time can be set from 0.1 to 1.5 s.
- F. PC–MMV (pressure control–mandatory minute volume)

Tidal volume is set with V_{T} . Duration of breaths is determined by T_1 . Mandatory breaths are only provided if spontaneous breathing is inadequate to meet the prescribed minute ventilation. The spontaneous breaths can be supported with pressure support.
- G. PC–APRV (pressure control–airway pressure release ventilation)

Not typically used for the neonate.
- H. SPN–CPAP/PS (spontaneous–continuous positive airway pressure/pressure support)

Every inspiratory effort that meets trigger criteria is supported. Fast or slow pressure rise can be selected for the supported breaths.
- I. SPN–CPAP/VS (spontaneous–continuous positive airway pressure/volume support)

All spontaneous breaths that meet trigger criteria trigger a volume-supported breath.
- J. SPN–PPS (spontaneous–proportional pressure support)

With strong breaths, high pressure support occurs and with shallow breaths, low pressure support occurs. Apnea and minute volume must be set appropriately.
- K. Volume guarantee

Volume guarantee can be switched on for PC–SIMV, PC–CMV, PC–AC, and PC–PSV ventilation modes. In the Neo Mode, exhaled volume is used to control breaths.
- L. Apnea ventilation
 1. Ventilator will automatically switch to volume-guaranteed mandatory ventilation when this is activated if the following occur:
 - a. Either no expiratory flow is measured
 - b. Insufficient inspiratory gas is delivered during the set apnea alarm time (T_{apn}).
 2. Ventilation parameters are R_{apn} and V_{Tapn} .
 3. Patient can breathe spontaneously with synchronization of breaths.

4. When sufficient spontaneous breathing returns, the ventilator automatically switches to the previous ventilation mode.
5. The following conditions must be met:
 - a. Apnea ventilation must have been active for at least 2 min.
 - b. The alarm message—MV low—is not active.
 - c. Ratio of MV_{Spon} to MV must be $> 25\%$ and ratio of MV leak to MV is $< 40\%$ or 80% of mandatory breaths are triggered spontaneously.

M. Sigh

1. Sigh can be activated in all modes except PC-APRV.
2. The sigh is set in the form of intermittent PEEP.
3. When activated, the end expiratory pressure PEEP increases by the set value of the intermittent PEEP.
4. The time between sigh phases is set by the therapy control interval sigh. The therapy control (Cycles Sigh) controls how many respiratory cycles are covered by the sigh phase.

VIII. Management

- A. The multiple modes in both pressure and volume regulation make choosing an appropriate ventilatory mode difficult at times. Effective use of the various modes requires consideration of the pathophysiology of the lung disorder, how the specific mode interacts with this, and utilizing graphics to make appropriate adjustments as the pulmonary mechanics change over time.
 1. Ventilation (PaCO_2) is managed by adjusting the tidal volume of each supported breath and resultant minute ventilation. To be most effective, one must avoid underinflation and overinflation for lung protection. Tidal volumes should be maintained between 4 and 7 mL/kg. Remember that less is not always better as it may predispose the lung to atelectotrauma.
 2. Oxygenation is dependent on keeping the lung in the mid position of the pressure-volume curve and uniformly inflated to recruit optimal surface area. This is best accomplished by using an adequate mean airway pressure, achieved by altering the PEEP, PIP, T_{Ins} , V_{T} , and rate of the selected mode. Changing FiO_2 will additionally effect oxygenation.
 3. The goal of assisted ventilation is to prevent lung injury while providing needed respiratory support for the patient. Much information has been focused on avoiding volutrauma. Because of this concern, individuals have attempted to use smaller tidal volumes. This may lead to loss of lung volume, thereby, leading to atelectotrauma. The lung is most vulnerable to injury during recruitment as portions of the lung that are partially inflated will become overinflated, and opening of atelectatic areas may lead to shearing forces that injure those areas. The best way to prevent lung injury is to keep the lung at an optimal lung volume; avoid strategies that allow for de-recruitment and overdistension.

B. Pressure vs. volume

1. The advantage of the volume-targeting is that as compliance improves the PIP will automatically decrease, preventing overdistension and volutrauma.
2. However, volume ventilation can also lead to lung injury. A patient who develops atelectasis of 50% of the lung would have the actual volume delivered to the open lung at twice the set volume, which is not lung protective.
3. Using a pressure-targeted mode can be as effective as volume but requires much more diligent observation and more frequent adjustments of the ventilator.

C. Weaning

1. When weaning from a pressure mode, decreasing PIP or rate and following minute ventilation allows one to assess the effectiveness of the patient's endogenous respiratory efforts. If the patient is ready to come off the ventilator, minute ventilation should change very little as supported breaths are decreased.
2. In the volume mode, since most breaths are supported, weaning the rate is not effective, as it is only the minimum number of breaths that will be decreased. One must either change to SIMV or wean the tidal volume or pressure support and observe minute ventilation to see that it has changed very little.

Chapter 45

SERVO-i Ventilator and Neurally Adjusted Ventilatory Assist (NAVA)

Jennifer Beck and Louis Fuentes

I. Introduction

- A. The SERVO-i ventilator (Maquet, Solna, Sweden) has the capability to support ventilation for all patient ranges, age, size, and weight, including very low birth weight infants.
- B. Many of its features are specific for neonatal ventilation, including flow-triggering in all modes, tubing compliance compensation, and apnea support with backup ventilation.
- C. The exhalation valve on the SERVO-i is an active expiratory valve that is able to provide accurate levels of PEEP and enhances comfort for spontaneously breathing patients. The active expiratory valve utilizes a time constant valve controlling algorithm to measure the compliance and resistance of each mechanical breath in an effort to reduce the expiratory work of breathing for the patient.
- D. The new generation exhalation valve is also necessary to use new modalities such as BiVent and Nasal CPAP for the infant population.
- E. The SERVO-i ventilator has the capability of monitoring the electrical activity of the diaphragm (Edi) and using the Edi for controlling the assist during Neurally Adjusted Ventilator Assist (NAVA).

II. Modes

- A. The SERVO-i offers a variety of conventional modes as well as combination modes. The SERVO-i offers both invasive and noninvasive modes of ventilation (NIV), including NAVA and NIV-NAVA.

J. Beck, PhD (✉)

Keenan Research Centre in the Li Ka Shing Knowledge Institute of St-Michael's Hospital,
St-Michael's Hospital, Room 611, 6th floor, 209 Victoria Street,
Toronto, ON, Canada, M5B 1T8
e-mail: Beckj@smh.ca

L. Fuentes, RRT

Maquet Critical Care, 45 Barbour Pond Drive, Wayne, NJ 07470, USA

- B. The ventilator may be set to flow trigger or pressure trigger in all modes of ventilation. During NAVA and NIV-NAVA, the Edi serves as the principle trigger.
- C. All modes can be patient-triggered.
- D. Control modes of ventilation: Spontaneous breaths have the same characteristics (flow, inspiratory time, volume or pressure) as the set ventilator breaths.
 1. Pressure control (PC). This mode of ventilation employs a variable flow rate which is microprocessor-controlled to provide a constant inspiratory pressure.
 - a. Tidal volume is variable
 - b. Peak inspiratory pressure is constant
 - c. Square pressure wave form
 - d. Decelerating flow wave form [a variable flow rate differentiates this from time-cycled, pressure-limited ventilation, which incorporates a constant (continuous) flow]
 - e. Clinician set parameters
 - (1) Peak inspiratory pressure level (above PEEP)
 - (2) Inspiratory time
 - (3) Ventilator rate
 - (4) PEEP
 - (5) FiO_2
 - f. High and low minute ventilation alarms
 - g. High pressure alarm
 - h. High and low respiratory rate alarms
 - i. High and low end expiratory pressure alarms
 - j. Trigger sensitivity level
 2. Volume control (VC)
 - a. Tidal volume is fixed
 - b. Peak pressure is variable
 - c. Square flow wave form (flow is regulated based on set tidal volume and inspiratory time)
 - d. Accelerating pressure wave form
 - e. Clinician-set parameters
 - (1) Tidal volume
 - (2) Inspiratory time (controls flow rate)
 - (3) Pause time (optionally added to inspiratory time to help increase mean airway pressure, does not affect flow rate)
 - (4) Ventilator rate
 - (5) PEEP
 - (6) FiO_2
 - (7) High and low minute ventilation alarms
 - (8) High pressure alarm

- (9) High and low respiratory rate alarms
 - (10) High and low end expiratory alarms
 - (11) Trigger Sensitivity level
3. Pressure regulated volume control (PRVC). Pressure regulated volume control combines a variable flow rate with the advantage of setting a targeted tidal volume. When PRVC is first initiated, the ventilator delivers a VC breath, and the measured pause pressure is used as the pressure level for the next breath. PRVC has the ability to vary flow similar to pressure control for breath delivery. This mode produces the same flow, and pressure patterns as PC but targets the tidal volume by monitoring delivered V_T on each breath and adjusting the PIP on the subsequent breath.
- a. Tidal volume is set
 - b. Peak pressure is variable
 - c. Decelerating flow wave form (the same as PC)
 - d. Square pressure wave form
 - e. Clinician-set parameters
 - (1) Tidal volume
 - (2) Inspiratory time
 - (3) Ventilator rate
 - (4) PEEP
 - (5) FiO_2
 - (6) High and low minute ventilation alarms
 - (7) High pressure alarm
 - (8) High and low respiratory rate alarms
 - (9) High and low end expiratory alarms
 - (10) Trigger sensitivity level
- E. Modalities for spontaneously breathing patients (breaths are patient initiated)
1. Volume support (VS). Volume support is a modality for patients with an intact respiratory drive. This modality supports the patient's inspiratory effort with an assured or targeted tidal volume. Backup ventilation is set so that if a patient becomes apneic, the ventilator will alarm and change-over to configurable backup ventilation settings which are predetermined by the clinician. Backup ventilation is set based on an apnea time, set by the clinician, with configurable settings that will revert back to the spontaneous mode once the respiratory effort is sensed by the ventilator.
 - a. Tidal volume is set.
 - b. Peak pressures are variable (based on lung compliance and respiratory effort).
 - c. Flow is decelerating.
 - d. Clinician-set parameters.
 - (1) Minimum tidal volume
 - (2) Inspiratory time (for backup ventilation should apnea occur)

- (3) Ventilator rate (for backup ventilation should apnea occur)
 - (4) PEEP
 - (5) FiO_2
 - (6) High and low minute ventilation alarms
 - (7) High pressure alarm
 - (8) High and low respiratory rate alarms
 - (9) High and low end expiratory alarms
 - (10) Trigger sensitivity level (Flow or Pressure)
 - (11) Inspiratory cycle off
2. Pressure support (PS). Pressure support is a mode for patients with an intact respiratory drive. This mode supports the patient's inspiratory effort with a set inspiratory pressure. Backup ventilation is automatic if the patient has apnea. Backup ventilation is set based on an apnea time, set by the clinician, with configurable settings that will revert back to the spontaneous mode once the respiratory effort is sensed by the ventilator.
- a. Tidal volume is variable.
 - b. Peak inspiratory pressure is set.
 - c. Decelerating flow.
 - d. Clinician-set parameters.
 - (1) Inspiratory pressure
 - (2) FiO_2
 - (3) PEEP
 - (4) High and low minute ventilation alarms
 - (5) High pressure alarm
 - (6) High and low respiratory rate alarms
 - (7) High and low end expiratory pressure alarms
 - (8) Trigger sensitivity level (Flow or Pressure)
 - (9) Inspiratory Cycle off
3. Neurally Adjusted Ventilatory Assist (NAVA). The SERVO-i offers NAVA as an option, for both invasive and noninvasive ventilation. NAVA uses the diaphragm electrical activity (Edi) to trigger, cycle-off, and control the level of assist. Therefore, NAVA delivers assist in synchrony with and in proportion to the patient's spontaneous breathing efforts. NAVA provides partial ventilatory assist, used in spontaneously breathing patients. NAVA takes advantage of pneumatic control as a backup in case that Edi fails to do so. Backup ventilation, as in PSV, is based on an apnea time, set by the operator, and can be configured according to clinical practice. The ventilator reverts to NAVA once the apnea is over and Edi has returned.
- a. Tidal volume is variable and controlled by the patient and the NAVA level
 - b. PIP is variable and controlled by the patient and the NAVA level
 - c. Flow is variable and controlled by the patient and the NAVA level

d. Clinician-set parameters

- (1) NAVA level (the proportionality factor between Ed_i and delivered pressure above PEEP, units are cm H₂O per μ V)
- (2) Trigger sensitivity level (Ed_i, Flow, or Pressure)
- (3) Cycle off is fixed and nonadjustable. Cycle off is relative to the peak Ed_i per breath. The cycle off occurs at 70% of the Ed_i peak for normal and high Ed_i signals and 40% for low Ed_i signals.
- (4) FiO₂
- (5) PEEP
- (6) Pressure support level settings (see above) in the case where NAVA reverts to PSV
- (7) Backup ventilation settings (similar to pressure control settings, see above)
- (8) High and low minute ventilation alarms
- (9) High pressure alarm (during NAVA, the ventilator limits 5 cm H₂O below this alarm value)
- (10) High and low respiratory rate alarms
- (11) High and low end expiratory pressure alarms
- (12) Low Ed_i Activity Low Alarm

4. Continuous positive airway pressure (CPAP)

- a. CPAP is a mode for spontaneously breathing patients who do not require any assistance in overcoming the work of breathing imposed by lung disease or the endotracheal tube.
- b. Clinician-set parameters

- (1) FiO₂
- (2) Pressure level
- (3) High and low minute ventilation alarms
- (4) High pressure alarm
- (5) High and low respiratory rate alarms
- (6) High and low end expiratory pressure alarms

F. Combination modes of ventilation. In addition, the above modes are offered in combination. This provides the clinician the ability to support ventilator delivered breaths and spontaneously triggered breaths with different parameters.

1. SIMV volume control with pressure support
2. SIMV pressure control with pressure support
3. SIMV/PRVC with pressure support

G. Automode

1. Automode is an option that senses the patient's respiratory effort and changes from a control mode (VC, PC, and PRVC) to a spontaneous mode, such as PSV or VS.

2. If cessation of the respiratory drive occurs, Automode will place the patient back in control ventilation after a user-determined timeout threshold has been met for no spontaneous patient efforts triggered by the patient
 - a. Volume control changes to volume support
 - b. PRVC changes to volume support
 - c. Pressure control changes to pressure support

H. Control panel and display.

1. The SERVO-i ventilator is equipped with a touch sensitive user interface, which is computer based.
2. The user interface, or the control panel, includes a continuous display of the set and measured values; graphic monitoring of flow, pressure, and volume; and 24 h trend monitoring.
3. The user interface/control panel. The user interface is computer-based with a luminescence screen and a combination of soft touch keys, and control knobs. This interface provides numerous menus and functions for the clinician to choose. They include the following:
 - a. Patient category indicator. The ventilator has a “patient category indicator” to set different internal parameters for adult/infant and infant/neonatal ventilation. These parameters control the following:

- (1) The level of continuous flow for flow and/or pressure triggering:

Adult/pediatric	Infant
2.0 L/min	0.5 L/min

- (2) Maximum inspiratory peak flow:

Adult/pediatric	Infant
200 L/min	33 L/min

- (3) Tidal volume range

Adult/pediatric	Infant
100–4,000 mL	2–350 mL

- (4) Apnea alarm/back up ventilation ranges

Adult/pediatric	Infant
15–45 s, default 20 s	5–45 s, default 10 s

- (5) Maximum flow rate

Adult/pediatric	Infant
200 L/min	33 L/min

- b. Mode indicator. Lists current mode of ventilation
- c. Automode indicator. Indicates if Automode is on or off.
- d. Nebulizer. This ventilator may be equipped with an ultrasonic nebulizer. When the nebulizer is connected, this indicator allows the clinician to set the time for the nebulizer to run. Option Aerogen nebulizer is integrated into the software with an option hardware module to plug the unit into.
- e. Admit patient. Stores and displays individual patient information, identification number, name, age, and weight.
- f. Status. Provides internal information on the status of the following:
 - (1) General system information
 - (2) O₂ cell/O₂ sensor
 - (3) Expiratory cassette
 - (4) Batteries
 - (5) CO₂ module (if integrated)
 - (6) Wye sensor measuring (if integrated)
 - (7) Installed options
 - (8) Preuse check
- g. Alarm settings
 - (1) High pressure
 - (2) Upper and lower minute
 - (3) Upper and lower respiratory rate
 - (4) Low end expiratory pressure (PEEP)
- h. Graphic display. When the unit is connected to a patient, there is a continuous display
 - (1) Flow–time
 - (2) Pressure–time
 - (3) Volume–time
 - (4) CO₂–time
 - (5) Flow–volume (optional)
 - (6) Pressure–volume (optional)
 - (7) Edi (optional)
- i. Digital readouts of the following are also continuously displayed
 - (1) PIP
 - (2) Pressure during end-inspiratory pause
 - (3) P_{aw} (mean airway pressure)
 - (4) PEEP (end expiratory pressures)
 - (5) Set PEEP+ Intrinsic PEEP
 - (6) CPAP (NIV Nasal CPAP only)
 - (7) Respiratory Rate
 - (8) FiO₂

- (9) Inspiratory time
 - (10) Time constant
 - (11) I:E ratio (displayed during controlled breaths)
 - (12) Spontaneous expiratory minute volume (Bi-Vent)
 - (13) Duty cycle time (T_i/T_{tot}) during spontaneous breaths and Bi-Vent
 - (14) MVe (minute ventilation)
 - (15) Inspired tidal volume
 - (16) Exhaled tidal volume
 - (17) Inspired minute volume
 - (18) Expiratory minute volume
 - (19) Leak % (NIV)
 - (20) End inspiratory flow
 - (21) End tidal carbon dioxide concentration (CO_2 analyzer—optional)
 - (22) Volume of expiratory CO_2 per minute (CO_2 analyzer—optional)
 - (23) CO_2 tidal elimination (CO_2 analyzer—optional)
 - (24) Dynamic characteristics
 - (25) Static compliance
 - (26) Elastance
 - (27) Inspiratory resistance
 - (28) Expiratory resistance
 - (29) Work of breathing (patient)
 - (30) Work of breathing (ventilator)
 - (31) P0.1: Indicator for respiratory drive
 - (32) Shallow breathing index
 - (33) Stress index (optional for volume control only, fixed flow)
 - (34) Edi Peak and Edi Minimum (optional NAVA and NIV NAVA)
- j. Trend monitoring. The user interface has a comprehensive trend monitoring with information stored for 24 h with a time resolution of 1, 3, 6, 12, and 24 h. Data can be downloaded.
- (1) Measured parameters (listed above)
 - (2) Ventilator changes
 - (3) Event log
- k. Suction support. A suction support key, when selected offers an adjustable FiO_2 for pre- and postoxygenation, silences the ventilator and stops flow for 60 s. If the patient is reconnected to the ventilator prior to 60 s, the ventilator resumes ventilation.
- l. Additional features
- (1) CO_2 monitor. The SERVO-i is equipped with a port to monitor end-tidal CO_2 ($ETCO_2$) using the Novametrix $ETCO_2$ sensor.
 - (2) Nebulizer. The SERVO-i has a port to run an ultrasonic nebulizer. The nebulizer has an automatic shut off, which may be set to run for a maximum of 30 min.

- (3) BiVent. BiVent is a mode of ventilation for spontaneously breathing patients. It provides two levels of CPAP from which the patient may breathe. It is set with both a high pressure (P_{high}) (1–50 cm H₂O) and a long inspiratory (T_{high}) (0.2–10 s) time and a low pressure (T_{peep}) (1–50 cm H₂O) with a short inspiratory time. It is a strategy that can be utilized for used for lung protection in disease states such as ARDS, believed to help minimize cyclic recruitment/derecruitment by utilizing higher mean airway pressures.
- (4) Edi monitoring during all modes of ventilation and when ventilator is in Stand By
- (5) Heliox: A heliox enabled SERVO-i ventilator system compensates monitoring flow delivery when HeO₂ is used. HeO₂ gas is connected to the ventilator via a heliox adapter, which is connected to the Air/HeO₂ inlet.

Available gas mixtures are as follows:

Helium–Oxygen mixture 80:20

Helium–Oxygen mixture 79:21

Helium–Oxygen mixture 78:21

- (6) MR conditional option. The SERVO-i is conditionally approved for use in the MR Suite with open scanners up to 10 mt (100 G) and 20 mt (200 G) tunnel scanners. The allowable field strength of the scanner for the MR conditional option is 1.0, 1.5, and 3.0 T.
- (7) Stress index: Stress index option is only intended for adults in volume control ventilation or SIMV (VC)+Pressure support.
- (8) Open lung tool: Provides a breath-by-breath analysis of the following parameters to allow end users to evaluate the trending of lung dynamics pre- and postventilator changes, therapy, and recruitment maneuvers. Parameters monitored are as follows:
 - (a) End inspiratory pressure
 - (b) PEEP
 - (c) Tidal volume (V_T)
 - (d) Dynamic compliance
 - (e) Tidal CO₂ elimination (if option installed)

I. Noninvasive ventilation

1. The SERVO-i has an optional NIV capability for all patient categories from the 500 g neonate to the 250 kg adult. NIV is ventilator support for patients that are not intubated and/or tracheotomized. This support feature is utilized with various noninvasive interfaces such as masks, nasal prongs, nasal pillows and nasopharyngeal prongs. During NIV, the following displayed values are compensated for leakage: inspired tidal volume (VT_I), exhaled tidal volume (VT_E), exhaled minute ventilation (MV_e), and inspired minute ventilation (MV_i).

2. Available modes in NIV are Pressure Control, Pressure support, Nasal CPAP (infant patient category only) and NIV NAVA. During the NIV option the ventilator automatically adjusts for leakage in the system to maintain set inspiratory and PEEP pressure. The NIV function has a variable trigger that adjusts to the variation in leakage in an attempt to optimize patient-triggered support. Alarm settings are similar to the invasive modes of ventilation with the option to silence nuisance alarms in the presence of high leakage. Leakage compensation in NIV can be set to low flow or high flow depending on the expected interface leakage during NIV support.

Infant:

Low flow: 7.5 LPM

High flow: 15 LPM

Disabled: The ventilator will continue to deliver assist even when the leakage is excessive.

Disclosure Dr. Beck has made inventions related to neural control of mechanical ventilation that are patented. The license for these patents belongs to MAQUET Critical Care. Future commercial uses of this technology may provide financial benefit to Dr. Beck through royalties. Dr Beck owns 50% of Neurovent Research Inc (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with MAQUET Critical Care.

Suggested Reading

- Biban P, Serra A, Polese G, Soffiati M, Santuz P. Neurally adjusted ventilatory assist: a new approach to mechanically ventilated infants. *J Matern Fetal Neonatal Med.* 2010;23 Suppl 3:38–40.
- Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P. Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. *Intensive Care Med.* 2008;34(11):2010–8.
- Nishimura M, Hess D, Kacmarek RM. The response of flow-triggered infant ventilators. *Am J Respir Crit Care Med.* 1995;152(6 Pt 1):1901–9.
- Piquilloud L, Vignaux L, Bialais E, Roeseler J, Sottiaux T, Laterre PF, Jolliet P, Tassaux D. Neurally adjusted ventilatory assist improves patient-ventilator interaction. *Intensive Care Med.* 2011; 37(2):263–71.
- Sinderby C, Beck J. Neurally adjusted ventilatory assist for infants in critical condition: editorial. *Pediatr Health.* 2009;3(4):297–301.

Chapter 46

SLE5000 and SLE4000 Infant Ventilators

Barbara Pilgrim and Sunil K. Sinha

I. Introduction

- A. The SLE5000 is a combined conventional and High-Frequency Oscillation ventilator with respiratory monitoring.
- B. The SLE4000 is a dedicated conventional ventilator with respiratory monitoring.

II. Ventilator features

- A. Patented valveless technology
- B. Designed for use in neonates and infants from 350 g to 20 kg
- C. Constant flow of 8 LPM fresh gas
- D. Time-cycled, pressure-limited
- E. Volume limiting

III. Ventilation modalities

- A. Continuous positive airway pressure
- B. Continuous mandatory ventilation (CMV)
- C. Patient triggered ventilation (PTV)
- D. Pressure support ventilation (PSV)
- E. Synchronized intermittent mandatory ventilation (SIMV)
- F. Targeted tidal volume (TTV) on all conventional modalities.
- G. High-frequency oscillation ventilation (HFOV)
- H. High-frequency oscillation ventilation combined with CMV

B. Pilgrim (✉)

SLE Ltd, Twin Bridges Office Park, 232 Selsdon Road, Croydon, Surrey CR2 6PL, UK
e-mail: Bpilgrim@sle.co.uk

S.K. Sinha, MD, PhD, FRCP, FRCPC

Department of Neonatal Medicine, The James Cook University Hospital,
University of Durham, Marton Road, Marton-in-Cleveland, Middlesbrough TS4 3BW, UK
e-mail: sunil.sinha@tees.nhs.uk

IV. Design details and principles of operation

A. The SLE5000 infant ventilator consists of an electronic system in the upper section of the ventilator and a pneumatic system in the lower.

B. The electronic system

1. The electronic system comprises three autonomous subsystems, one responsible for monitoring the patient, another responsible for controlling the valves of the pneumatic system, and another for the user interface (touch screen and displayed data).
2. They are connected together by three serial communication links in a delta configuration.
3. The ventilator has an internal battery that can power the ventilator in the event of a main power fail. If the mains power fails with the battery fully charged, then operation will continue for 60 min depending on ventilation mode.

C. Pneumatic system

1. The pneumatic system comprises the tubing and electromechanical valves necessary to provide the gas in conventional and oscillatory ventilation modes.
2. The two gas controlling functions are blending and pressure generation.
3. Blending
 - a. The method used for blending air and oxygen, in known proportions, is to pressure regulate the two supplies (air and oxygen) so that they produce equal flow rates. Each supply is then allowed into a mixing chamber for a time period equivalent to the proportions required.
 - b. As an example, delivering oxygen at a set flow rate into a mixing chamber for 1 s and air at the same flow rate for 2 s will result in a mixture of one part oxygen to two parts air (resulting in a mix of 47.3%).
4. Pressure generation: There are three nozzles within the exhalation block in the pneumatic subsystem.
 - a. One generates negative pressure in the patient circuit.
 - b. The other two generate positive pressure.
 - c. The pressures generated from the three nozzles are controlled by three electronically controlled pressure regulators.
 - (1) The negative and one of the positive nozzle pressures can also be switched on and off rapidly with in-line (high speed) solenoid valves.
 - (2) The other positive nozzle (the mean jet) is used to generate steady pressures in ventilation (CPAP or PEEP pressures in conventional ventilation, and mean pressures in HFO modes).
 - (3) These three nozzles (or jets) are used in various combinations to generate all ventilation modes.

5. Conventional ventilation

- a. In non-HFO modalities, the negative (or reverse) jet is used in a steady mode to provide a small amount of flow to offset the inadvertent patient circuit pressure generated from the fresh gas flow of 8 LPM.
 - b. The mean jet is also used in a steady mode to generate the baseline pressure (CPAP or PEEP).
 - c. The forward jet is used to generate the PIP during inspiration.
 - d. The rise time of the inspiratory phase is controlled by dynamically controlling the forward jet pressure regulator rather than switching a steady pressure with the high speed valves.
 - (1) This provides a smooth rise in pressure and allows user adjustable rise times rather than abrupt changes and pressure “ringing,” which can result from high speed switching.
 - (2) The fall of the inspiratory wave is also controlled by the forward jet pressure regulator to bring the pressure down quickly and smoothly; using the high-speed valves to do this results in difficulties for the monitor subsystem in trying to detect a patient breath attempt by monitoring the pressure alone.
 - (3) Once the pressure has been brought close to the base pressure, after about 100 ms, the forward jet solenoid is switched off to prevent any further artifact causing false triggering.
 - (4) All jet pressures sum in the exhalation block. For example, to ventilate a patient with a PEEP pressure of 5 cm H₂O and a PIP pressure of 30 cm H₂O, the mean jet will be set to generate a continuous circuit pressure of 5 cm H₂O, and the forward jet will be set to generate a circuit pressure varying between 0 (exp. phase) and 25 cm H₂O (insp. phase).
 - (5) Since the jet pressures will sum, this will result in the desired patient pressure.
6. HFO ventilation. The ventilator is capable of functioning as a dedicated HFOV device with active exhalation.
- a. In pure HFO, the mean jet pressure regulator is used to set the mean pressure.
 - b. The forward and reverse jet pressure regulators are used to generate steady positive and negative delta P components that will be superimposed on the mean pressure.
 - c. These components are switched quickly using the high-speed solenoid valves to generate the HFO pressures.
 - (1) For example, to ventilate a patient with a mean pressure of 10 cm H₂O and a delta P pressure of 60 cm H₂O, the mean jet will be set to generate a continuous pressure of 10 cm H₂O, the

forward jet will be set to generate a continuous pressure of 30 cm H₂O and the reverse jet will be generating a continuous pressure of -30 cm H₂O.

- (2) The HFO rate is determined by the rate of switching between the forward and reverse pressures on the high-speed valves. Because the jet pressures sum, the resulting patient pressures will be switching between -20 and +40 cm H₂O. Thus, if mean HFO pressures up to 35 cm H₂O are required and the mean jet is only generating pressures up to about 20 cm H₂O, it will be necessary to apply a higher pressure on the forward pressure regulator and a lower pressure on the reverse pressure regulator. Using this method, the desired mean must be less than half the desired ΔP pressure plus 20 cm H₂O.

7. Trigger mechanisms

- a. Pressure triggering. This senses the rate of change of pressure at the patient manifold when the onset of inspiration is detected.

The sensitivity is adjustable within an uncalibrated range.

Back-up breath rate is set in PTV ventilation to deliver the mechanical breath if a trigger event is not sensed. This is recognized if triggering breath is *not* flashing on the screen. It is sometimes difficult for the VLBW infant to consistently trigger pressure support with this mode of triggering.

- b. Flow triggering. This mechanism requires the use of a flow sensor. The SLE5000/4000 uses a heated-wire anemometer.

The sensitivity is adjustable between 0.2 and 2.0 LPM. Backup ventilation is delivered in the absence of a recognized trigger event. Flow triggering is easier for the VLBW infant and allows both inspiratory and expiratory synchronization using flow-cycling.

8. Alarms

There are a large number of alarms and safety features, and users should pay attention to these while operating the machine and know how to react to alarms by referring to the operator's manual provided by the manufacturer.

9. LCD screen displays: numerous data can be displayed, including wave forms and pulmonary mechanics, ventilator functions, and measured variables.

10. Other features

- a. A restrictor remains a feature of the SLE5000 patient circuit. As the fresh gas flow is 8 LPM, the restrictor is calibrated for this and is colored green to differentiate from the SLE2000 restrictor, which is purple.

- b. The pressure waveform modification is now part of the software and is located within the tools menu.
 - c. Targeted tidal volume (TTV*PLUS*) 20% leak compensation. This allows the user to set a volume that is appropriate for the infant being ventilated. The leak compensation is deliberately limited to prevent overshoot on the next breath. All volume measurements are end tidal volume.
 - d. Pressure support ventilation with flow-cycling, has automatic compensation in the presence of a leak thereby ensuring that all breaths are flow triggered and flow terminated.
 - e. Complete respiratory monitoring with measurements of C20/C and DCO₂ (gas transport coefficient for carbon dioxide) and loops and waveforms.
 - f. Ability to trend all measured parameters for 24 h.
 - g. Ability to take a snapshot of a loop, save it, and compare future loops with this reference loop to observe changes in compliance.
 - h. The user is able to deliver nitric oxide into the patient circuit and to remove and scavenge expired nitrogen dioxide through the exhalation block and scavenging system.
11. Advanced modes of ventilation
- a. PSV can be used in isolation, provided there is consistent respiratory effort, or together with SIMV if there is not. The latest software in the SLE5000/4000 has an algorithm to compensate for leaks, thereby ensuring that all breaths are flow-terminated.
 - b. TTV
 - (1) This is a pressure-cycled, volume-limiting mode of ventilation.
 - (2) The selected volume limits the pressure, and the volume automatically accommodates to changes in resistance and compliance.
 - (3) SLE5000/4000 with the latest 4.3 version of software introduces leak compensation of 20%. This is referred to as TTV*PLUS*.
 - c. High-frequency oscillatory ventilation
 - (1) The delivery of pressures in HFO in the SLE5000 is different from that of the SLE2000.
 - (2) It is derived from the fast switching of the high speed solenoid valves.
 - (3) The SLE5000 is able to oscillate infants up to 20 kg.
 - (4) The practical principles of HFO still apply. By using a flow sensor the user has access to the DCO₂ measurement, which may be an aid to assessing alveolar ventilation and thereby CO₂ elimination. This may be helpful where there is no form other of CO₂ monitoring other than blood gas analysis.

- (5) The use of the flow sensor allows accurate measurements of end tidal volumes and minute volumes.
- (6) There is also the option of viewing a flow–volume loop.

Suggested Reading

- Dale Gertsman Childhood outcome after early High Frequency Oscillation Ventilation for Neonatal RDS.
- Dimitiou, Greenhough A Comparison of two Inspired:Expired ratios during High Frequency Oscillation Ventilation.
- Greenough A 2006 Performance of neonatal ventilators in Volume Targeted ventilation mode The Author(s)/Journal Compilation © 2007 Foundation Acta/Acta Paediatrica 2007 Pp 176-180.
- Henderson-Smart DJ, Cools F, Butha T, Offringa M, High Frequency Oscillation versus Conventional ventilation in acute pulmonary dysfunction in preterm infants The Cochrane Library 2007, Issue 3.
- Hickling 2002 Reinterpreting the Pressure Volume curve in patients with ARDS Current Opinion in Critical Care 2002, 8:32–38.
- Johnson 2002 High Frequency Oscillation Ventilation for preventing Chronic Lung Disease of prematurity N Engl J Med 2002;347(9).
- Leipala 2002 Accuracy of pressure displayed on High Frequency Oscillation Ventilators.
- Leipala 2005 An in vitro assessment of gas trapping during High Frequency Oscillation Ventilation Institute of Physics Publishing.
- Martin Keszler Volume Targeted Ventilation NeoReviews 2006;7(5).
- Martin CJ Kneyber High Frequency Oscillation Ventilation and paediatric cardiac surgery? Yes it can!.
- McCallion N 2005 Volume Targeted versus Pressure Limited ventilation in the neonate www.archdischild.com.
- McCallion N, Davis PG, Morley CJ Volume Target versus Pressure Limited ventilation in the neonate. Cochrane Collaboration 2011
- Patel 2009 Work of Breathing during SIMV with and without Pressure Support British Medical Journal.
- Pillow J 1999 Effects of I/E Ratio on Mean Alveolar Pressure during High Frequency Oscillation Ventilation Journal of Applied Physiology.
- Product Brochures and data sheet. <http://www.sle.co.uk>.
- Rimensberger P 2000 First intention HFO with early lung volume optimization, improves pulmonary outcome in the very low birth weight infants with RDS Pediatrics 2000;105(6).
- Rimensberger P 2003 ICU Cornerstone: High Frequency oscillation here to stay! Critical Care 2003;7.

Chapter 47

Bunnell Life Pulse High-Frequency Jet Ventilator

Martin Keszler

- I. The Bunnell Life Pulse® (Bunnell, Inc., Salt Lake City, UT) is the only Food and Drug Administration (FDA)-approved neonatal HFJV device currently available in the USA. Other HFJV devices manufactured abroad have been used in Europe and elsewhere.
- II. The Life Pulse is a microprocessor-based time-cycled, pressure-controlled infant ventilator that continuously monitors airway pressure and automatically adjusts the pressure that drives pulses of gas across the injector cannula to achieve the set peak inspiratory pressure measured in the proximal endotracheal tube.
- III. Small pulses of heated, humidified gas are injected into a special endotracheal tube adaptor (Life Port®); the pulses are generated by a pinch valve inside a patient box located close to the airway. This arrangement minimizes dampening of the pulses and allows more effective pulse delivery and unimpeded exhalation.
- IV. The pressure transducer for monitoring proximal airway pressure is also located in the patient box, resulting in a higher fidelity signal.
- V. An intermittent puff of gas purges any condensation or secretions and maintains patency of pressure monitoring line.
- VI. Independently set variables
 - A. Inspiratory pressure (PIP, range 8–50 cm H₂O)
 - B. Ventilator rate (240–660 breaths/min = 4–11 Hz)
 - C. Jet valve on (inspiratory) time (T_i), (range 0.02–0.034 s)
- VII. PEEP and superimposed low rate IMV (when desired) are generated by a conventional ventilator used in tandem with the Life Pulse.

M. Keszler, MD (✉)

Department of Pediatrics, Women and Infants' Hospital of Rhode Island,
Brown University, 101 Dudley Street, Providence, RI, USA

e-mail: mkeszler@wihri.org

- VIII. The FiO_2 of the two ventilators is adjusted separately (it should be maintained at the same level), or both ventilators can be supplied from a common source using a single blender (preferable).
- IX. Displayed parameters
- A. PIP (cm H_2O)
 - B. Pressure amplitude (ΔP , cm H_2O)
 - C. PEEP (cm H_2O)
 - D. Mean airway pressure ($\text{P}\bar{\text{a}}\text{w}$, cm H_2O)
 - E. Servo pressure (PSI)
 - F. I:E ratio (this is a value determined from the Jet valve on time and rate)
- X. The ventilator goes through a self-check when first turned on to ensure that all components are functioning and the circuit is intact.
- XI. The ventilator settings automatically start with default values of PIP 20 cm H_2O , rate 420 (7 Hz) and valve on time of 0.02 s when the device is turned on and these are displayed in the “NOW” row in the Control panel.
- XII. The user selects “NEW” settings in the row below and activates them by pressing the “Enter” button.
- XIII. Alarms are automatically set 20% above and below current levels for Servo Pressure and ± 1.5 cm H_2O for $\text{P}\bar{\text{a}}\text{w}$, once the values stabilize and the ventilator reaches the “Ready” state. Subsequently, the alarm limits can be adjusted manually, if desired.
- XIV. As a safety feature, the Servo Pressure is locked at its current value when the $\text{P}\bar{\text{a}}\text{w}$ or Servo Pressure alarm is activated. The patient will remain ventilated with that same Servo Pressure until:
- A. The alarm limits are changed.
 - B. The Reset button is pressed (not recommended until troubleshooting the situation to ensure safe operation).
 - C. Settings are changed and the Enter button is pushed.
- XV. The alarm situation may resolve spontaneously if the $\text{P}\bar{\text{a}}\text{w}$ returns to the target range; if the alarm condition persists, the clinician needs to address the situation to restore the servo-control of PIP.
- XVI. It is essential to understand the meaning of changes in Servo Pressure and to evaluate the circuit and patient before proceeding.
- XVII. When more gas volume is needed to reach set PIP, Servo Pressure goes up. High Servo Pressure may result from the following:
- A. Improved lung compliance/increased lung volume.
 - B. Leak in the circuit (large leak around endotracheal tube, accidental extubation, partial disconnect, cracked connector).
 - C. Kinking of the patient circuit (obstruction of the jet line).
 - D. Partial occlusion of the pressure line leading to dampened pressure reading.
 - E. Increased leak through a bronchopleural fistula.

- XVIII. When less gas volume is needed to reach set PIP, Servo Pressure goes down. Low Servo Pressure may result from the following:
- A. Worsening lung compliance (atelectasis, pneumothorax)
 - B. Mainstem bronchus intubation
 - C. Obstruction of endotracheal tube
 - D. Increased airway resistance
- XIX. Additional alarm messages may appear indicating
- A. Jet valve fault
 - B. Ventilator fault
 - C. Low gas pressure (supply gas)
 - D. Cannot meet PIP
 - E. Loss of PIP
 - F. High PIP
- XX. The ventilator must be in the “Ready” state with the “Ready” light illuminated before the system is stable, alarms are set, and it is safe to leave the bedside after any change in settings or after the “Reset” button is pressed.
- XXI. The “Ready” state occurs when the PIP has reached within +2.0 and -1.5 cm H₂O of the set PIP. If the “Ready” condition is not met 3 min after the ENTER or RESET button is pushed, the CANNOT MEET PIP alarm will result.
- XXII. Like any servo-controlled device, the actual PIP will fluctuate around the set value.
- XXIII. The “Silence” and “Reset” buttons are located close together. They serve a different function.
- A. Use the “Silence” button as the primary button to silence the ventilator alarm while troubleshooting.
 - B. “Reset” should be reserved for the rare situation when for whatever reason the ventilator has not been able to reach steady state and activate the “Ready” button or after troubleshooting and determining that higher or lower P_{aw} or Servo Pressure are appropriate.
- XXIV. An efficient low volume humidifier is built into the device/patient circuit, assuring optimal heating and humidification of inspired gases.
- XXV. The humidifier panel allows the user to independently set the Cartridge and Circuit temperatures within the range of 32–42°C.
- XXVI. A water pump automatically maintains an optimal water level in the humidification cartridge.
- XXVII. Temperature of the gas as it leaves the patient circuit is continuously displayed. Cartridge and circuit temperatures can be displayed by pressing a key on the humidifier panel.
- XXVIII. Suctioning can be done in one of two ways.
- A. The jet ventilator can be placed in standby mode and suctioning done in the usual fashion.

- B. Alternately, suctioning is done with the ventilator continuing to operate and constant (continuous) suction is applied while the suction catheter is advanced and then withdrawn. This is necessary because the jet ventilator will force gas past the suction catheter and cause overpressure, unless continuous suction is applied. This method is **NOT RECOMMENDED FOR ROUTINE USE**, but may be useful in unstable infants who may not tolerate the reduction in support after suctioning while the ventilator is working up to set pressures.
- XXIX. Inhaled nitric oxide can be safely and effectively delivered via the Life Pulse ventilator by splicing the INOMAX® DS Injector Cartridge into the high-pressure line between the ventilator and the humidification cartridge and attaching the monitoring line to a T-connector inserted in the jet gas delivery line distal to the pinch valve.
- XXX. Clinicians in the USA should be aware that the Food and Drug Administration has only approved the Life Pulse for the treatment of PIE and for rescue of infants with refractory respiratory failure complicated by air leak.

Suggested Reading

- Product Brochures and data sheet. <http://www.sle.co.uk>
- Henderson-Smart DJ, Cools F, Butha T, Offringa M. High frequency oscillation versus conventional ventilation in acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev.* 2007
- Greenough A. Performance of neonatal ventilators in volume targeted ventilation mode. *Acta Paediatr.* 2006;176–80
- Hickling KG. Reinterpreting the pressure volume curve in patients with ARDS. *Current Opin Crit Care.* 2002;8:32–8.
- Johnson AH. High frequency oscillation ventilation for preventing chronic lung disease of prematurity. *N Engl J Med.* 2002;347(9).
- Keszler M. Volume targeted ventilation. *NeoReviews.* 2006;7(5).
- Leipala. Accuracy of pressure displayed on high frequency oscillation ventilators. www.archdis-child.com. 2002
- Leipala. An in vitro assessment of gas trapping during high frequency oscillation ventilation. Institute of Physics Publishing. 2005
- McCallion N. Volume targeted versus pressure limited ventilation in the neonate. www.archdis-child.com. 2005
- Patel. Work of breathing during SIMV with and without pressure support. *Br Med J.* 2009
- Pillow J. Effects of I/E ratio on mean alveolar pressure during high frequency oscillation ventilation. *J Appl Physiol.* 1999
- Rimensberger P. First intention HFO with early lung volume optimization, improves pulmonary outcome in the very low birth weight infants with RDS. *Pediatrics.* 2000;105(6).
- Rimensberger P. ICU cornerstone: high frequency oscillation here to stay! *Critical Care.* 2003;(7)
- Dimitiou GA. Comparison of two inspired: expired ratios during high frequency oscillation ventilation
- Gertsman D. Childhood outcome after early high frequency oscillation ventilation for Neonatal RDS
- Kneyber MCJ. High frequency oscillation ventilation and paediatric cardiac surgery? Yes t can!
- McCallion N, Davis PG, Morley CJ. Volume target versus pressure limited ventilation in the neonate. *Cochrane Collaboration.* 2011

Chapter 48

Sensormedics 3100A High-Frequency Oscillatory Ventilator

David J. Durand and Jeanette M. Asselin

I. Physiology of high-frequency oscillatory ventilation (HFOV)

A. Conceptual difference between conventional and high-frequency ventilation

1. With conventional ventilation, gas is moved from the upper airway to the alveoli primarily by *bulk flow* (“pouring gas into and out of the alveoli”).
2. With HFOV, gas movement is accomplished primarily by the *mixing* of gas in the upper airway with gas in the alveoli (“shaking gas into and out of the alveoli”).

B. Characterizing HFOV “breaths”

1. The SensorMedics 3100A (CareFusion, Inc., San Diego, CA) generates a pressure wave which, when analyzed at the hub of the endotracheal tube, is approximately a sine wave.
2. This pressure wave is characterized primarily by four factors, each of which can be independently adjusted.
 - a. Mean airway pressure (the “average” pressure throughout the respiratory cycle).
 - b. Amplitude (the “size” of the pressure wave, or “tidal volume”).
 - c. Frequency (the number of breaths per minute).
 - d. The Inspiratory–Expiratory ratio can also be adjusted, but is kept at 1:2 for essentially all neonatal patients.

D.J. Durand, MD (✉)

Division of Neonatology, Department of Neonatology, Children’s Hospital & Research Center
Oakland, 747 52nd St., Oakland, CA 94609, USA

e-mail: ddurand@mail.cho.org

J.M. Asselin, RRT, MS

Neonatal/Pediatric Research Group, Children’s Hospital & Research Center Oakland,
747 52nd St., Oakland, CA 94609, USA

S.M. Donn and S.K. Sinha (eds.), *Manual of Neonatal Respiratory Care*,
DOI 10.1007/978-1-4614-2155-9_48, © Springer Science+Business Media, LLC 2012

C. Oxygenation and ventilation

1. Oxygenation is proportional to mean airway pressure.
 - a. The higher the mean airway pressure, the more alveoli are open throughout the respiratory cycle. This decreases atelectasis and improves ventilation–perfusion matching.
 - b. Increasing mean airway pressure increases average lung volume, and is reflected by increased lung volume on chest radiography.
2. Ventilation (or CO₂ removal) is approximately proportional to (Frequency) × (Amplitude)².
 - a. This means that small changes in amplitude have a greater impact on CO₂ exchange than do changes in frequency.
 - b. For most patients, a frequency is chosen and left constant, while CO₂ exchange is affected by changing the amplitude.
3. Effect of frequency on amplitude
 - a. The endotracheal tube and upper airway act as a *low pass filter*. This means that low frequency pressure waves are passed from the ventilator to the alveoli without being attenuated, while high-frequency pressure waves are attenuated. The higher the frequency, the greater the attenuation.
 - b. A simplified example of the attenuation of pressure amplitude at high frequencies is outlined below. Imagine a ventilator that is set to deliver an amplitude of 20 cm H₂O (e.g., PIP 25 cm H₂O, PEEP 5 cm H₂O).
 - (1) At a low frequency (e.g., 30 breaths/min), this pressure amplitude of 20 cm H₂O is completely transmitted to the alveoli. The alveolar pressure changes from 5 to 25 cm H₂O as the ventilator cycles.
 - (2) At an intermediate frequency (e.g., 120 breaths/min), the pressure amplitude will be slightly attenuated as it travels from the hub of the endotracheal tube to the alveoli, since neither the inspiratory time nor the expiratory time is adequate for the pressure to equalize between the upper airway and the alveoli. At the alveolar level, the breath will have a PIP of less than 25 and a PEEP of more than 5. Thus, the amplitude of the breath will have been *attenuated* from 20 cm H₂O to something slightly less than 20 cm H₂O. This is the phenomenon that causes air trapping (sometimes called inadvertent PEEP) at inappropriately high rates on conventional ventilation.
 - (3) At an even higher frequency (e.g., 600 breaths/min), the attenuation is far more significant. A breath with an amplitude of 20 cm H₂O at the hub of the endotracheal tube may be attenuated to less than 5 cm H₂O at the alveoli.

- c. Thus, if everything else is constant, *decreasing frequency will increase alveolar amplitude*. This is because at a lower frequency, more of the pressure wave will be transmitted to the alveoli. Since amplitude has a greater impact on CO₂ exchange than does frequency, *decreasing frequency will increase CO₂ exchange*.
- d. This complex relationship between frequency and CO₂ exchange is one of the reasons why frequency is not the primary parameter to be adjusted when optimizing ventilation.

II. Mechanics of the SensorMedics 3100 HFOV. There are six parameters can be adjusted on the SensorMedics 3100

A. Mean airway pressure

1. Mean airway pressure is set by adjusting the pressure adjust knob.
2. Increasing mean airway pressure recruits alveoli, leading to improved ventilation–perfusion matching, and improved oxygenation.
3. Increasing mean airway pressure also leads to increased lung inflation, as seen on chest radiography.
4. When placing a patient on HFOV, start with a mean airway pressure that is approximately 20% above the mean airway pressure on conventional ventilation.
5. Follow chest radiographs closely to determine degree of lung inflation.
 - a. In most patients, the lungs should be inflated so that the top of the right hemidiaphragm is between 8 and 10 ribs.
 - b. Patients on HFOV should have chest radiographs obtained frequently enough that both over- and underdistension are avoided. A typical schedule usually includes radiographs:
 - (1) 30–60 min after starting HFOV
 - (2) 2–6 h after starting HFOV
 - (3) 12 h after starting HFOV
 - (4) q 12–24 h until stable on HFOV
 - (5) After any large (>20%) change in mean airway pressure
 - (6) After any large (>20%) change in FiO₂
6. Changes in mean airway pressure
 - a. Increase mean airway pressure if the lungs are underinflated and/or the patient is not oxygenating adequately.
 - b. Decrease mean airway pressure if the lungs are overinflated and/or if the patient's oxygenation is improving.
 - c. To cause a small change in lung inflation and/or oxygenation, change the mean airway pressure by 10–20%.
 - d. To cause a larger change in lung inflation and/or oxygenation, change the mean airway pressure by 20–40%.

- B. Amplitude is set by adjusting power (in arbitrary units) and is measured as Delta Pressure (cm H₂O).
1. Increasing the power leads to an increase in the excursion of the ventilator diaphragm. This increases the amplitude of the pressure wave, and is reflected in an increase in the delta pressure, which is measured at the hub of the endotracheal tube. Remember that this delta pressure is markedly attenuated by the time it reaches the alveoli.
 2. Increasing the amplitude leads to an increase in chest movement (“chest wiggle”) and a decrease in PaCO₂.
 3. Relatively small (10–20%) changes in amplitude will result in significant changes in PaCO₂.
 4. When placing a patient on HFOV, adjust the amplitude so that the patient is comfortable without much spontaneous respiratory effort, and so the “chest wiggle” looks appropriate. Follow PaCO₂ closely (it can change dramatically), and consider using a transcutaneous CO₂ monitor to help with initial adjustments in amplitude.
- C. Frequency, measured in Hz (1 Hz = 1 breath/s or 60 breaths/min). For neonatal patients, frequency is usually 6–12 Hz (360–720 breaths/min).
1. Use higher frequencies for small babies with dense lung disease.
 2. Use lower frequencies for large babies, babies with mild disease, and babies with nonuniform disease.
 3. In general, use a lower frequency for patients with nonhomogeneous lung disease, airway disease, or air trapping. If a patient has an unacceptable degree of air trapping which does not respond to decreasing mean airway pressure, consider decreasing the frequency by at least 1–2 Hz.
 4. Typical frequencies:
 - a. Preterm infant with severe RDS: 10–12 Hz, sometimes higher
 - b. Preterm infant with mild RDS or early chronic lung disease: 8–10 Hz
 - c. Preterm infant with significant chronic lung disease: 6–8 Hz
 - d. Term infant with severe pneumonia or meconium aspiration syndrome: 6 Hz
- D. % Inspiratory Time is almost always left at 33%, or an inspiratory–expiratory ratio of 1:2.
- E. Flow, measured in liters per minute (LPM)
1. As with other types of ventilators, more flow is needed for large patients than for small patients.
 2. Although the ventilator is always calibrated and “set up” with a flow of 20 L/min, this should be decreased for premature infants. Typical flow settings:
 - a. Premature infant <1,000 g: Flow 6–8 LPM
 - b. Premature infant 1,500–2,500 g: Flow 10–12 LPM
 - c. Term infant with severe meconium aspiration syndrome: Flow 15–20 LPM

F. FiO_2 . Adjustments in FiO_2 have the same impact on oxygenation for a patient on HFOV as they do for a patient on other forms of ventilation.

G. Optimizing settings

1. In general, the approach to HFOV includes avoiding the extremes of over- and underinflation, minimizing oxygen exposure, and weaning as aggressively as tolerated. There are multiple approaches to “optimizing” lung volume on HFOV, all of which are based on the assumption that patients are optimally ventilated when atelectasis has been reversed, and patients are on the deflation limb of the pressure–volume curve. Achieving optimal lung volume involves progressively recruiting atelectatic alveoli by increasing mean airway pressure until FiO_2 is able to be decreased, suggesting that ventilation:perfusion matching has improved.
 - a. Optimizing lung volume can be done only in conjunction with chest radiographs and careful attention to FiO_2 . While increasing mean airway pressure can be very effective at recruiting alveoli and decreasing FiO_2 , it can also lead to significant overdistension. In general, “optimal” mean airway pressure usually results in a lung which is inflated so the top of the right hemi-diaphragm is at approximately the level between the 8th and the 10th posterior rib, and an FiO_2 , which is less than 0.3–0.4.
 - b. Weaning mean airway pressure is done by judiciously decreasing pressure (usually in 1 cm H_2O decrements) for patients who have an FiO_2 which is acceptable. However, if a decrease in mean airway pressure results in a significant increase in FiO_2 or in clinical lability, the mean airway pressure may have been weaned too much.
 - c. Weaning amplitude is done by judiciously decreasing delta pressure (usually by 10%) for patients who have a PaCO_2 in their “target range.” However, if a decrease in amplitude results in a significant increase in PaCO_2 , work of breathing, or clinical lability, the amplitude has probably been weaned too far.
2. Optimizing frequency is an imprecise process. In most cases, the frequency range listed above is adequate. However, if the patient appears to have air trapping, manifested by an overinflated chest radiograph and poor oxygenation or ventilation, consider decreasing the frequency by 1–2 Hz. Remember that decreasing frequency will decrease the pressure attenuation, and therefore increase the delivered pressure amplitude at the alveolar level, resulting in decreased PaCO_2 .

H. Weaning and extubating from HFOV

1. Most patients can be extubated directly from HFOV. The approach to preparing an infant for extubation from HFOV is essentially the same as for an infant on conventional ventilation.
 - a. Decrease both mean airway pressure and amplitude as the patient improves.

- b. As the patient improves, and as amplitude decreases, the patient will do more spontaneous breathing. If the amplitude decreases sufficiently, the patient will essentially be on “oscillatory CPAP” rather than oscillatory ventilation.
- c. When the patient is achieving most of the CO₂ elimination by spontaneous breathing, and the mean airway pressure has been decreased sufficiently, the patient can be extubated.
- d. General guidelines for extubation from HFOV are similar to those for extubation from conventional ventilation. As with conventional ventilation, clinicians have become progressively more aggressive about extubation from HFOV over the last decade. Our current approach is to extubate infants from HFOV when:
 - (1) Mean airway pressure is less than 8–10 cm H₂O
 - (2) FiO₂ is less than 0.3–0.4
 - (3) There is good spontaneous respiratory effort

I. HFOV or “conventional” ventilation?

1. There are clear theoretical advantages of HFOV over “conventional” ventilation for patients with severe restrictive lung disease (severe atelectasis).
 - a. With HFOV, the alveolus never deflates to the degree that it does with conventional ventilation. Thus, surface forces are less likely to cause atelectasis. In any patient with a tendency to develop atelectasis (e.g., RDS), this should be a significant advantage, since preventing atelectasis is a key element in avoiding lung injury.
 - b. With HFOV, the lung is not distended as much as it is with a typical tidal volume, so there is less chance of causing alveolar or airway over-distension, a primary cause of both acute and chronic lung injury.
 - c. Because oxygenation and ventilation are “uncoupled” during HFOV, changes in one do not usually affect the other, and dual changes can often be accomplished simultaneously.
2. Multiple animal models have shown advantages of HFOV over conventional ventilation, particularly in models of severe RDS or with severe acute lung injury.
3. The human data on the advantages of HFOV over conventional ventilation is less compelling. In general, reports and clinical trials of HFOV have focused on either the role of HFOV in managing patients with severe lung disease, or in preventing BPD in very preterm infants. Recent meta-analyses of the clinical trials comparing HFOV to conventional ventilation for the prevention of BPD conclude that any advantages of HFOV are relatively small.
 - a. Interpreting the large trials of HFOV vs. conventional ventilation is hampered by the fact that essentially all of the trials were conducted

using both HFOV and conventional strategies that are no longer used. Extrapolating these studies to the current era of vigorously avoiding intubation, and of early extubation, is difficult.

4. There are several conclusions which can be drawn from the animal and human trials of HFOV:
 - a. HFOV is as at least as effective as conventional ventilation in supporting oxygenation and ventilation in patients with significant restrictive disease.
 - b. HFOV is at least as safe as conventional ventilation, when used properly.
 - c. HFOV is superior to conventional ventilation for infants with severe pulmonary interstitial emphysema or bronchopleural fistula. However, HFOV is probably not as effective as HFJV in treating these patients.
 - d. HFOV may be superior to conventional ventilation for patients with severe restrictive lung disease.
 - e. HFOV probably offers no advantages over conventional ventilation in patients with minimal lung disease.
5. General indications for HFOV in most centers which are experienced with HFOV include:
 - a. Treatment of air leak syndromes, including pulmonary interstitial emphysema or bronchopulmonary fistula.
 - b. Severe restrictive lung disease, including RDS, meconium aspiration syndrome, or pneumonia.
 - c. Severe lung hypoplasia.
 - d. Small preterm infants at high risk of developing BPD. This indication is more controversial than those listed above.

Suggested Reading

- Chang H. Mechanisms of gas transport during ventilation by high-frequency oscillation. *J Appl Physiol.* 1984;56:553–63.
- Cools F, Askie LM, Offringa M, Asselin JM, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet.* 2010;375:2082–91.
- Courtney SE, Durand DJ, Asselin JM, et al. High frequency oscillatory ventilation vs conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med.* 2002;347:643–52.
- Froese AB, Kinsella JP. High-frequency oscillatory ventilation: lessons from the neonatal/pediatric experience. *Crit Care Med.* 2005;33(Suppl):S115–21.
- Kacmarek RM, Malhotra A. High-frequency oscillatory ventilation: what large-animal studies have taught us! *Crit Care Med.* 2005;33(Suppl):S148–54.

- Keszler M, Durand DJ. Neonatal high-frequency ventilation: past, present, and future. *Clin Perinatol.* 2001;28:579–607.
- Pillow JJ. High-frequency oscillatory ventilation: mechanisms of gas exchange and lung mechanics. *Crit Care Med.* 2005;33(Suppl):S135–41.
- Vitali SH, Arnold JH. Bench-to-bedside review: ventilator strategies to reduce lung injury – lessons from pediatric and neonatal intensive care. *Crit Care.* 2005;9:177–83.

Part IX
Adjunctive Therapies

Chapter 49

Hemodynamic Support

Keith J. Barrington

I. Introduction

A. Neonatal cardiovascular physiology differs in many ways from the physiology of the more mature human.

1. Cardiac function

- a. Neonatal myocardium is structurally, metabolically, and functionally limited.
- b. Basal contractility is near to maximal levels, and therefore any further demands on cardiac function, such as those resulting from increases of afterload, may not be met.
- c. Increases in afterload as a result of vasoconstriction often lead to decreases in ventricular output.
- d. Drug responses are often also quite different in the newborn; metabolic immaturity of the myocyte may lead to responses which are in a different direction in the newborn. For example, phosphodiesterase-3 inhibitors (e.g., milrinone) may lead to negative inotropic responses in the newborn, in contrast to the positive inotropic responses seen in the older subject.
- e. Only studies restricting the investigation to the newborn or the pre-term newborn give adequate information.

2. Vascular responses

The development of vascular receptors is poorly studied. Alpha-mediated vasoconstriction is seen with the administration of catecholamine agents, even in very immature babies, but the gestational age at which other vascular responses may occur (those mediated by other catechol

K.J. Barrington, MD, ChB (✉)
Department of Neonatology, CHU Sainte Justine, 3175 Cote Ste Catherine,
Montreal, QC, Canada H3T 1C5
e-mail: Keith.barrington@umontreal.ca

receptors, or other categories of responses, such as those mediated by endothelin or acetylcholine) are unknown.

3. Shunts

- a. Because of the presence of shunts, newborn infants with normal hearts do not have a single variable called “cardiac output.”
- b. Total perfusion of the body is the sum of SVC flow and IVC flow.
- c. In contrast, left ventricular output (LVO) only reflects systemic perfusion when the ductus arteriosus is closed.
- d. When the ductus is open, LVO is the sum of pulmonary venous return and any net shunting across the foramen ovale.
- e. Right ventricular output (RVO) is the sum of systemic venous return and any net left-to-right shunting across the foramen ovale; as this shunt is often small, RVO can often be used as an indicator of total systemic perfusion.

B. Normal transition

1. The fetal circulation

- a. In utero the pulmonary vascular resistance is very high which keeps pulmonary blood flow low (less than 15% of the combined ventricular output).
 - b. The majority of blood ejected by the right ventricle crosses the ductus and perfuses the low resistance placental circulation; thus right ventricular afterload in utero is low.
 - c. Most upper body flow in utero is derived from the left ventricular output.
2. At the time of birth the ductus arteriosus constricts and the right ventricular output perfuses the lungs, after which pulmonary vascular resistance starts to fall; thus, right ventricular afterload transiently increases at birth, and then falls as the PVR decreases.

II. Hemodynamic problems

A. PPHN (see also Chap. 64)

1. Pathophysiology

- a. This condition results from the failure of pulmonary vascular resistance to fall or a recurrence of high resistance after the initial transition.
- b. This may occur as a complication of meconium aspiration, pneumonia, pulmonary hypoplasia, other respiratory disorders such as respiratory distress syndrome, or occasionally as an isolated phenomenon in babies with clear chest radiographs.
- c. Right-to-left ductal shunting, although pathognomonic, is seen only in those with severe disease and an open ductus.
- d. Many other infants have intracardiac shunting across the foramen ovale; such shunting depends on an interatrial pressure gradient. Right

atrial pressures will be elevated in the presence of right ventricular failure, which may result from the high right ventricular afterload. Thus, right ventricular function is an important determinant of a good outcome in infants with PPHN.

- e. Finally, hypoxemia may result from intrapulmonary shunting (that is, ventilation–perfusion mismatch).

2. Clinical evaluation

- a. PPHN may accompany respiratory distress, or occur in babies with little distress; such infants need a high FiO_2 .
- b. Preductal saturation (right hand) and postductal saturation (a foot) may show a gradient, but its absence does not rule out the disease.
- c. Most infants with severe respiratory failure have some elevation of the pulmonary vascular resistance.

3. Supplementary testing

- a. Echocardiography may show right-to-left or bidirectional shunts, high estimated pulmonary artery pressure, or abnormal septal curvature (right-to-left bowing).
- b. If congenital heart disease is suspected, a hyperoxia test may be helpful, but can also be misleading.

4. Therapy

- a. Supportive therapy, assisted ventilation, warmth, oxygen, and fluids are used.
- b. Sedation may help in certain cases.
- c. The only proven directly acting therapy is inhaled nitric oxide (Chap. 55), which can be commenced at between 2 and 20 ppm. Hyperoxia should be avoided, as it may impair nitric oxide-mediated pulmonary vasodilation and increase pulmonary vascular reactivity.
- d. Hyperventilation should be avoided as progressive systemic hypotension may occur.
- e. Bicarbonate should be avoided, as its use has been associated with increased need for ECMO and poorer outcomes.
- f. Cardiac supportive therapy may be required, but it is unclear which agent has the best effect. Epinephrine use at low to moderate doses (0.05–0.2 mcg/kg/min) improves systemic oxygen delivery in animal models.

B. Septic shock

1. Pathophysiology

- a. There are little data regarding the usual hemodynamic features of septic shock in the newborn.
- b. Older patients with gram-negative septic shock commonly have excessive vasodilation accompanied by a normal or increased cardiac output and hypotension, so-called “warm shock.”

- c. It is not clear if this is true in newborn infants, who often have different organisms (e.g., group B streptococcus) and have different cardiovascular physiology. Neonatal *animals* with group B streptococcus demonstrate vasoconstrictive “cold shock,” with hypotension being a preterminal event.
2. Clinical evaluation
 - a. In cold shock, signs of peripheral vasoconstriction are common: prolonged capillary filling, oliguria, and inactivity.
 - b. In warm shock, pulses may be bounding, but signs of inadequate tissue oxygen delivery may be seen (e.g., lactic acidosis and poor urine output).
 3. Supplementary testing
 - a. Echocardiography may be helpful for estimating cardiac filling, contractility, and systemic blood flow, and in determining therapeutic interventions.
 - b. There is no clear evidence that this improves outcomes, but it does allow more rational therapy.
 4. Therapy
 - a. There is little good evidence regarding therapeutic options in infants with septic shock.
 - b. A physiology-based approach would suggest that infants with clinical shock but with adequate blood pressure may benefit from dobutamine (which increases systemic perfusion without having much effect on blood pressure).
 - c. Infants with shock and hypotension may preferably be treated with epinephrine, which appears to increase both blood pressure and systemic perfusion.
 - d. Combinations of drugs have unpredictable effects. Pharmacokinetics and receptor status of babies vary considerably; therefore, dose responses are extremely variable and doses need to be individualized.
 - e. In adults with septic shock, there is little evidence that clinical outcomes vary according to the drug chosen; randomized trials comparing different agents show differences in short term clinical responses, but generally not in survival.
 - f. Fluid boluses are often administered, based on the assumption that sepsis leads to a functional hypovolemia.
 - (1) Although this may be true in certain cases, a recent trial in older infants and children showed an increase in mortality in children with early septic shock who received a fluid bolus.
 - (2) If fluid boluses are administered, crystalloids and colloids have different hemodynamic responses, with a greater and more prolonged increase in perfusion with colloids than with saline, but with little

or no evidence of differential clinical outcomes, the agent of choice in the newborn is uncertain.

C. Hypovolemic shock

1. Pathophysiology

- a. Hypovolemia can result from blood loss (e.g., ruptured vasa previa), or occasionally in infants following placental abruption (in this situation the blood lost is usually mostly maternal).
- b. Partial umbilical cord occlusion, as may occur with a tight nuchal cord, or cord prolapse, will occlude initially the umbilical veins, prior to the arteries, reducing circulating blood volume.
- c. Large volume fetomaternal hemorrhage will also lead to hypovolemia, but is rare before 28 weeks' gestation, mostly occurring in late preterm and term infants.
- d. Neonatal animal models suggest that blood pressure and perfusion can be maintained up to the loss of about 20 mL/kg by vasoconstriction; after that, further blood loss leads to shock and hypotension.

2. Clinical evaluation: Infants are usually pale, tachycardic, and poorly perfused with prolonged capillary refill.

3. Supplementary testing:

- a. Echocardiographic assessment of cardiac filling may be helpful but clear indices of circulating blood volume do not exist.
- b. Central venous pressure (CVP) measurements are of limited usefulness, as they are often low in the newborn, and remain low despite volume administration. CVP may provide useful trend data.

4. Therapy

- a. Administration of volume.
- b. Saline will temporarily restore perfusion in emergency resuscitation, blood, as soon as available, is required to restore oxygen carrying capacity.

D. Cardiogenic shock

1. Pathophysiology

- a. Cardiomyopathy
- b. Congenital heart disease (e.g., HLHS)
- c. Asphyxial injury

2. Clinical evaluation

- a. Poor perfusion and tachycardia are the hallmarks of primary cardiac dysfunction.
- b. Metabolic acidosis with increasing serum lactate, and oligo- or anuria are danger signs.

3. Supplemental testing
 - a. Echocardiography is essential; identification of the coronary artery origins should be considered important unless another diagnosis is likely.
 - b. Structural heart disease and cardiomyopathy should be ruled out.
 4. Therapy
 - a. Avoiding excessive preload and those therapies which increase after-load makes physiologic sense.
 - b. Dobutamine and low dose epinephrine are reasonable first choices.
- E. Extreme prematurity: Hypotension or shock?
1. Pathophysiology
 - a. Many extremely preterm infants receive cardiovascular intervention, very often for a *numerically* low blood pressure.
 - b. Numerous studies show that there is no correlation between mean arterial pressure and systemic perfusion; most preterm hypotensive infants have low blood pressure for reasons of low vascular resistance and are supplying adequate oxygen to their vital tissues.
 - c. Hypotensive babies with good clinical perfusion can have good outcomes without intervention.
 - d. There is no clear answer regarding the appropriateness of treatment for hypotension in infants with either clinical signs of good perfusion, or those with documented normal systemic blood flow.
 - e. Many centers do not intervene medically for such infants, and institute close surveillance; usually blood pressure will spontaneously rise over the subsequent few hours.
 - f. Hypotension in association with poor perfusion is a very hazardous situation with poor outcomes; some babies in this situation will be found to be septic, and others may have primary cardiac dysfunction.
 2. Clinical evaluation
 - a. An overall evaluation including clinical signs of poor perfusion and supplementary tests is required to determine whether an extremely preterm infant with a numerically low blood pressure has inadequate perfusion.
 - b. The clinical evaluation includes capillary filling time, warmth of peripheries, urine output, and the level of spontaneous activity.
 3. Supplementary testing
 - a. Echocardiography, for measurement of systemic flow (SVC flow less than 40 mL/kg/min is associated with increased risk of intraventricular hemorrhage and poor long-term outcome).

- b. An elevated or rising serum lactate is a sign of inadequate tissue oxygen delivery, as long as it is correctly sampled and processed, and a combination of an elevated lactate and a prolonged capillary refill is associated with low systemic perfusion.
 - c. Near infra-red spectroscopy to measure cerebral oxygen tension has promise but more work is required. It may also prove useful for determining intestinal perfusion.
4. Therapy
- a. If there is no evidence of peripheral underperfusion, then hypotension probably does not need to be treated.
 - b. For infants with hypotension and signs of poor perfusion or poor systemic flow, therapeutic approaches are uncertain. Low to moderate dose epinephrine (or perhaps a combination of dopamine and dobutamine) is physiologically reasonable as a way of improving cardiac function, and elevating blood pressure as well.
 - c. Fluid boluses are overused, and hypotensive extremely preterm infants are rarely hypovolemic; in the presence of a history compatible with volume loss, 10 mL/kg of normal saline can be tried empirically.

Suggested Reading

- Aschner JL, Poland RL. Sodium bicarbonate: basically useless therapy. *Pediatrics*. 2008; 122(4):831–5.
- de Waal K, Kluckow M. Functional echocardiography; from physiology to treatment. *Early Hum Dev*. 2010;86(3):149–54.
- Dempsey EM, Barrington KJ. Treating hypotension in the preterm infant: when and with what: a critical and systematic review. *J Perinatol*. 2007;27(8):469–78.
- Miletin J, Pichova K, Dempsey E. Bedside detection of low systemic flow in the very low birth weight infant on day 1 of life. *Eur J Pediatr*. 2009;168(7):809–13.
- Roze JC, Tohier C, Maingueneau C, et al. Response to dobutamine and dopamine in the hypotensive very preterm infant. *Arch Dis Child*. 1993;69:59–63.

Chapter 50

Nutritional Support of the Ventilated Infant

David Adamkin

I. Introduction

- A. Respiratory distress is a leading cause of neonatal morbidity and mortality, and mechanical ventilation remains the most common therapeutic modality applied in neonatal intensive care units.
- B. Aggressive nutritional strategies should minimize the interruption of growth as much as possible as the early fetus transitions to extrauterine life. These strategies promote the following:
 - 1. Reducing postnatal weight loss
 - 2. Earlier return to birth weight
 - 3. Improved catch-up growth
- C. The guiding principle for these strategies is that undernutrition is by definition, nonphysiologic and undesirable. Any measure that diminishes undernutrition is inherently good provided that safety is not compromised.
- D. Improving nutritional status and growth will optimize neurodevelopmental outcome.
 - 1. Considerable evidence suggests that early growth deficits have long lasting consequences including short stature and poor neurodevelopmental outcomes.
 - 2. Data linking neurodevelopmental consequences with inadequate early nutrition include preterm infants fed a preterm formula containing higher protein and energy over the first postnatal month. They had higher neurodevelopmental indices at both 18 months and 7–8 years of age compared to preterm infants fed term formula.

D. Adamkin, MD (✉)
Neonatal Department, University of Louisville Hospital, 571 S. Floyd Street,
Suite 342, Louisville, KY 40202, USA
e-mail: david.adamkin@louisville.edu

3. Another study demonstrated improved neurodevelopmental and growth outcomes at 18–22 months of age for extremely low-birth weight infants (ELBW, <1,000 g) who had higher growth velocities for weight and head circumference during the NICU hospitalization.

E. Initially, most ELBW newborns receiving mechanical ventilation are supported exclusively by parenteral nutrition, later by enteral nutrition alone. In addition, a significant number of ELBW infants treated with mechanical ventilation develop BPD and associated feeding disorders that have a major adverse effect on subsequent growth and development.

II. Requirements for protein and energy

A. The two methods for estimating protein intake necessary to maintain approximate in utero growth of a fetus of the same gestational age are:

1. Factorial method, which includes an estimate of the amount of protein deposited in utero corrected for efficiency of absorption and deposition as well as an estimate of the inevitable urinary nitrogen losses. The main advantage of the factorial method is that it provides estimates of energy requirements, which may be applied to ELBW infants where there are no empirical estimates available.
2. Empirical method, which determines the actual intakes that support intra-uterine rates of growth and nitrogen accretion. Only the empirical method provides estimates for catch-up growth. Empirical method does not estimate energy requirements.
3. Table 50.1 shows enteral protein and energy requirements determined by the factorial approach. Protein requirements decrease with increasing body size.

B. Energy requirements are lower during parenteral nutrition compared to enteral nutrition because energy is neither utilized for thermic effect of feeding nor malabsorbed in stools.

C. Energy expenditure measurements in critically ill very low birth weight infants (VLBW, <1,500 g BW) receiving assisted ventilation are extremely difficult to perform using any existing measurement techniques. Studies suggest a mean energy expenditure of approximately 54 kcal/kg.

1. Technical limitations hampered these investigations, including the minimal inspired oxygen level at which the patients could be studied.
2. Smaller infants had lower energy intakes but lower energy expenditure of the same magnitude.
3. Critically ill ELBW infants have limited energy stores; it is important to provide adequate energy sources early, which should include early intravenous amino acids (see “Total parenteral nutrition”).
4. In general, a total energy intake varying from 90 to 100 kcal/kg/day is sufficient for most neonates receiving mechanical ventilation as long as they are normothermic and receiving parenteral nutrition. Additional intakes

Table 50.1 Enteral protein and energy requirements of preterm infants

Body weight (g)	Protein (g/kg/day)	Energy (kcal/kg/day)	P/E (g/100 kcal)
500–700	4.0	105	3.8
700–900	4.0	108	3.7
900–1,200	4.0	119	3.4
1,200–1,500	3.9	127	3.1
1,500–1,800	3.6	128	2.8
1,800–2,200	3.4	131	2.6

Adapted from Ziegler, J Ped Gastro/Nutr 2007

P/E = ratio of protein to energy, expressed as grams of protein per 100 kcal.

ranging from 10 to 20 kcal/kg/day are indicated for infants who are premature, physically active, and receiving full enteral feedings.

D. Intravenous carbohydrates should supply 50% of total calories on TPN. Glucose infusion rate (GIR) will depend on volume of fluid and the percent dextrose chosen. As the amount of fluid is changed, the amount of glucose infused will change.

1. A steady infusion of 6–8 mg/kg/min of glucose should be provided parenterally.
2. $GIR (mg/kg/min) = \% \text{ glucose} \times \text{total mL} \times 100 \text{ mg/1,440 (min/day)}/wt (kg)$.
3. Excessive glucose intake >18 g/kg/day or >13 mg/kg/min, 60 kcal/kg/day increases CO₂ production and may adversely affect respiratory gas exchange. Excessive energy as glucose induces lipogenesis, which is an inefficient process and increases energy expenditure.
4. Glucose intakes at or below energy expenditure have no effect on respiratory gas exchange (CO₂ production).

E. Glucose intolerance can limit delivery of energy to the infant to a fraction of the resting energy expenditure, resulting in negative energy balance.

1. Administration of early intravenous amino acids after birth helps prevent hyperglycemia in the majority of ELBW infants. Stimulation of endogenous insulin secretion and increased insulin activity by specific parenteral amino acids may explain how early amino acids prevent hyperglycemia.
2. Regular insulin may be necessary for hyperglycemia (serum glucose >150–200 mg/dL) at a GIR <6 mg/kg/min.
3. Prophylactic infusion of insulin to increase glucose utilization and energy intake in the euglycemic infant does not increase protein balance. It decreases proteolysis and protein synthesis by approximately 20%.
4. Table 50.2 is a guide for using TPN.

F. Aggressive nutrition therapy, including early intravenous amino acid infusion, theoretically allows the transition from fetal to extrauterine life with minimal interruption of growth and development.

Table 50.2 Parenteral nutrition guide

Nutrient	Standard	Advance by	Acceptable Labs	Notes
Fluid	DOL 1-3: 80-100 mL/kg DOL 4: 100-120 mL/kg DOL 5: 130-150 mL/kg	↑ by 10-20 mL/kg/day	Na 130-145 mEq/L K 3.5-5.5 mEq/L	Adjust fluid based on I and O's, and electrolytes
Dextrose	Peripheral: D 10-12.5% Central: D 10-15%	Adjust as fluid adjusts keeping glucose delivery at 6-8 mg/kg/min	Glucose 45-130 mg/dL	Dextrose calories not to exceed 50% of total calories. Remember that the glucose delivered will increase with an increase in the fluid rate
Lipids	3 g/kg/day	Begin with 1-2 g/kg/d and ↑ by 1 g/kg/day until goal is met	Triglyceride ≤200 mg/dL	Calories from fat not to exceed 55% of total calories
Protein	3.5 g/kg/day	Begin with 2-2.5 g/kg and ↑ by 1 g/kg/day until goal is met	BUN 6-40 mg/dL Creatinine 0.8-1.2 mg/dL	Calories from protein not to exceed 12% of total calories NPC 150-200/g nitrogen
Cysteine Carnitine	40 mg/g of amino acid 8 mg/kg ≤1250 g begin on DOL 1 ≥1,250 g begin on DOL 14			Not to exceed 100 mg/kg/day Carnitine is a cofactor required for the oxidation of fatty acids
Sodium	3 mEq/kg/day	Adjust per labs and fluid status	Na 130-145 mg/dL	No sodium until Na level is ≤130 mg/dL
Potassium Magnesium	2 mEq/kg ≥1,000 g 0.25 mEq/dL ≤1,000 g 0.1 mEq/dL	Adjust per labs and fluid status Adjust per labs	K 3.5-5.5 mEq/L Mg 1.7-2.1 mg/dL	Watch for ↑ levels in the first few days of life
Calcium Phosphorus	1-3 mEq/kg 0.5-1.5 mM/kg	Adjust per solubility and labs Adjust per solubility and labs	Ca 7.6-10.4 mg/dL PO ₄ 5-7 mg/dL	Maintain a 2:1 ratio with PO ₄ Maintain a 2:1 Ca to PO ₄ ratio

Chloride	1–2 mEq/kg	Adjust per labs	Cl 95–110 mEq/L	Chloride can be used to adjust acetate
Acetate	1 mEq/kg	Adjust per labs	CO ₂ 18–24 mEq/L	Acetate can only be manipulated by ↑ Chloride
Pediatric MVI	1 mL/kg/d			Given to all infants when TPN begins
Iron	200 mcg/kg			Begin at DOL 1 for all patients regardless of weight
Zinc	200 mcg/kg			Added to infants weighing ≤3 kg
Iodine				Only given to infants receiving TPN or > 4 weeks (1 mcg/kg/d)
Copper	10 mcg/kg			Added to infants weighing ≤3 kg. There is 20 mcg of copper in the Trace Pack
Manganese	6 mcg/kg			Added to all TPN
Chromium	0.2 mcg/kg			Added to all TPN
Selenium	2 mcg/kg			Added to all TPN
Trace Pack	0.2 mL/kg			Added to all TPN
Heparin	0.5–0.7 units/mL			Maximum 1 unit/mL (100 units/kg)
Osmolarity				Not to exceed 1,200 mOsm/L in a peripheral line. Adjust protein or sodium if osmolarity is too high

Adapted and modified from Bhatia J, Gates A. Neonatal nutrition handbook. 6th ed. 2006

1. The administration of amino acids from the first postnatal hours to avoid a period of early malnutrition is the first strategy to prevent growth failure in ventilated ELBW infants and to promote enhanced neurodevelopment.
 2. An increase in blood urea nitrogen (BUN) after the start of TPN is not an adverse effect or sign of toxicity; rather, it is related to metabolism of the amino acids or protein.
 3. Several controlled studies have demonstrated the efficacy and safety of amino acids initiated within the first 24 h after birth. No recognized metabolic derangements, including hyperammonemia, metabolic acidosis, or abnormal aminograms, have been observed.
 4. Glucose tolerance improves in infants receiving early amino acids. The amino acids stimulate insulin secretion. Insulin activity falls in the absence of parenteral amino acids in these infants. Similarly, nonoliguric hyperkalemia may be prevented. Early amino acids stimulate insulin activity preventing intracellular energy failure, which will occur if insulin activity is reduced. Glucose transport is reduced at the cellular membrane level with a resultant decrease in Na^+ , K^+ ATPase activity and leakage of intracellular potassium. This is avoided with early amino acid therapy.
 5. Early TPN amino acids at dosage of 1.5–3.0 g/kg/day may be initiated within hours of birth using stock solutions of 4% amino acids with 10% concentration of dextrose.
 6. Intakes up to 4.0 g/kg/day for ELBW infants may be used when enteral feedings are delayed or withheld for prolonged periods.
 7. Intake of amino acids should not exceed 12% of total calories.
 8. A BUN of up to 40 mg/dL has been observed in neonates in early life with and without TPN. After the initial 5–7 days, BUN levels decrease.
 9. Modification of amino acid intake should not be based on BUN concentration alone. A continuously rising BUN value may indicate a mismatch between production and excretion.
 10. See Table 50.2.
- G. Intravenous lipids serve as a source of linoleic acid to prevent or treat essential fatty acid deficiency (EFAD) and as an energy source. Larger quantities serve as a partial replacement for glucose as a major source of calories (balanced TPN).
1. Use 20% lipid emulsion to decrease risk of hypertriglyceridemia, hypercholesterolemia, and hyperphospholipidemia.
 2. Premature infants can clear 0.15–0.2 g/kg/h. Lipid infusion hourly rate correlates best with plasma lipid concentrations. Hourly infusion should not exceed 0.15–0.20 g/kg/h. However, small for gestational age infants and infants with sepsis may not be able to clear standard doses of intravenous lipids and demonstrate hypertriglyceridemia.

III. Total parenteral nutrition (TPN)

- A. TPN is the main mode of alimentation for critically ill neonates receiving mechanical ventilation, especially during the immediate neonatal period when they cannot be fed enterally.
- B. TPN is usually continued until enteral feedings are providing sufficient volume to replace TPN.
- C. Parenteral nutrition solutions should supply all necessary nutrients at maintenance rates, including electrolytes and minerals, to correct the common biochemical abnormalities that occur during the neonatal period (Table 50.2).
 1. Premature infants receiving parenteral nutrition are at risk of developing vitamin A deficiency because of their low hepatic stores and low serum-binding protein levels at birth.
 2. There are also significant losses of vitamin A into the delivery system used for parenteral nutrition.
 - a. In 2005, the largest randomized, controlled trial was performed in 807 premature infants with a birth weight of less than 1 kg who received 5,000 IU of vitamin A IM three times per week for the first month of life.
 - b. The results showed a modest but beneficial effect of vitamin A supplementation in reducing the incidence of BPD.
- D. The “routine” use of intravenous lipid emulsions has not been universally accepted in critically ill ventilated ELBW infants because of potential pulmonary complications.
 1. No differences in gas exchange were found in infants randomly assigned to various lipid doses (including controls without lipids) when using lower rates and longer infusion times of intravenous lipids (<0.2 g/kg/h).
 2. For the late preterm infant with increased pulmonary vascular resistance (PVR) or any preterm infant with respiratory failure, it appears a more prudent approach with intravenous lipids should be taken.
 3. Figure 50.1 shows that the high polyunsaturated fatty acid content of lipid emulsions as linoleic acid may lead to pathways resulting in vasoactive prostaglandins, leukotrienes, and thromboxanes through their conversion from arachidonic acid. This may exacerbate pulmonary hypertension.
 4. The oxidation of fat produces less CO_2 for the same amount of oxygen consumed. This reduction in CO_2 production and its elimination may be beneficial for patients with compromised lung function. Therefore, lipids partially replace glucose as a source of energy (balanced TPN).
 5. Initiate lipids the day following birth after starting the amino acid stock solution at a dose 0.5 or 1.0 g/kg/day for ELBWs with respiratory disease.

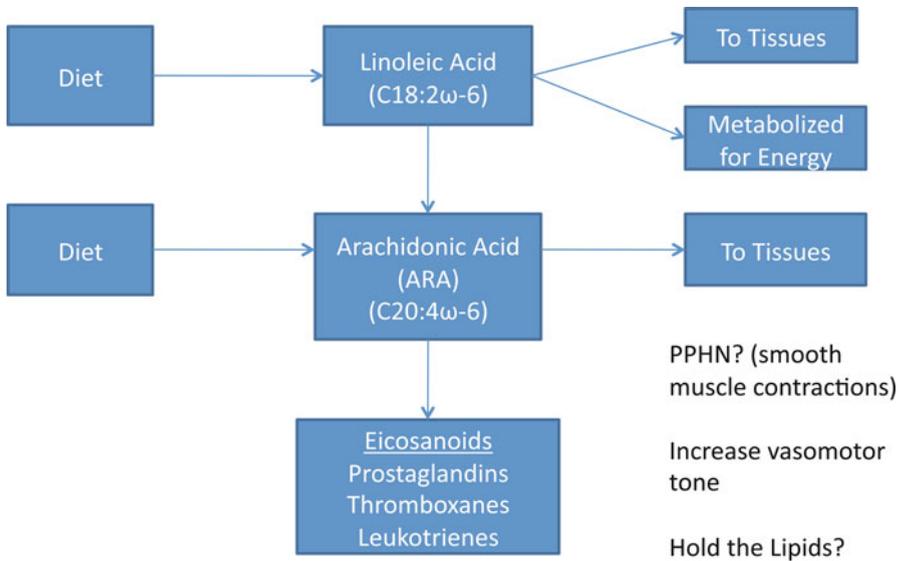


Fig. 50.1 Metabolic Derivatives of Linoleic Acid and ARA (Arachidonic acid). Modified from Adamkin DH, Clin Perinatol Dec 2006

6. Plasma triglycerides are monitored after each increase in dose, and levels are maintained <200 mg/dL.
7. Maximum lipid administration is usually 3 g/kg/day.
8. See Table 50.2.

IV. Enteral nutrition

- A. Enteral protein feeding requirements have been reevaluated and emphasize the concept of lean body mass gain. The contribution of protein to match fetal lean mass growth ex utero is more important than weight gain.
 1. Additional protein is also necessary for early catch-up growth to compensate for the cumulative protein deficit, which develops in the first weeks of life.
 2. An increase in the protein–energy (P/E) ratio is mandatory to improve the lean body mass accretion and to limit fat mass deposition.
 3. Human milk plays a significant role in promoting lean body mass and avoidance of maldistribution of adipose tissue.
 4. Table 50.3 shows revised recommendations for protein intake and protein energy ratio for pre term infants according to postconceptual age and need for catch-up. Table 50.1 presents requirements based on the reference fetus. These may be taken together to address both growth and the need for catch-up.
 5. Modern preterm formulas and supplemented human milk provide protein intakes of 3.6–4.3 g/kg/day at an energy intake of 120 kcal/kg/day.

Table 50.3 Revised recommended protein intake and protein–energy ratio for premature infants according to postconceptional age and the need for catch-up

	Without need of catch-up growth	With need of catch-up growth
26–30 weeks PCA: 16–18 g/kg/day LBM 14% protein retention	3.8–4.2 g/kg/day P/E: 3.0	4.4 g/kg/day P/E: 3.3
30–36 weeks PCA: 14–15 g/kg/day LBM 15% protein retention	3.4–3.6 g/kg/day P/E: 2.8	3.6–4.0 g/kg/day P/E: 3.0
36–40 weeks PCA: 13 g/kg/day LBM 17% protein retention	2.8–3.2 g/kg/day P/E: 2.4–2.6	3.0–3.4 g/kg/day P/E: 2.6–2.8

Based on Rigo, in Tsang, *J Pediatr* 2006;149:S80–88

PCA post conceptual age, LBM lean body mass, P/E protein/energy ratio

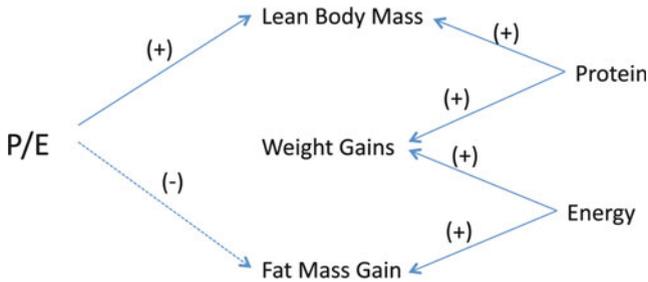


Fig. 50.2 Impact of protein–energy ratio (P/E) on body composition. With permission from World Scientific Publications Company

This includes a newer “higher” protein preterm formulas with P/E ratio of 3.3–3.6 instead of the 3.0 in standard protein formulas.

6. Figure 50.2 shows the impact of P/E ratio on body composition.

B. Enteral feeding guideline practicum

1. Begin minimal enteral/trophic (<25 mL/kg/day) feedings by three days of life in ELBW infants after physiologically stable unless contraindications exist.
2. *Human milk is the definitive preference for feeds.*
3. Advancing feeds in a safe yet more standardized fashion is helpful.
4. Each institution should have guidelines for stopping feeds and identifying feeding intolerance.
5. Any situation associated with gut hypoxia or decreased intestinal blood flow may contraindicate enteral feeding.
6. Nutrition advances of ≤20 mL/kg/day do not increase the incidence of NEC.

7. Dilute formulas and dilute human milk fail to provide sufficient energy intake and fail to stimulate motor activity of the GI tract.
 8. Slow bolus feeds (“compressed”), those lasting at least 30 min to an hour or two, may be preferable to continuous feeds, particularly in infants with feeding intolerance.
 9. Gastric residuals do not indicate NEC, or impending NEC; other signs of NEC are much more important.
 10. Gastric residuals may have a protective function, serve as markers of gut maturation, and help the clinician advance feeding volumes.
- C. Human milk provides substantial benefits for the preterm infant and is the feeding of choice and may include the use of donor breast milk.
1. It should be encouraged unless contraindications exist.
 2. The substantial benefits of breast milk for the preterm infant and the importance of mother’s contribution should be emphasized.
 3. Breast pumping and hand expression should be initiated within the first 6 postpartum hours.
 4. The value of colostrum should be emphasized. Fresh colostrum should be collected and used in first feeds.
 5. Lactation consultations should occur, ideally, on DOL 1, or when mother is available (e.g., in cases where baby has been transferred from another hospital).
- D. Human milk fortification may be necessary in ELBW infants and some VLBW infants to provide optimal nutrient intake.
1. Since the composition of mothers’ milk varies greatly from one mother to another, and the concentration of nutrients in preterm milk changes over time, it is difficult to determine the actual intake.
 2. To confer the potential nonnutritional advantages yet provide optimal nutrient intake, human milk should be supplemented or fortified, with protein, calcium, phosphorus, vitamin D, and sodium.
 3. There are multiple fortification strategies available. One is mixing human milk with formula, to avoid using powders that are not sterile.
 4. However, the disadvantages include diluting the amount of human milk fed to the infant and concerns that the “mixing” may decrease the benefits of the human milk.
 5. Two powdered human milk fortifiers are available in the USA and may be added to make 22 and 24 kcal/oz fortified human milk. Powders may be associated with *Enterobacter sakazakii*. These powders may soon be removed by the manufacturer.
 6. There is now a fortifier made from human milk to make 24 kcal/oz human milk.
 7. These fortification strategies are shown in Table 50.4.
 8. Sterile concentrated liquid fortifiers which may be added to human milk and do not dilute the milk as much as mixing with formula have recently been released.

Table 50.4 Human milk fortification

Milk at 100 cal	mL	Prot (g)	Fat (g)	CHO (g)	Ca (mg)	P (mg)
Preterm human (PTHM)	150	2.1	5.8	9.9	37	19
PTHM + SSC 30 4:3 ratio	125	2.58	6.23	8.7	113	62
PTHM + SHMF 1 pkt/25 mL	125	3.0	5.24	10.4	175	98
PTHM + EHMf 1 pkt/25 mL	125	3.1	4.4	12.4	115	58
PTHM +SSC30 1:1ratio (25 cal/oz)	120	2.7	6.1	9.0	122	68
Enfamil HMFAL	125	4	6	8.1	118	65
Proclact + 4	125	3.3	5.8	8.7	117	54

Reprinted with permission, Adamkin, Nutritional Strategies for the VLBW. Cambridge Press 2009
PTHM Preterm Human Milk (PTHM 1.5 g protein/100 mL), *SSC30* Similac Special Care (Ross Laboratories, Columbus, Ohio), *EHMF* Enfamil Human Milk Fortifier (Mead Johnson, Evansville, IN), *EHMfAL* Enfamil Human Milk Fortifier Acidified Liquid, *Proclact+4* Proclacta Biosciences, Monrovia, California

- E. Caloric-dense enteral feedings are intended for use in critically ill VLBW infants unable to tolerate sufficient feeding volumes (volume restricted) to meet their needs for growth using standard premature formulas or fortified breast milk.
1. Until recently, various mixtures of powders and “manipulation” of milk to make concentrated formulas were used. These are not sterile and provide inadequate protein.
 2. Providing enough protein is the challenge in the moderate to severely fluid restricted infants.
 3. The recent introduction of a 30-kcal/oz liquid ready-to-feed preterm formula increases nutrient density of feeding without increasing the fluid volume.
 4. The mixing of powdered formula and concentrated liquids has been replaced by a safer and far superior product for feeding caloric dense milk to formula-fed VLBW infants.
 5. The VLBW infant can receive the same quantity of protein as with standard preterm formulas but with less volume.
 6. The calories from fat are increased and carbohydrate calories are lower versus standard preterm formula.
 7. The osmolarity at 30 cal/oz is 325 mOsm/L vs. preterm formula at 280 mOsm/L.
 8. There is a human milk fortifier prepared from human donor milk which allows the formulation of 26–30 kcal/oz human milk.
 9. This can also be added to mother’s milk or donor milk to provide exclusive human milk even in VLBW infants requiring fluid restriction.

Table 50.5 Hypercaloric dense feedings with formula/human milk mixture or formula

Milk at 100 calories	ml	Prot (g)	Fat(g)	CHO (g)	Ca (mg)	P (mg)
PTHM + SHMF + SSC 30 To 27 cal/oz	111	3	6	9	178	100
PTHM + SHMF + SSC 30 To 28 cal/oz	106	3	6.23	8.5	179	100
SSC 30	100	3	6.61	7.7	180	100
SSC 27	111	3.15	6.09	8.9	180	100

PTHM preterm human milk, *SHMF* Similac human milk fortifier (Abbott Nutritionals, Columbus, Ohio), *SSC30* Similac Special Care 30

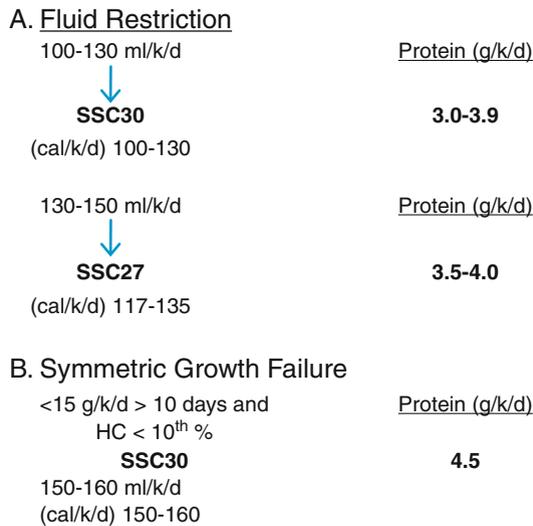


Fig. 50.3 Caloric dense feedings with formula. Reprinted with permission from Adamkin DH, Nutritional Strategies for the Very Low Birthweight Infant, Cambridge Press, 2009

10. Table 50.5 and Fig. 50.3 show the caloric density strategy using human milk and formula combination for volume-restricted VLBW infants typically with significant lung disease.
 11. Table 50.6 shows caloric dense feedings with exclusive human milk feedings.
- F. Postdischarge nutrition is another strategy with nutrient-enriched formulas and multinutrient fortifiers for human milk to promote catch-up growth in ELBW infants.
1. The first postnatal year provides an important opportunity for human somatic and brain growth to compensate for earlier deprivation.
 2. Available data suggest that many smaller/sicker preterm infants are in a state of suboptimal nutrition at the time of discharge and are frequently below the tenth percentile on the growth curve (extrauterine growth restriction).

Table 50.6 Caloric dense human milk feeding for very low birth weight infants ($\leq 1,500$ g BW)

	Fortifier			
	Prolact +4	+6	+8	+10
<i>Per 100 ml</i>				
OMM or BBM	80/20	70/30	60/40	50/50
Energy	83	91	98	104
Protein (g)	2.4	2.8	3.3	3.8
OSM	<335	337	347	349
<i>Per 120 kcal/kg/day</i>				
Protein	3.5	3.7	4.0	4.3
Volume	145	132	122	115
Ca	186	169	156	177
P	102	92	85	99

Reprinted with permission from Adamkin DH. Nutritional strategies for the very low birthweight Infant. Cambridge Press; 2009

3. These VLBW infants have also accumulated significant nutrient deficits for protein, energy, calcium, and phosphorus by the time of discharge.
4. Nutrient-enriched formula for preterm infants after hospital discharge (postdischarge formula [PDF]) is generally intermediate in composition between preterm and term formulas.
5. Compared to term formula (TF), PTF contains an increased amount of protein with sufficient additional energy to permit utilization.
6. PDF contains extra calcium, phosphorous, and zinc, which are necessary to promote linear growth.
7. Table 50.7 shows the nutrient concentrations provided by various diets at 200 mL/kg/day after discharge.
8. Studies demonstrated that the use of either PTF or PDF after discharge in preterm infants results in improved growth, with differences in weight and length persisting beyond the period of intervention.
9. Such findings suggest that nutrition during the post-discharge period may have longer-term effects on growth trajectory.
10. Several nonrandomized controlled trials have shown that breast-fed infants do not grow as well as their formula-fed counterparts after discharge.
11. Options include replacing some breast feeds with nutrient-enriched formula feeds or fortifying expressed breast milk.
12. A Post-Discharge Feeding Study provided half of the human milk fed each day to human milk-fed ($\geq 80\%$ feeding per day) preterm infants with four packets of a powdered multinutrient human milk fortifier for 12 weeks after discharge and showed improved growth at 1 year.
13. Discharge preterm infants (GA ≤ 34 weeks or birthweight $< 1,800$ g) on a PDF.
14. Follow anthropometrics carefully postdischarge and maintain the PDF strategy for 9–12 months corrected age, especially for VLBW infants.

Table 50.7 Macronutrients supplied by commonly used formulas for preterm infants at the time of discharge, assuming an intake of 200 mL/kg/day

	Target	Human milk	Similac ^a Advance w/Fe 20 kcal/oz	Enfamil Lipil ^b w/Fe 20 kcal/oz	Similac ^a Advance w/Fe 20 kcal/oz	Enfamil Lipil ^b w/Fe 20 kcal/oz
Calories/kg	120–130	138	136	136	150	148
Protein (g/kg)	2.5–3.5	2.0	2.8	2.8	4.2	4.2
Fat (g/kg)	6.0–8.0	7.8	7.2	7.2	8.2	7.8
CHO (g/kg)	10–14	13.2	14.6	14.6	15.4	15.8
Vitamin A (IU/kg)	1,000	780	406	406	686	666
Vitamin D (IU)	200–400	4	80	80	104	118
Vitamin E (IU/kg)	6–12	2.0	4.0	2.6	5.4	6.0
Ca (mg/kg)	150–175	50	106	106	156	178
P (mg/kg)	90–105	26	56	72	92	98
Fe (mg/kg)	2–4	0.2	2.4	2.4	2.6	2.6

Adapted from American Academy of Pediatrics. Pediatric nutrition handbook. 5th ed. 2004, Appendices A and E

Adapted from Greer FR, Post discharge nutrition: what does the evidence support? *Semin Perinatol.* 2007;31(2) with permission

^aFrom Abbott Nutritional Products

^bFrom Mead Johnson Nutritionals

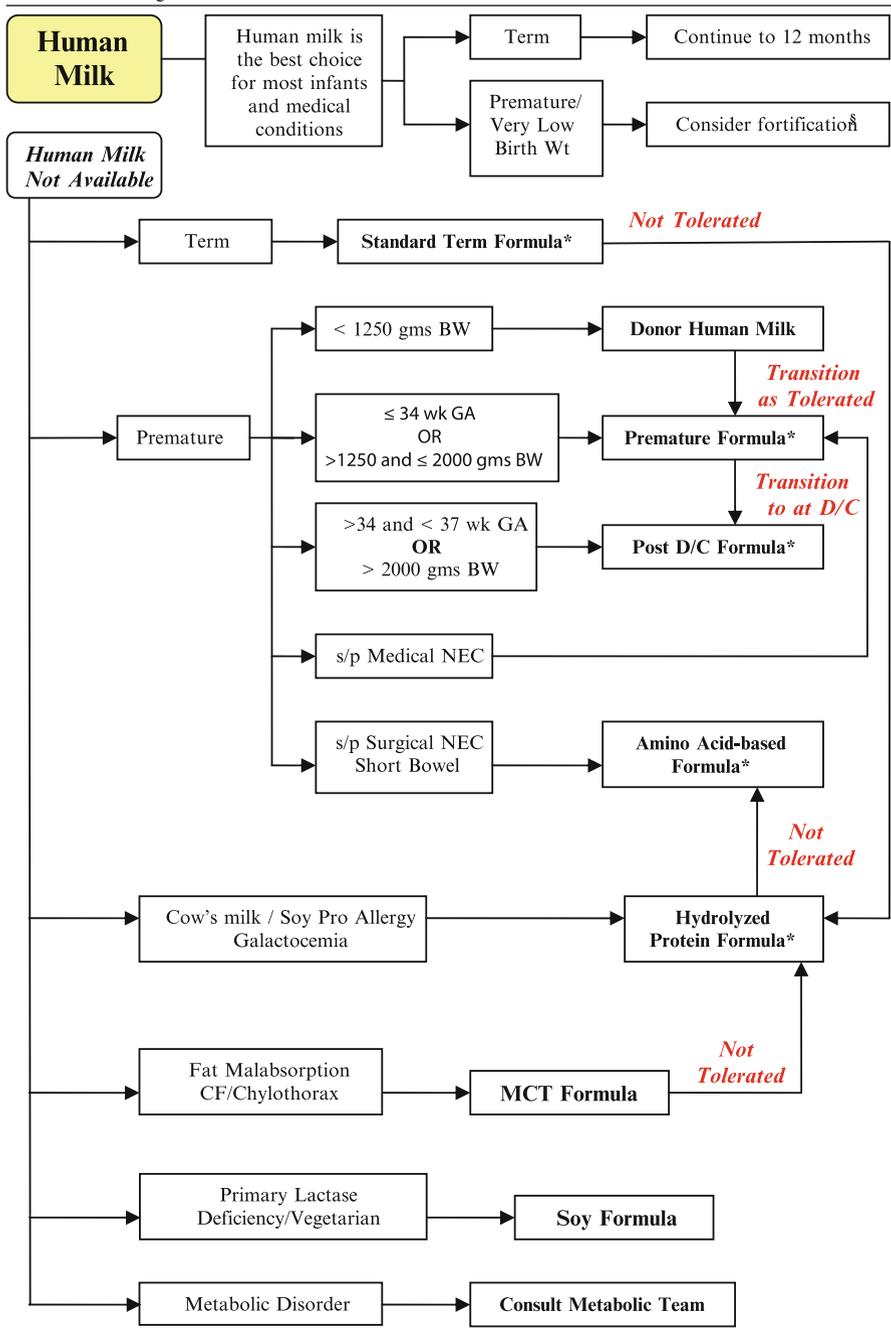
15. VLBW infants discharged on human milk require an individualized approach based on anthropometrics and whether or not there is evidence of osteopenia of prematurity.
16. Human milk-fed babies with growth failure or evidence of osteopenia may receive fortification by alternating breast feedings with the PDF or fortification strategies alluded to in the human milk and caloric dense sections above.
17. Growth postdischarge should be monitored with the CDC, NCHS Growth Curves and not the IHDP Curves.

G. Table 50.8 and Fig. 50.4 provide suggestions for use of human milk or formulas in infants.

V. Feeding Disorders

- A. Feeding disorders may develop in infants treated with mechanical ventilation, impairing long-term growth, nutritional status, and developmental outcome.
- B. In general, feeding disorders are first recognized after the patient is extubated and then fails multiple attempts to be orally fed.
- C. Oropharyngeal hypersensitivity, defined as a pathologic aversion to oral stimulation, is evidenced by an avoidance behavior to the introduction of any type of oral feeding.

Table 50.8 Feeding flowchart



From Adamkin/McKinney, University of Louisville, January 2011

* For fluid sensitivity/BPD/CHF consider a calorie dense nutrition strategy.

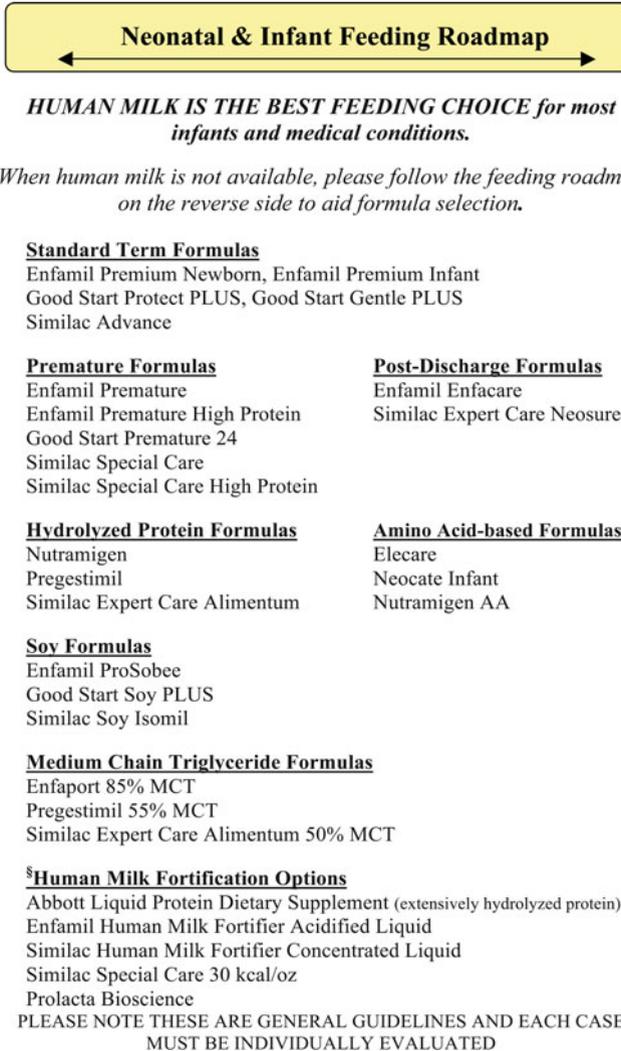


Fig. 50.4 Feeding roadmap. From Adamkin/McKinney, University of Louisville, January 2011

1. This disorder results from prolonged endotracheal intubation, frequent oral and nasal pharyngeal suctioning, prolonged use of nasal and oral gastric feeding tubes, and the use of nasal cannula oxygen at high flow rates.
2. Delay in the critical time to learn how to feed may result in the loss of rooting and sucking reflexes and contribute to the feeding problem.
3. The treatment of oropharyngeal hypersensitivity includes a program of desensitization of the infant's oral pharynx with positive stimulation and attempts to minimize negative stimuli. The latter implies replacement of nasogastric and orogastric feeding tubes with gastrostomy tubes and the

use of tracheostomy instead of continuing endotracheal intubation if mechanical ventilation needs to be continued.

- D. Swallowing disorders may also be observed after prolonged courses of mechanical ventilation.
1. These disorders may effect the three phases of swallowing: oral, pharyngeal, and esophageal.
 2. Swallowing disorders can be seen in association with congenital anomalies, such as micrognathia, choanal atresia, cleft lip and palate, tracheoesophageal fistulas, and laryngeal clefts. They can also be acquired and are seen in infants with severe laryngotracheomalacia, BPD, and neurologic insults that result in cerebral palsy.
 3. Assessment of swallow dysfunction includes a comprehensive history, physical examination, and evaluation of neurologic, pulmonary, and gastrointestinal status. Videofluoroscopy is the radiologic evaluation of choice to detect abnormalities in the different phases of swallowing and the risk of aspiration.
 4. Treatment depends on the signs, etiology, and feeding history and usually requires special therapy in five categories: positioning, oral sensory normalization, modification of food consistency, adaptation of feeding devices, and oral feeding exercises.
- E. Pathologic gastroesophageal reflux (GER) may be seen in infants who received mechanical ventilation, especially in those who develop BPD, neurologic insults resulting in cerebral palsy, and tracheomalacia or subglottic stenosis from prolonged endotracheal intubation.
1. The clinical presentation of pathologic GER includes the presence of frequent gastric residuals, episodes of vomiting, failure to thrive, and aspiration pneumonia.
 2. Medical management has included antacids, H₂ receptor antagonists, and proton pump inhibitors. These, however, have been linked to the development of NEC.
 3. In severe cases of GER that are refractory to medical management, Nissen fundoplication may be indicated.

Suggested Reading

- Adamkin DH. Feeding the preterm infant. In: Bhatia J, editor. Perinatal nutrition: optimizing infant health and development. New York, NY: Marcel Dekker; 2004. p. 1.
- Adamkin DH. Pragmatic approach to in-hospital nutrition in high risk neonates. *J Perinatol.* 2005;25(suppl):S7–S11.
- Adamkin DH. Nutrition Management of the Very Low Birthweight Infant. *NeoReviews.* 2006a;7(12):e602.
- Adamkin DH. Postdischarge nutritional therapy. *J Perinatol.* 2006b;26 suppl 1:S27–30.

- Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? *Semin Perinatal*. 2007;31:48–55.
- Ehrenkranz RA, Younes N, Lemons J, et al. Longitudinal growth of hospitalized very-low-birth-weight infants. *Pediatrics*. 1999;104:280–89.
- Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? *Pediatrics*. 2001;107:270–73.
- Ernst KD, Radmacher PG, Rafail ST, et al. Postnatal malnutrition of extremely low birthweight infants with catch-up growth postdischarge. *J perinatol*. 2003;23:447–82.
- Kleinman RE, editor. Nutritional needs of the preterm infant. *Pediatric nutrition handbook*. 5th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2004. p. 23–24.
- Kuscel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. (Cochrane Review) *The Cochrane Library* 2005.
- Leitch CA, Denne SC. Energy expenditure in the extremely low birth weight infant. *Clin Perinatol*. 2000;27:181.
- Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. *BMJ*. 1998;317:1481–87.
- O'Connor DL, Khan S, Welshuhn K, et al. Growth and nutrient intakes of human milk-fed preterm infants provided with extra energy and nutrients after hospital discharge. *Pediatrics*. 2008;121(4):766–76.
- Poindexter BB, Karn CA, Denne SC. Exogenous insulin reduces proteolysis and protein synthesis in extremely low birth weight infants. *J Pediatr*. 1998;132:948–53.
- Rigo J, Senterre J. Nutritional needs of premature infants: current issues. *J Pediatr*. 2006;149:S80–88.
- Stefano JL, Norman ME, Morales MC, et al. Decreased erythrocyte Na-K⁺-ATPase activity associated with cellular potassium loss in extremely-low-birth-weight infants with nonoliguric hyperkalemia. *J Pediatr*. 1993;122:276.
- Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very-low-birth-weight infant. *Clin Perinatol*. 2002;29:225–44.

Chapter 51

Surfactant Replacement Therapy

Fernando Moya and Maria-Cristina Javier

I. Introduction

- A. The administration of exogenous surfactant has been the standard of care for two decades for infants who have respiratory distress syndrome (RDS).
- B. It is considered one of the most significant breakthroughs in neonatology. Exogenous surfactant administration specifically prevents and treats surfactant deficiency and significantly changes the clinical course and outcome of infants with RDS.
- C. These infants have a surfactant lipid pool of less than 10 mg/kg compared to surfactant lipid pool sizes in term infants of around 100 mg/kg. Furthermore, preterm infants with RDS have a lower percent of saturated phosphatidylcholine species, less phosphatidylglycerol, and less surfactant-associated proteins in their pulmonary surfactant.

II. Structure and function of pulmonary surfactant

The main function of pulmonary surfactant is to diminish respiratory work by reducing the surface tension at the air–liquid interface in the alveolus. It also stabilizes the respiratory tracts, improves mucociliary transport, prevents the formation of edema, and contributes to lung defense against pathogens.

A. Synthesis and main phospholipids

- 1. Pulmonary surfactant is synthesized and secreted into the alveolar spaces by type II epithelial cells. Its composition is fairly similar in various mammalian species.
- 2. It is a macroaggregate of about 90% highly organized lipids (about 85% are phospholipids) and 10% surfactant-specific proteins.

F. Moya, MD (✉) • M.-C. Javier, MD
Department of Neonatology, New Hanover Regional Medical Center, Coastal Carolina
Neonatology, PLLC, 2131 South 17th Street, Wilmington, NC 28401, USA
e-mail: Fernando.Moya@ccneo.net

3. Dipalmitoyl phosphatidylcholine (DPPC) is the most abundant lipid (75%) and is the main surface active species. Its structure is suited to form a stable monolayer generating the low surface tension required to prevent alveolar collapse at end-expiration. DPPC at physiologic temperature is in a crystalline gel, but because of its rigid structure, it is unable to adsorb and spread quickly.
4. Spreading is facilitated by the presence of surfactant-associated proteins (see below). Also, the presence of unsaturated phospholipids gives the structure fluidity to facilitate adsorption and distribution in the air–fluid interface.

B. Surfactant-associated proteins

1. There are four surfactant-associated proteins. The hydrophobic surfactant proteins, SP-B and SP-C, promote the rapid adsorption of phospholipids at the air–liquid interface and account for the sustained low surface-tension activity after dynamic compression. The contribution of SP-B and SP-C to both structural organization and functional durability is essential given that:
 - a. Lethal respiratory failure occurs after birth in newborn infants with SP-B deficiency resulting from alterations in the SP-B gene located in chromosome 2. Many such mutations have now been identified, which are usually inherited as an autosomal recessive condition.
 - b. The amount of SP-B and SP-C is decreased in the surfactant of infants with RDS and those evolving to or with established bronchopulmonary dysplasia (BPD).
 - c. Dominantly inherited mutations in the SP-C gene, which lead to inadequate SP-C synthesis or the accumulation of an abnormal SP-C precursor, have been described recently. However, they present clinically as a form of chronic interstitial lung disease in childhood.
2. The hydrophilic surfactant proteins SP-A and SP-D are complex glycoproteins that belong to the collectin family, a subgroup of the lectin superfamily.
 - a. These proteins play a lesser role in the surface tension lowering ability of pulmonary surfactant and its metabolism; however, they have an important role in the innate lung defense barrier against pathogenic organisms.
 - b. Genetic mutations of their genes have been described in humans, but they do not present with respiratory failure in the newborn period.

III. Exogenous surfactants

- A. For exogenous surfactant to be effective it should be able to adsorb into the lung air–fluid interface very rapidly once administered, thereby achieving

very low surface tension during expiration, as well as to re-spread efficiently during inspiration.

- B. Administration of exogenous surfactant to a surfactant-deficient preterm human newborn decreases the minimum pressure required to open the lung, increases the functional residual capacity and maximal lung volumes, and prevents lung collapse at low pressures.
- C. Types of exogenous surfactants.
 - 1. There are several exogenous surfactants currently available and a few more are under development.
 - 2. Although all exogenous surfactants are not alike, they are generally grouped into two categories depending upon whether they are derived from animal lungs or are of synthetic origin. Moreover, synthetic surfactants are now further subdivided depending upon whether they do or do not contain peptide mimics (Table 51.1).
- D. Animal-derived surfactant preparations are purified and extracted with organic solvents from either lung minces or lung lavage from either bovine or porcine sources.
 - 1. Their phospholipid concentration varies but is usually at or above 80% and all contain variable amounts of SP-B and SP-C, but not SP-A or SP-D.
 - 2. There are several significant differences in the composition of these preparations that may bear an effect on their short-term clinical performance. For instance, the concentration of SP-B is substantially lower in the lung-minced preparation compared to surfactants derived from lung lavage extracts. The porcine-derived surfactant contains the most phospholipids per unit volume of all surfactants.
- E. Synthetic surfactant preparations are composed of one or two phospholipids, usually DPPC and phosphatidylglycerol.
 - 1. Colfosceril palmitate (Exosurf[®]) was for almost 20 years the most widely used synthetic, protein-free surfactant. However, it is no longer available.
 - 2. Recently, a new generation of synthetic surfactants containing phospholipids and chemically or genetically engineered peptides that mimic SP-B or SP-C has been developed. Lucinactant (Surfaxin[®]) is composed of DPPC, palmitoyl-oleoyl phosphatidylglycerol (POPG), and palmitic acid. It also includes a synthetic 21 amino acid peptide (sinapultide) consisting of repeats of lysine and leucine, whose spatial structure and function resembles that of SP-B. It is not yet approved by the FDA.
 - 3. Another synthetic surfactant composed of DPPC, POPG, palmitic acid, and recombinant SP-C obtained by expression in a prokaryotic system has been recently developed. However, to date there are no published experiences involving neonates.

Table 51.1 The different surfactants currently available or under development

Generic name (commercial name)	Origin	Characteristics	Protein	First dose mg/kg (ml/kg)	Additional doses, maximal number mg/kg (ml/kg)
Animal derived surfactants					
Calfactant (Infasurf [®])	Calf lung lavage	Chloroform/methanol extracted	SP-B/SP-C	105 (3)	Max two doses at least q12h, 105 (3)
(BLES [®])	Cow lung lavage	Chloroform/methanol extracted	SP-B/SP-C	135 (5)	Max two doses at least q6h, 135 (5)
Beractant (Survanta [®])	Minced bovine lung extract	Enriched with DPPC, tripalmitoyl-glycerol and free fatty acids	SP-C/low SP-B content	100 (4)	Max three doses at least q6h, 100 (4)
Poractant (Curosurf [®])	Minced porcine lung extract	No neutral lipids (liquid-gel chromatography)	SP-B/SP-C	100–200 (1.25–2.5)	Max two doses at least q12h, 100 (1.25)
Synthetic surfactants with no peptides					
Colfosceril palmitate (Exosurf [®]) ^a	Synthetic	DPPC + hexadecanol (9%) + tyloxapol (6%)	0	67 (5)	Max two doses at least q12h, 67 (5)
Synthetic surfactants with peptides					
Lucinactant (Surfaxin [®])	Synthetic	DPPC/POPG 3/1 + free fatty acids (palmitic acid)	Sinapultide (3%)	175 (5.8)	Max three doses at least q6h, 175 (5.8)

^aNo longer available

IV. Surfactant responses

The clinical response to exogenous surfactant administration can be divided into three stages:

- A. Stage one: acute treatment response (occurs within minutes). The initial response results from the biophysical properties of surfactant and depends on rapid distribution of surfactant to distal lung areas. An improvement in oxygenation is usually the first clinical response to surfactant instillation. Because of this continuous monitoring of oxygen saturation during and after administration is essential. Moreover, the improvement in gas exchange after administration may be quite rapid and ventilation pressure and volume must be adjusted by observing chest expansion, monitoring tidal volume, and intermittently measuring blood gases. This acute response to surfactant appears to be faster when preparations that contain more SP-B are administered.
- B. Stage two: sustained response to the initial surfactant dose (hours post administration).
 1. It results from improving lung mechanics and recycling of surfactant components from the air spaces into type II cells, where the lipids are, in part, diverted into lamellar bodies for resecretion.
 2. Thus, surfactant treatment quickly increases the metabolic pool for endogenous metabolism. In general, recycling is more efficient in the preterm lung, where recycling rates as high as 80–90% have been measured (Jobe 2006).
 3. This, however, does not guarantee that only one dose of surfactant will be effective. In fact, about 20–30% of infants receiving surfactant may remain on mechanical ventilation with $\text{FiO}_2 > 30\text{--}40\%$ several hours after the first dose and are eligible for retreatment.
 4. A poor response to a properly administered initial surfactant dose, especially if the infant was exposed to antenatal steroids, is often associated with asphyxia, infection, or a variable degree of lung hypoplasia.
 5. There is no proven benefit to giving more than two additional doses.
- C. Stage three: continued response to the initial surfactant dose (days or perhaps weeks post-administration). It is attributed to the long half-life of both endogenous and exogenous surfactant components within the airspaces—about 3 days for infants with RDS. The net balance of a slow synthesis, secretion, metabolism, and clearance of surfactant and its components allow the infant with RDS to accumulate a large amount of surfactant over many days.

V. Efficacy of surfactant use for RDS

- A. Overall efficacy of surfactant.
 1. Surfactant administration for prevention or treatment of RDS is very effective as shown in many randomized trials and meta-analyses.

Of note, most placebo-controlled trials of surfactant use were conducted before widespread use of antenatal steroids (most trials reported <40% exposure).

2. Historically, surfactant was used either in a prophylactic or in a rescue approach.
 - a. The former involved administration within the first 30–60 min after birth regardless of respiratory status and usually to very preterm newborns at high risk for RDS. This resulted in administration of surfactant to variable proportions of infants that would not have ever developed RDS.
 - b. Rescue (treatment) administration was done in infants with established signs of respiratory failure and usually radiographic confirmation of RDS. In this approach, infants that were intubated and requiring $\text{FiO}_2 > 30\text{--}35\%$ were deemed eligible for treatment, which often occurred several hours after birth.
 - c. Several trials also assessed the benefit of an early rescue strategy (early administration to symptomatic infants before 2 h of life) compared to classic rescue treatment.
 - d. Over time, these distinctions have become more elusive, especially more recently with the advent of widespread use of continuous positive airway pressure (CPAP) as the initial form of respiratory support, even in extremely preterm neonates. These points notwithstanding, a large body of data from randomized trials has demonstrated:
 - (1) A consistent reduction of about 40% in the odds of neonatal death after surfactant administration of either animal-derived or synthetic products given either for prophylaxis or rescue treatment compared to placebo.
 - (2) Both types of surfactants and administration strategies have also resulted in a significant 30–50% reduction in the odds of pulmonary air leaks (pneumothorax, interstitial emphysema).
3. In spite of widespread use of surfactant the incidence of BPD has not decreased, although it has been suggested that the severity of this condition has been ameliorated. Likewise, the occurrence of other complications of prematurity has not been significantly reduced by surfactant therapy.
4. Overviews of prophylactic versus rescue administration of surfactant from controlled trials demonstrated that prophylaxis resulted in reductions in mortality and pneumothorax compared to waiting for significant RDS to develop. However, these comparisons are more of historical importance, given how much the approach to surfactant has evolved and the many improvements in other aspects of perinatal care that can impact fetal development and outcomes.
5. More recently, surfactant has been administered using the INSURE (INTubate-SURfactant-Extubate) approach, in which surfactant is given

after elective endotracheal intubation, followed by a variable period of mechanical ventilation. This approach is generally well tolerated and results mainly in decreases in the need for mechanical ventilation, but no overall decreases of mortality or BPD have yet been demonstrated. Moreover, this approach may be more suited for infants above 25–26 weeks of gestation not requiring intubation during delivery room resuscitation. For those infants at high risk for RDS, in which an endotracheal tube has already been placed, there is probably very little additional morbidity from giving surfactant.

6. Several recent randomized trials (COIN, SUPPORT, CURPAP trials) have examined whether using CPAP versus the more traditional approach of intubation and giving surfactant in the delivery room reduces BPD and mortality among very preterm infants between 24 and <29 weeks.
 - a. These trials have been quite different in design and inclusion/exclusion criteria than previous surfactant trials. Therefore, it is much harder to draw generalizable conclusions from their results.
 - b. They only permitted surfactant administration at much higher FiO_2 than what been previously studied and recommended (over 50% FiO_2 in SUPPORT and 60% FiO_2 in COIN trial).
 - c. In the SUPPORT trial, the ventilation criteria for extubation, albeit different among the two groups, was much higher than levels previously used for surfactant redosing. This notwithstanding, the investigators suggested that early use of CPAP in the delivery room reduces the need for mechanical ventilation and the proportion of infants getting surfactant. Moreover, they reported a trend towards less BPD among those infants getting initial CPAP and, in post hoc analysis, less mortality of infants between 24 and <26 weeks; however, no specific data on what proportion of these infants ultimately received surfactant was reported.
 - d. To the contrary, delaying surfactant administration may also increase the risks of pneumothorax and overall air leaks. Moreover, given that in both, the COIN and SUPPORT trials, more than 50% of infants <26 weeks randomized to CPAP were intubated early, it seems reasonable to consider giving surfactant to them once the endotracheal tube has been placed and they need supplemental oxygen.

VI. Head-to-head comparisons of surfactants

- A. Many randomized trials have compared the efficacy of animal-derived surfactant to synthetic surfactants. Previous meta-analyses grouped surfactants by their origin, i.e., natural versus synthetic; however, given the enormous differences in composition and mode of administration, better comparison data are derived from head-to-head comparisons of surfactants. Even though it is not the purpose of this chapter to enumerate all of these comparisons conducted to date, below are some conclusions from these data.

- B. Administration of a surfactant preparation that contains surfactant proteins or their synthetic mimics generally leads to a more rapid onset of action as determined by weaning of FiO_2 and ventilatory support. Moreover, the onset of action is faster among animal-derived surfactants that contain more SP-B compared to those with lesser amounts of this protein.
- C. The aforementioned effect is probably related to the lower occurrence of pneumothorax when surfactants containing surfactant proteins are compared to those without any protein.
- D. In spite of these findings, updated data from these head-to-head comparison trials have not demonstrated any overall differences in mortality or BPD as a result of using different surfactants. The sole exception to this is the trial comparing poractant to pumactant.
- E. Two randomized clinical trials compared the peptide-containing synthetic surfactant lucinactant to colfosceril palmitate, beractant and poractant. They reported more survivors without BPD with lucinactant compared to colfosceril. However, there was no significant difference in survival without BPD between the three protein-containing surfactants. Moreover, there were no differences in other common complications of prematurity. Colfosceril is no longer available.

VII. Administration and practical concerns

- A. All animal-derived surfactants require warming to room temperature before administration. The formulation of lucinactant studied to date requires a warming step to 44°C in a heating block for 15 min before administration. Surfactant treatment should be accomplished after clinical ascertainment of proper endotracheal tube placement. Performing a chest radiograph prior to giving surfactant is only indicated when conditions such as pneumothorax need to be ruled out.
- B. Manufacturer's recommended doses are indicated in Table 51.1.
 - 1. Dosing is usually divided in two aliquots (although some manufacturers recommend four aliquots) and administered via a 5-French catheter passed into the endotracheal tube while the infant is ventilated to ensure maximal dispersion.
 - 2. It is best to avoid disconnecting the infant from the ventilatory circuit during administration in order to provide continuous positive end expiratory pressure to avoid losing lung volume. As per manufacturers' recommendations, the infant's head and torso should be rotated $30\text{--}45^\circ$ to the right for the first half-dose and to the left for the remaining aliquot. Poractant can also be administered in one rapid bolus without positioning, interruption of mechanical ventilation, or bagging. Some studies have reported safe administration using a dual-lumen endotracheal tube.
 - 3. Transient oxygen desaturation and mild bradycardia are frequently observed during administration and may require adjustment of the ventilatory settings and FiO_2 or temporary interruption of surfactant

administration. Occasionally endotracheal tube obstruction and reflux of surfactant are seen.

4. Although some head-to-head comparisons of surfactants have revealed a few differences in these complications between the various preparations studied, most side effects were transient and did not lead to significant morbidity. Moreover, these differences did not seem to be related to the volume of administration and are more common with repeated dosing.

C. Administration of surfactant without intubation may be in the horizon.

1. One of the ways in which this has been accomplished is by performing laryngoscopy and giving surfactant using either a nasogastric or another tube.
2. In addition, small, nonrandomized studies have attempted to administer surfactant via aerosol delivery.
3. These have been generally either single-center experiences or experiences in relatively larger, more stable preterm infants. More clinical data will be needed before these approaches can be adopted widely.

VIII. Use of surfactant for other neonatal indications

Many experimental and clinical studies have suggested that the pathogenesis of various neonatal respiratory disorders, such as meconium aspiration syndrome (MAS), pneumonia/sepsis, BPD, and congenital diaphragmatic hernia (CDH), includes either inactivation of surfactant or deficient synthesis of its components. Therefore, these disorders have been thought as potential targets for surfactant therapy. However, the clinical evidence to support this is sketchy and sometimes not properly evaluated in randomized trials.

A. Meconium aspiration syndrome

1. Several randomized trials have shown that the administration of surfactant to infants with MAS improves oxygenation and reduces the need for ECMO.
2. There are certain caveats, though:
 - a. Most infants entered in these trials were quite sick and on high levels of support as determined by the oxygenation index.
 - b. Some studies have used a larger dose of phospholipid than that used for RDS.
 - c. The beneficial effects of surfactant may not appear until more than one dose is administered.
 - d. Primarily animal-derived surfactants have been studied when surfactant was given as a bolus, although a small randomized trial assessed the efficacy and safety of bronchoalveolar lavage with a dilute peptide-containing synthetic surfactant (lucinactant) in severe MAS.
 - e. A recent meta-analysis of all trials confirmed these benefits.

B. Pneumonia and sepsis

1. Administration of animal-derived surfactant can improve oxygenation and decrease ventilatory requirements in preterm and term infants with respiratory failure associated with group B streptococcal sepsis.
2. There is presently insufficient evidence to determine whether surfactant treatment improves the long-term outcome of septic newborns with respiratory failure and its use cannot be recommended for this purpose.

C. Bronchopulmonary dysplasia

1. Data from animal studies and infants evolving to or with established BPD have demonstrated quantitative and qualitative abnormalities of surfactant.
2. Observational studies showed transient improvements in oxygenation and ventilatory support among infants with BPD given exogenous surfactant. These have been confirmed in two recent placebo-controlled randomized trials using either lucinactant or calfactant. However, no major impact on prevention of BPD has been reported to date. Therefore, administration of surfactant for infants evolving to BPD remains under study and cannot be widely recommended.

D. Congenital diaphragmatic hernia

1. Data from animal models of CDH and some infants with this condition have implicated a quantitative deficiency of surfactant components in its pathogenesis.
2. To date, there are no randomized trials examining this important clinical question. However, evidence from large observational databases does not support its routine use in the management of these infants regardless of whether they are term or preterm.

Suggested Reading

- Blanco O, Perez-Gil J. Biochemical and pharmacological differences between preparations of exogenous natural surfactant used to treat Respiratory Distress Syndrome: role of the different components in an efficient pulmonary surfactant. *Eur J Pharmacol.* 2007;568:1–15.
- El Shahed AI, Dargaville P, Ohlsson A, Soll RF. Surfactant for meconium aspiration syndrome in full term/near term infants. *Cochrane Database Syst Rev.* 2007;(3):CD002054.
- Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf[®] combined with nCPAP to prevent RDS in preterm neonates. *J Aerosol Med Pulm Drug Deliv.* 2010;23:303–9.
- Griese M. Pulmonary surfactant in health and human lung diseases: state of the art. *Eur Respir J.* 1999;13:1455–76.
- Jobe AH. Pharmacology review: why surfactant works for respiratory distress syndrome. *NeoReviews.* 2006;7:e95–106.
- Kribs A, Hartel C, Kattner E, et al. Surfactant without intubation in preterm infants with respiratory distress: first multi-center data. *Klin Paediatr.* 2010;222:13–7.

- Lally KP, Lally PA, Langham MR, Hirschl R, et al. Congenital Diaphragmatic Hernia Study Group. Surfactant does not improve survival rate in preterm infants with congenital diaphragmatic hernia. *J Pediatr Surg*. 2004;39:829–33.
- Laughon M, Bose C, Moya F, et al. A pilot randomized, controlled trial of later treatment with a peptide-containing, synthetic surfactant for the prevention of bronchopulmonary dysplasia. *Pediatrics*. 2009;123(1):89–96.
- Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358:700–8.
- Moya F, Gadzinowski J, Bancalari E, et al. A multicenter, randomized, masked comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. *Pediatrics*. 2005;115:1018–29.
- Moya F, Javier MC. Myth. All surfactants are alike. *Semin Fetal Neonatal Med*. 2011;16(5):269–74.
- Moya F, Maturana A. Animal-derived surfactants versus past and current synthetic surfactants: current status. *Clin Perinatol*. 2007;34:145–77.
- Notter RH. Lung surfactant: basic science and clinical applications. New York: Marcel Dekker Inc.; 2000.
- Perez-Gil J, Keough KM. Interfacial properties of surfactant proteins. *Biochim Biophys Acta*. 1998;1408:203–17.
- Pfister RH, Soll R, Wiswell TE. Protein-containing synthetic surfactant versus protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. *Cochrane Database Syst Rev*. 2009;(4):CD006180.
- Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;(4):CD006069.
- Sandri F, Plavka R, Ancore G, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. *Pediatrics*. 2010;125:e1402–9.
- Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. *Cochrane Database of Syst Rev* 2009;2:Art. No.: CD007836. doi:10.1002/14651858.CD007836.
- Sinha SK, Lacaze-Masmonteil T, Valls I, Soler A, et al. A randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics*. 2005;115:1030–8.
- Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;(4):CD003063.
- SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Network. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362:1970–8.
- Whitsett JA, Weaver TE. Hydrophobic surfactant proteins in lung function and disease. *N Engl J Med*. 2002;347:2141–8.
- Wright JR. Immunoregulatory functions of surfactant proteins. *Nat Rev Immunol*. 2005;5:58–68.

Chapter 52

Pharmacologic Agents

Varsha Bhatt-Mehta and Steven M. Donn

I. Pharmacologic agents (other than antimicrobials and surfactant) that may be used commonly during respiratory support include analgesics, bronchodilators, corticosteroids, diuretics, inotropes, neuromuscular blocking agents, sedatives, and pulmonary vasodilators. The following is a list of frequently used drugs with recommended indications, doses, and relevant side effects. These do differ according to various sources. Individual and institutional practices, therefore, may also be different.

II. Analgesics (Chap. 54).

A. Acetaminophen

1. Indication: treatment of mild to moderate pain, postoperative pain, and fever. It is an analgesic and antipyretic with no anti-inflammatory properties. Well absorbed orally and, less predictably, rectally. Conjugated in the liver and excreted in urine. Half-life is about 4 h.
2. Dose: intravenous (IV), rectal, or oral administration.

IV: Loading dose: 20 mg/kg followed by 7.5–10 mg/kg/dose every 12 h (maximum daily dose 30 mg/kg/day).

Oral: 10–15 mg/kg/dose every 6–8 h; maximum daily dose: 60 mg/kg/day.

Rectal: Loading dose: 30 mg/kg; then 20 mg/kg/dose every 6–8 h; maximum daily dose: 90 mg/kg/day.

V. Bhatt-Mehta, MS(CRDSA), PharmD, FCCP (✉)
Department of Pediatrics, C.S. Mott Children's Hospital, College of Pharmacy,
University of Michigan, 1540 East Medical Center Drive, Ann Arbor, MI 48109-4225, USA
e-mail: varsham@umich.edu

S.M. Donn, MD, FAAP
Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA

3. Relevant side effects: edema (peripheral), hypertension, hypervolemia, hypotension, tachycardia, atelectasis, abnormal breath sounds, dyspnea, hypoxia, pleural effusion, pulmonary edema, stridor, wheezing, Muscle spasms, pain in extremity.

B. Fentanyl

1. Indication: short-acting opioid analgesic used for perioperative pain relief. The short action is more a function of rapid redistribution into fat and muscle depots because the elimination half-life is actually quite long—4 h in the adult and probably twice as long in the newborn. Morphine may be a better alternative for sustained pain relief.
2. Dose: IV, intramuscular (IM), or intranasal administration. Fentanyl at anesthetic doses will provide good pain relief for about 1 h in the newborn.

Anesthetic doses: 5–15 mcg/kg IV.

Analgesic doses: 1–5 mcg/kg/dose IM/IV repeated 30–60 min later as needed. Continuous IV infusions of 1–3 mcg/kg/h are effective for a period, but tolerance develops rapidly and, if the infusion is continued for more than 4–5 days, serious signs of withdrawal may follow discontinuation.

Intranasal: Children ≥ 10 kg: 1.5 mcg/kg once (maximum: 100 mcg/dose); reported range: 1–2 mcg/kg. Some studies that used an initial dose of 1.5 mcg/kg allowed for additional incremental doses of 0.3–0.5 mcg/kg to be administered every 5 min, not to exceed a total dose of 3 mcg/kg depending upon pain type and severity.

3. Relevant side effects: respiratory drive will usually be abolished and assisted ventilation will be needed. Respiratory depression may also occur unexpectedly, presumably following redistribution from fat or muscle depots.

C. Morphine

1. Indication: best studied opiate analgesic for use in the newborn period. For relief of severe pain, such as necrotizing enterocolitis or following surgery.
2. Dose: IV, IM, and oral. IM and IV doses are the same. The absorption of morphine by the oral route is poor and should not be used for treatment of acute pain.

Pain: For severe pain, an IV loading dose of 100–150 mcg/kg followed by an infusion of 10–20 mcg/kg/h is probably required. For mild to moderate pain in the nonventilated baby, an IV dose of 100 mcg/kg once every 6–12 h may be sufficient depending upon post-natal age.

Procedures: For elective intubation, IV morphine at 50–100 mcg/kg at least two and preferably 5 min before intubation is recommended.

3. Relevant side effects: respiratory depression, urinary retention, and diminished peristalsis can occur with normal doses, and hypotension, bradycardia, and seizures can occur with overdose.

III. Bronchodilators and respiratory stimulants

A. Aminophylline/theophylline

1. Indication: Treatment of apnea of prematurity (AOP), though caffeine is easier and safer to use. Therapeutic range for treatment of AOP is 7–12 mcg/mL and for treatment of bronchospasm in older infants is 10–20 mcg/mL. Aminophylline is the IV form of theophylline which is administered orally. When using aminophylline, the dose should be increased by 20% to account for the salt form.
2. Dose: Based on aminophylline. A loading dose of 6 mg/kg followed by 2–4 mg/kg IV every 8–12 h based on postnatal age will generally abolish AOP in most babies. Treatment can be continued with oral theophylline.

Plasma concentrations must be measured to ensure therapeutic range and to avoid toxicity since the therapeutic index is narrow.

3. Relevant side effects: common side effects include tachycardia, hyperactivity, and gastrointestinal disturbances. Toxicity occurs at plasma levels exceeding therapeutic range and is manifested by excessive tachycardia, nausea and vomiting, and convulsions.

B. Caffeine

1. Indications: drug of choice for the treatment of AOP for many clinicians. More recently, caffeine has been shown to reduce the incidence and severity of bronchopulmonary dysplasia and is used as early as day 1 in intubated infants. It has a wider therapeutic index compared to theophylline, is well absorbed orally, and only needs to be given once daily. It is most commonly given as caffeine *citrate*, 1 mg of which is equivalent to 0.5 mg of caffeine *base*.
2. Dose: Caffeine is usually prescribed as the citrate salt. Administer a loading dose of 20 mg/kg of caffeine citrate orally or IV, followed by a once daily dose of 5 mg/kg. Both the loading dose and the maintenance dose can be safely doubled if necessary. Therapeutic concentrations of caffeine range from 10–20 mg/L. Toxicity occurs at concentrations exceeding 50 mg/L. Since the therapeutic index is wide, routine monitoring of plasma concentration is not necessary. It should be measured, however, if toxicity or therapeutic ineffectiveness is suspected at common doses.

3. Relevant side effects: common side effects include tachycardia, hyperactivity, and gastrointestinal disturbances. Toxicity is manifested by tachycardia, nausea and vomiting, and convulsions.

C. Albuterol (USA)/Salbutamol (UK)

1. Indications: Selective β_2 adrenergic agonist, bronchodilator. Adult half-life is 6 h. Well absorbed orally. However, increased hyperactivity is an undesirable side effect that is more prominent with oral dosing. In clinical practice, oral use is avoided to the extent possible.
2. Dose: Albuterol/Salbutamol may be used by inhalation or orally. Inhaled drug may be delivered by nebulization or metered dose inhaler. For nebulization, 1.25 mg/dose, nebulized 3–4 times daily, is a commonly used regimen. Metered dose inhalers deliver 90mcg/spray. 1–2 puffs administered into the ventilator circuit is the most frequently reported dose.
3. Relevant side effects: tachycardia, tremor, irritability (even at normal doses). Evidence to support its routine use in BPD is lacking.

D. Ipratropium

1. Indication: anticholinergic bronchodilator, synergistic with β -agonists. Ipratropium is a synthetic derivative of atropine.
2. Dose: Ipratropium is used by inhalation only. Inhaled drug may be delivered by nebulization or metered dose inhaler. When used by nebulization, 25 mcg/kg/dose, three times a day, is commonly used. Metered dose inhaler provides 21 mcg/actuation. Common dose: 1–2 actuations (puffs) every 8 h.
3. Relevant side effects: tachycardia, tremor, irritability (even at normal doses). These side effects may be exacerbated when used concomitantly with albuterol. Evidence to support its routine use in BPD is lacking.

E. Epinephrine

1. Indications: Direct acting sympathomimetic agent with a more marked effect on β -adrenoreceptors than on α -adrenoreceptors. Used for treatment of stridor following extubation or from any other cause or bronchodilation.
2. Dose: used by inhalation nebulization: Racemic epinephrine (2.25% solution): 0.05 mL/kg (maximum dose: 0.5 mL) diluted in 2 mL NS; others have reported use of 0.5 mL as a fixed dose for all patients; use lower end of dosing range for younger infants.
3. Relevant side effects: tachycardia, tremor, irritability, even at normal doses. These side effects may be exacerbated when used concomitantly with albuterol or ipratropium.

IV. Diuretics

A. Bumetanide

1. Indications: Loop diuretic more potent than furosemide and with similar mechanism of action. Half-life in newborns is 2–6 h.
2. Dose: IV, IM, or oral routes of administration can be used. The dose is the same for any route. 5–50 mcg/kg q6h IV, IM, or PO.
3. Relevant side effects: causes very significant urinary losses of sodium, chloride, calcium, and bicarbonate. Overuse can cause significant contraction alkalosis with blood pH exceeding 7.55. Evidence to support its routine use in bronchopulmonary dysplasia (BPD) is lacking.

B. Chlorothiazide

1. Indications: Benzothiazide diuretic usually combined with spironolactone for additional diuretic effect, although spironolactone is a weak diuretic. Spironolactone has the added advantage of conserving potassium during chronic diuretic use. This is probably the safest diuretic combination for long-term control of fluid retention in congestive cardiac failure and BPD in the newborn, although it can result in considerable urinary calcium losses.
2. Dose: IV and oral routes of administration may be used.

IV: For acutely ill infants who are *nil per oral* 10–20 mg/kg/day in two divided doses is used by IV injection.

Oral: The usual oral dose is 20–40 mg/kg/day (usually combined with 1–2 mg/kg of spironolactone) administered orally in two divided doses.

3. Relevant side effects: contraction alkalosis and electrolyte disturbances are extremely common and should be closely monitored during initial stages of treatment. Potassium supplements are not usually needed if both drugs are given together. However, if BOTH potassium supplements and spironolactone are used together serum potassium should be monitored closely. Evidence to support its routine use in BPD is lacking.

C. Furosemide (USA)/frusemide (UK)

1. Indications: A loop diuretic which inhibits active chloride reabsorption in the loop of Henle and the distal tubule resulting in reduced passive sodium reabsorption and diuresis. Causes significant urinary losses of sodium, chloride, potassium, bicarbonate, and calcium. Stimulates renal synthesis of prostaglandin E₂ and may increase the risk of patent ductus arteriosus. It is ototoxic and enhances the ototoxic effect of aminoglycosides. Chronic use may cause nephrolithiasis or nephrocalcinosis. There is some evidence for a direct effect improving short-term lung function in BPD if nebulised furosemide is given.

2. Dose: IV, oral, and nebulization are acceptable routes of administration.

IV: For acute treatment of fluid overload, 1 mg/kg IV given once or twice a day (or more frequently as indicated by the clinical condition). While there is no defined maximum dose suggested in the literature, excessive use may lead to acute contraction alkalosis, severe electrolyte abnormalities and hypotension. In renal failure, a single 5 mg/kg dose may help to reduce ischemic tubular damage.

Oral: 2–4 mg/kg orally two or more times a day for symptomatic control of fluid overload is commonly used.

Nebulization: although not a common route of administration, furosemide may be used by nebulization in BPD, 1 mg/kg of the IV preparation diluted in 2 mL of 0.9% saline and given by nebulizer once every 6 h may improve pulmonary compliance without affecting renal function.

3. Relevant side effects: electrolyte disturbances are extremely common especially with higher doses. Patients on long-term treatment should receive potassium chloride to prevent hypokalemia. May lead to nephrolithiasis, nephrocalcinosis, and osteopenia with chronic use. Evidence to support its routine use in BPD is lacking.

D. Spironolactone

1. Indication: Competitive inhibitor of aldosterone resulting in potassium sparing diuresis. Usually used in combination with a thiazide diuretic such as chlorothiazide, since spironolactone itself is a weak diuretic.
2. Dose: 1 mg/kg orally twice daily. Up to 4 mg/kg/24 h may be safely used, if necessary, but should be closely monitored.
3. Relevant side effects: hyperkalemia is the most common side effect. Serum potassium should be closely monitored. Evidence to support its routine use in BPD is lacking.

V. Inotropes (see also hydrocortisone) (Chap. 49)

A. Dobutamine

1. Indications: A synthetic inotropic catecholamine with primarily β_1 adrenergic activity, but in high doses it exhibits both α and β_2 effects. It stimulates myocardial contractility and increases cardiac output. Because it has less effect than dopamine on systemic vascular resistance, it has less effect in raising blood pressure (however, effectively increasing tissue perfusion is likely to be a more important goal than reaching a specific blood pressure target). Tachycardia may occur at high dosage and tissue ischemia may occur if the infusion infiltrates.
2. Dose: IV route only.

Start with a dose of 5 mcg/kg/min by continuous IV infusion, increasing to 10–20 mcg/kg/min if needed. Do not give bicarbonate or other alkaline

solutions through the same catheter, as this will inactivate dobutamine.
Never give this through an arterial catheter.

3. Relevant side effects: tachycardia is most common.

B. Dopamine

1. Indication: A naturally occurring catecholamine precursor of noradrenaline.
2. Dose: IV route only. At low doses (2–5 mcg/kg/min), dopamine causes coronary, mesenteric, and renal vasodilation (though it is questionable whether this is of clinical significance), while at high doses (6–20 mcg/kg/min) it causes vasoconstriction. It is best given via a central vein, and it is inactivated by bicarbonate or other alkaline solutions. *Never give this through an arterial catheter.*
3. Relevant side effects: hypertension, tachycardia, and irregular heart beat are most common.

C. Milrinone

1. Indications: A selective phosphodiesterase inhibitor, which works by increasing cyclic AMP concentration. It acts as an inotrope but also has some vasodilator action resulting in increased cardiac output. Used only for short periods as long-term oral use in adults was associated with an unexplained increase in mortality. The volume of distribution in infancy is much higher than in adults; thus, it is necessary to use a loading dose.
2. Dose: IV route only. Term neonates: Loading dose: 50–75 mcg/kg administered over 15–30 min followed by a continuous infusion of 0.5 mcg/kg/min; titrate to effect; range: 0.25–0.75 mcg/kg/min has been used.
3. Relevant side effects: ventricular arrhythmias including ventricular ectopic activity, ventricular tachycardia, and ventricular fibrillation, supraventricular arrhythmias, hypotension, angina/chest pain (rare), and torsade de pointes (rare). Hypokalemia, Thrombocytopenia, and abnormal liver function tests have also been reported with prolonged use of milrinone.

D. Noradrenaline (norepinephrine)

1. Indications: Sympathomimetic vasoconstrictor. Mainly causes increased cardiac contractility, increased heart rate, and increased myocardial oxygen consumption (β_1 stimulation). High dose infusion can also increase peripheral vasoconstriction (α_1 stimulation), resulting in significantly increased cardiac afterload and a decrease in cardiac output.
2. Dose: IV route of administration only. In acutely hypotensive infants, the starting dose is 0.1 mcg/kg/min of noradrenaline base via a central vein. This may be increased to a maximum of 1.5 mcg/kg/min as long as extremity perfusion and urine output are carefully monitored. *Never give this through an arterial catheter.*

3. Relevant side effects: respiratory distress, cardiac arrhythmias, palpitations, bradycardia, tachycardia, hypertension, chest pain, pallor Local: organ ischemia (from vasoconstriction of renal and mesenteric arteries), ischemic necrosis, and sloughing of superficial tissue after extravasation.

E. Adrenaline (epinephrine)

1. Indications: Direct acting sympathomimetic agent with a more marked effect on β -adrenoceptors than on α -adrenoceptors. Used in the treatment of cardiac arrest secondary to electromechanical dissociation or as an infusion to treat serious hypotension (though this may cause significant vasoconstriction and is likely to affect renal perfusion).
2. Dose: IV, endotracheal (ET), intraosseous (IO), intracardiac

Dosing: Neonatal

Cardiopulmonary resuscitation (NRP, 2010):

IV: 0.01–0.03 mg/kg (0.1–0.3 mL/kg of 1:10,000 solution) every 3–5 min as needed.

ET: (Note: IV route preferred) ET: 0.05–0.1 mg/kg (0.5–1 mL/kg of 1:10,000 solution) every 3–5 min until IV access established or return of spontaneous circulation.

Postresuscitation infusion to maintain cardiac output or stabilize: Continuous IV/IO infusion rate: 0.1–1 mcg/kg/min; doses <0.3 mcg/kg/min generally produce β -adrenergic effects and higher doses (>0.3 mcg/kg/min) generally produce alpha-adrenergic vasoconstriction; titrate dosage to desired effect.

Inotropic support: Continuous IV infusion rate: 0.1–1 mcg/kg/min; titrate dosage to desired effect.

Hypotension/shock, fluid-resistant: Continuous IV infusion: 0.1–1 mcg/kg/min; doses up to 2 mcg/kg/min may rarely be necessary, may be combined with inotropic support.

3. Relevant side effects: cardiac arrhythmias, palpitations, bradycardia, tachycardia, hypertension

VI. Skeletal muscle relaxants

A. Atracurium

1. Indication: Atracurium besylate is a nondepolarizing competitive antagonist of acetylcholine at the motor end plate of voluntary muscle. Its effect can be reversed by anticholinesterases such as neostigmine. A major advantage is that it *does not depend on either renal or hepatic function for degradation*.
2. Dose: IV route of administration only.

A single dose of 0.25–0.4 mg/kg IV will cause complete paralysis lasting about 20 min. For sustained paralysis, this dose must be followed by repeat IV doses of 0.25 mg/kg as needed to maintain paralysis or a continuous IV infusion of 400 mcg/kg/h may be used for sustained paralysis.

3. Relevant side effects: cardiovascular effects are minimal and transient. Occasionally, wheezing or increased bronchial secretions may be seen.

B. *Cis*-atracurium

1. Indications: *Cis*-atracurium besylate is a nondepolarizing competitive antagonist of acetylcholine at the motor end plate of voluntary muscle. It is an isomer of atracurium. Its effect can be reversed by anticholinesterases such as neostigmine. A major advantage is that it *does not depend on either renal or hepatic function for degradation*.
2. Dosing: For IV route only.

IV: Initial: 0.1 mg/kg followed by maintenance dose of 0.03 mg/kg as needed to maintain neuromuscular blockade.

Continuous infusion: 1–4 mcg/kg/min (0.06–0.24 mg/kg/h).

3. Relevant side effects: cardiovascular effects are minimal and transient. Occasionally, wheezing or increased bronchial secretions may be seen.

C. Pancuronium

1. Indications: a nondepolarizing competitive antagonist of acetylcholine similar to atracurium. This effect extends to autonomic cholinergic receptors as well as those in skeletal muscle. It is partially metabolized in the liver and excreted by the kidneys and has a variable duration of action in the newborn of the order of 2–4 h. Its effects can be reversed with atropine and neostigmine.
2. Dose: IV route of administration only. 0.1 mg/kg to produce complete paralysis within a couple of minutes and adjust repeat doses of 0.05–0.15 mg/kg based on the duration of the observed effect may be given. Dose must be adjusted for renal failure. While continuous infusions of 0.02–0.04 mg/kg/h are occasionally used, in neonates the half-life is prolonged, eliminating the need for continuous infusions in most cases.
3. Relevant side effects: tachycardia, hypotension, wheezing, bronchospasm; skeletal muscle atrophy with prolonged use.

D. Suxamethonium (Succinylcholine)

1. Indications: acts as a depolarizing competitive agonist of acetylcholine. Brief muscle contraction is seen before paralysis occurs. These contractions are reported as painful by adults. Used to produce skeletal muscle relaxation in procedures of short duration, such as ET intubation or endoscopic exams.

2. Dose: *IV route is preferred*. IM route is used for nonemergent intubation where IV access is not available.

IV: 1–2 mg/kg/dose.

IM: 2 mg/kg/dose if no IV access available.

These doses will provide paralysis for 5–10 min. A dose of atropine (15 mcg/kg) is often given before any dose of suxamethonium and should certainly be given before a second dose.

3. Relevant side effects: because of the risk of malignant hyperthermia, use of continuous infusion is *not* recommended. Rare reports of acute rhabdomyolysis, with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death have been reported in children with muscle myopathies. Avoid use in patients with serum potassium >5.5 mEq/L.

E. Vecuronium

1. Indication: A nondepolarizing competitive antagonist of acetylcholine similar to pancuronium. Metabolised by the liver and excreted in urine. Vecuronium, unlike pancuronium, is cardiostable, lacking side effects such as tachycardia, hypertension, or hypotension. Vecuronium is more cardiostable than atracurium even at high doses. Vecuronium is preferred in patients with renal failure.
2. Dose: IV route of administration only.

IV: 0.1 mg/kg/dose. These doses will cause complete paralysis lasting 1–2 h. Maintenance doses of 0.03–0.15 mg/kg/dose every 1–2 h may be used as needed. May be administered as a continuous infusion at 1–1.5 mcg/kg/min (0.06–0.09 mg/kg/h).

3. Relevant side effects: arrhythmias, tachycardia, hypotension, hypertension, respiratory insufficiency, bronchospasm, apnea.

VII. Steroids

A. Dexamethasone

1. Indications: Potent glucocorticoid similar to betamethasone. It is used in similar fashion to promote fetal lung maturation, although there is some evidence to suggest it is less effective. It appears to be beneficial in treating severe BPD, but the ideal treatment regimen has not yet been established and high-dose treatment in the neonatal period appears to be associated with an increased incidence of cerebral palsy in survivors. Treatment of babies with dexamethasone causes increased protein catabolism, which affects growth. Hypercalcuria, hypertension, hyperglycemia, gastrointestinal hemorrhage, left ventricular outflow tract obstruction, hypokalemia, and increased risk of infection are other well-recognized adverse effects.

2. Dose: IV route preferred.
 - a. Traditional regimen: 0.25 mg/kg base orally or IV twice daily for 7 days followed if necessary by a 9-day course of tapering dosage.
 - b. Durand regimen: 100 mcg/kg orally or IV twice daily for 3 days then 50 mcg/kg twice daily for 4 days.
 - c. DART Trial regimen: 60 mcg/kg orally or IV twice daily on days 1–3, then 40 mcg/kg twice daily on days 4–6, 20 mcg/kg twice daily days 7–8, and 8 mcg/kg on days 9 and 10.
 - d. Postintubation airway edema: IV: 0.25 mg/kg/dose given 2–4 h prior to scheduled extubation then every 8 h for a total of three doses; others have used 0.5 mg/kg/dose every 8 h for three doses with last dose administered 1 h prior to scheduled extubation; range: 0.25–0.5 mg/kg/dose for 1–3 doses; maximum dose: 1.5 mg/kg/day. A longer duration of therapy may be needed with more severe cases.
3. Relevant side effects: gastrointestinal perforation, hyperglycemia, leukocytosis, hypertension. Hypothalamic–pituitary–adrenal axis suppression, sodium and water retention, growth suppression, glucose intolerance, hypokalemia, and gastrointestinal bleeding. Prolonged use may cause muscle weakness, bone mineral density reduction, and fractures.

B. Hydrocortisone

1. Glucocorticoid with minimal mineralocorticoid effect. Primarily used for physiologic replacement, but can also be useful in the treatment of acute hypotension.
2. Dose: IV and oral administration possible.

BPD prevention (preterm neonates with prenatal inflammatory exposure): PNA \leq 48 h: IV: 1 mg/kg/day divided every 12 h for 9 or 12 days, followed by 0.5 mg/kg/day divided every 12 h for 3 days; dose may be needed during acute illness. Doses of 2 mg/kg IV followed by 1 mg/kg 8–12 hourly are effective in treating hypotension. The AAP suggests that for neonates with prenatal inflammatory exposure, low-dose hydrocortisone therapy (1 mg/kg/day) during the first 2 weeks of life may improve survival without BPD and without adverse neurodevelopmental outcomes.

Hypoglycemia (refractory to continuous glucose infusion of >12 – 15 mg/kg/min): oral or IV: 5 mg/kg/day divided every 8–12 h or 1–2 mg/kg/dose every 6 h.

3. Relevant side effects: Gastrointestinal perforation, hyperglycemia, leukocytosis. Hypothalamic–pituitary–adrenal axis suppression, sodium and water retention, growth suppression, glucose intolerance, hypokalemia, and gastrointestinal bleeding. Prolonged use may cause muscle weakness, bone mineral density reduction, and fractures.

VIII. Sedatives (Chap. 54)

A. Chloral hydrate

1. Indications: sedative, well absorbed orally, metabolized in the liver and excreted in urine. Acts within 30 min, half-life of active metabolite is 36 h.
2. Dose: Oral or rectal route of administration. 45 mg/kg as a single dose. Higher doses (75 mg/kg) have been used for sedation for imaging but can produce hypoxemia. 30 mg/kg orally every 6 h can be helpful in babies with cerebral irritability. Drug accumulation may occur if used for more than 48 h.
3. Relevant side effects: respiratory depression, apnea, gastric irritation.

B. Lorazepam

1. Indication: Benzodiazepine anxiolytic and sedative. Metabolized in the liver and excreted in urine. Does not have any active metabolites. Longer acting than midazolam.
2. Dose: IV and oral routes of administration. Usual: 0.05 mg/kg/dose (maximum dose: 2 mg/dose) every 4–8 h; range: 0.02–0.1 mg/kg.
3. Relevant side effects: risk of propylene glycol toxicity. Monitor closely if using for prolonged periods of time or at high doses. Bradycardia, circulatory collapse, hypertension or hypotension, respiratory depression, apnea.

C. Midazolam

1. Indication: Benzodiazepine anxiolytic and sedative. Metabolized in the liver and excreted in urine. 1-hydroxy midazolam is an active metabolite. Drug and metabolite accumulation may occur with repeated doses. IV infusion or rapid bolus dosage has been reported to produce seizures in some babies.
2. Dose: IV, intramuscular (IM), and intranasal routes. 0.15 mg/kg IV, IM, or intranasally produces rapid sedation and can be used for induction of anesthesia. (*Midazolam does not relieve pain*).

Procedures: 0.1 mg/kg IV may be used for sedation prior to elective intubation (together with morphine for pain relief and atracurium for paralysis).

Sedation: 0.1 mg/kg loading dose infused over 15–30 min is followed by 10–60 mcg/kg/h IV infusion can be used for sedation of ventilated babies for 3–4 days.

3. Relevant side effects: cardiac arrest, hypotension, bradycardia.

IX. Pulmonary vasodilators

A. Nitric oxide (Chap. 55)

1. Indications: Acts on receptors within the muscle of blood vessel walls to produce vasodilation. Rapidly inactivated by hemoglobin producing

methemoglobin. Half-life less than 5 s. Vasodilator effect is therefore limited to the pulmonary circulation. Methemoglobin levels need to be monitored and kept below 2.5%.

2. Dose: Given as a gas by inhalation. In babies and those more than ≥ 34 weeks' gestation start at 20 parts per million (ppm). If this produces a rise in postductal PaO₂ of at least 20 torr (3 kPa) with no alteration in ventilator settings, reduce the concentration to the lowest compatible with a sustained response, usually 5 ppm. Stop treatment quickly if there is no response. Once started on nitric oxide, babies are extremely sensitive to any interruption in supply.
3. Relevant side effects: methemoglobinemia, pulmonary edema, pulmonary hemorrhage, toxicity from nitrogen dioxide formation.

B. Tolazoline (no longer available in the USA)

1. Indication: Vasodilator affecting both pulmonary and systemic vessels with an adrenergic blocking effect. Seems to work best when severe acidosis has been corrected. Cardiotoxic in high dosage and accumulates in renal failure.
2. Dose: 1–2 mg/kg given as a rapid bolus ideally into a *peripheral or central vein that drains into the superior vena cava*. If a positive response is seen, an infusion of 200 mcg/kg/h may be helpful. 200 mcg/kg given as an intratracheal bolus instillation has anecdotally been reported to be effective.
3. Relevant side effects: May result in severe systemic hypotension.

C. Sildenafil

1. Indications: Treatment of pulmonary hypertension (*off label use*).
2. Dose: Oral administration only.

Pulmonary hypertension: Initial dose: 0.5 mg/kg/dose every 8 h; doses are increased by 0.25 mg/kg/dose every 24 h if needed and if tolerated to maximum of 2 mg/kg/dose every 6–8 h.

3. Relevant side effects: cerebrovascular hemorrhage, edema, flushing, hypotension, pulmonary hemorrhage, tachycardia, ventricular arrhythmia, dyspnea, epistaxis, nasal congestion, rhinitis, rhinorrhea, sinusitis.

Suggested Reading

Neonatal Formulary. 6th ed. Oxford: Wiley Blackwell Publications, BMJ Books; 2011.
Takemoto CK, Hodding JH, Kraus DM, editors. Pediatric dosage handbook. 17th ed. Hudson, OH: American Pharmaceutical Association. Lexi-Comp, Inc.; 2010.

Chapter 53

Automatic Control of Oxygen Delivery

Nelson Claire and Eduardo Bancalari

I. Introduction and rationale

- A. Supplemental oxygen is required to maintain adequate oxygenation in most preterm infants with respiratory insufficiency and this can be prolonged. Frequently, the inspired oxygen is excessive resulting in hyperoxemia and an increased risk of ROP, BPD, and oxidative damage to the CNS and other organs.
- B. Arterial oxygen saturation is monitored continuously by pulse oximetry (SpO_2) and the fraction of inspired oxygen (FiO_2) is titrated to maintain a clinically intended range of SpO_2 in what can be described as an open loop system.
- C. Because of their respiratory instability and limitations in intensive care staffing, SpO_2 is kept within the intended range only around 50% of the time. This is dependent on postnatal age, infant-to-nurse ratio and workload.
- D. Systems of automatic FiO_2 control have been developed to improve maintenance of SpO_2 within a desired range and reduce periods of extreme hypoxemia, hyperoxemia, and exposure to high FiO_2 .

II. General description

- A. Systems of automatic FiO_2 control consist of a pulse oximeter, the gas delivery device (i.e., ventilator, CPAP, hood, or cannula) and the closed

N. Claire, MSc, PhD (✉)

Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, 1611 NW 12th Avenue, Central Building, 740, Miami, FL 33136, USA
e-mail: NClaire@miami.edu

E. Bancalari, MD

Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, 1611 NW 12th Avenue, Central building, Room 740, Miami, FL 33136, USA

loop control algorithm that continuously reads SpO_2 and determines the FiO_2 to be delivered.

- B. In general, algorithms of automatic FiO_2 control a target SpO_2 range or level and continuous adjustments of FiO_2 are inversely related to the difference between the measured and target SpO_2 . The timing, magnitude and frequency of adjustment determine the automatic response to gradual or rapid changes in SpO_2 .

III. Effects on oxygenation, oxygen exposure, and workload

- A. Clinical studies have shown automatic FiO_2 control improves the maintenance of SpO_2 within a target range compared to manual adjustments made by the clinical staff and comparable or better than a fully dedicated nurse.
- B. Automatic FiO_2 control can achieve substantial reductions in time with hyperoxemia and wean the inspired O_2 more consistently than manual control.
- C. Infants with frequent hypoxemia episodes are a significant challenge to the staff. In these infants, automatic FiO_2 control does not prevent the episodes but reduces their severity and duration. On the other hand, because automatic FiO_2 control weans FiO_2 more consistently than manual control, episodes just below the target range can be more frequent during automatic control (Fig. 53.1).
- D. Studies under routine clinical conditions showed considerably fewer manual adjustments necessary during automatic FiO_2 control. This reduction in workload was not accompanied by unwanted effects.

IV. Practical considerations and possible limitations

- A. Advantages of automatic FiO_2 control are relative to the efficacy of manual control in maintaining the intended SpO_2 . Hence, advantages of automatic FiO_2 may be greater in centers with staff limitations and large workload as well as among infants who present with frequent fluctuations in oxygenation.
- B. During routine care SpO_2 is commonly kept above the target range to avoid hypoxemia. A more effective weaning during automatic FiO_2 control to avoid hyperoxemia can result in more mild episodes of low SpO_2 . This reflects important physiologic effects of specific target ranges of SpO_2 . Whether these mild episodes have adverse consequences or offset the benefits of less hyperoxemia is not known.
- C. Automatic FiO_2 control can lead to reduced attentiveness and mask conditions that can otherwise result in severe hypoxemia. Because in some situations increasing FiO_2 may not be the most appropriate response, automatic warnings when higher FiO_2 is consistently needed to keep SpO_2 in range should be utilized to prompt the clinician's intervention. On the other hand, the automatic response can avert more severe hypoxemia until corrective measures are taken. Adequate monitoring of ventilation to recognize these conditions should be part of standard staff training and more particularly prior to the use of automatic FiO_2 control.

because manual FiO_2 control does not adapt to the continuous changing needs of preterm infants. This can be overcome but it would require considerable resources.

- B. Automatic FiO_2 control is an alternative to improve the maintenance of oxygenation and minimize exposure to extreme SpO_2 ranges and inspired O_2 . Short term studies have shown its feasibility and efficacy in achieving these goals.
- C. Maintaining a balance between the avoidance of hypoxemia without inducing hyperoxemia or increased oxygen exposure may improve survival, long-term respiratory, ophthalmic, and neurodevelopmental outcome in preterm infants. The extent to which automatic FiO_2 control can achieve this balance and improve these competing outcomes can only be determined by large clinical trials.

Suggested Reading

- Claire N, Bancalari E, D'Ugard C, Nelin L, Stein M, Ramanathan R, Hernandez R, Donn SM, Becker M, Bachman T. Multicenter crossover study of automated adjustment of inspired oxygen in mechanically ventilated preterm infants. *Pediatrics*. 2011;127:e76–83.
- Claire N, D'Ugard C, Bancalari E. Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation: a pilot clinical trial. *J Pediatr*. 2009;155:640–5.
- Claire N, Gerhardt T, Everett R, Musante G, Herrera C, Bancalari E. Closed-loop controlled inspired oxygen concentration for mechanically ventilated very low birth weight infants with frequent episodes of hypoxemia. *Pediatrics*. 2001;107:1120–4.
- Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, Cole CH. AVIOx study group. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics*. 2006;118:1574–82.
- Sink DW, Hope SA, Hagadorn JI. Nurse:patient ratio and achievement of oxygen saturation goals in premature infants. *Arch Dis Child Fetal Neonatal Ed*. 2011;96:F93–8.
- Urschitz MS, Horn W, Seyfang A, Hallenberger A, Herberts T, Miksch S, Popow C, Müller-Hansen I, Poets CF. Automatic control of the inspired oxygen fraction in preterm infants: a randomized crossover trial. *Am J Respir Crit Care Med*. 2004;170:1095–100.

Chapter 54

Sedation and Analgesia

Elaine M. Boyle and Neil McIntosh

I. Definitions

- A. Stress: a normal adaptive physiologic response generated by certain external stimuli. There may be no conscious awareness and thus no associated suffering.
- B. Distress: suffering or maladaptive behavior resulting from emotional effects of excessive stress that may be affected by past experience. In newborn infants, an observer is only able to infer this from behavioral cues.
- C. Pain: a particular form of distress, easily described by adults in terms of a hurtful experience or emotion.
- D. Nociception: behavioral and physiologic effects of a noxious stimulus independent of associated psychological and emotional responses. This most accurately describes neonatal “pain”.

II. Potential causes of pain or distress (Table 54.1)

- A. Invasive interventions
- B. Repeated invasive or non-invasive interventions
- C. Pathological conditions
- D. Environmental factors

III. Indicators of pain in the newborn

- A. Behavioral responses
 - 1. Audible cry (not applicable to intubated infants)

E.M. Boyle, MBChB, MSc, PhD (✉)
Department of Health Sciences, University of Leicester, 22-28 Princess Road West,
Leicester, Leicestershire LE1 6TP, UK
e-mail: eb124@le.ac.uk

N. McIntosh, DSc(Med), FRCP, FRCPE, FRCPCH
University of Edinburgh, Child Life and Health,
20 Sylvan Place, Edinburgh, Scotland EH9 2BA, UK
e-mail: neil.mcintosh@ed.ac.uk

Table 54.1 Causes of possible distress or pain in the newborn infant

1.	Ventilation
	Endotracheal intubation
	Presence of endotracheal tube and fixation devices
	Distress of mandatory ventilator breaths
	Restriction of movement and posture required for ventilation
2.	Repeated acute invasive procedures
	Arterial/venous/capillary blood sampling
	Venipuncture
	Endotracheal suctioning
3.	Minor surgical procedures
	Chest drain insertion
	Suprapubic aspiration of urine
	Lumbar puncture
	Ventricular tap
4.	Coexisting infective/inflammatory conditions
	Necrotizing enterocolitis
	Osteomyelitis
	Meningitis
	Generalized sepsis
5.	Complications of necessary procedures
	Cellulitis or abscess from infiltrated intravenous infusion
	Cutaneous probe burns
6.	Post-operative following major surgery
	Patent ductus arteriosus ligation
	Laser therapy for retinopathy of prematurity
	Bowel repair/resection following perforation or necrotizing enterocolitis
7.	Disruptive handling
	Positioning for radiographs
	Ultrasound scans
	General caregiving procedures
8.	Environmental stress
	Excessive light, either daylight or from phototherapy
	Excessive and distressing sound from monitor alarms, incubator doors, etc.
	Unfamiliar tactile environment without physical containment
9.	Physiologic stress
	Drug withdrawal
	Respiratory insufficiency/air hunger
	Nutritional, i.e., hunger
10.	Repeated relatively noninvasive procedures
	Transcutaneous gas monitoring probe changes
	Bolus feeds
	Drug administration
	Blood pressure measurement using inflatable cuffs

2. Facial expression (characteristic brow bulge, eye squeeze, naso-labial furrowing, mouth or lip purse, tongue tautness, chin quiver)
3. Withdrawal of affected limb or extremity
4. Changes in tone (general increase in activity, flexion of trunk and extremities, “fetal” posturing or arching, leg extension, finger splaying or hand clenching)
5. Sleep cycle disturbances accompanied by twitches, jerks, irregular breathing, grimaces or whimpers
6. Self-regulatory or comforting behaviors such as lowered behavioral state, postural changes, hand-to-mouth movements, sucking, or an expression of “focused alertness”

B. Physiologic

1. Increase in heart rate
2. Increase in blood pressure
3. Changes in respiratory rate
4. Changes in oxygenation
5. Fluctuations in skin color and temperature
6. Increase in palmar sweating (applicable after 37 weeks’ gestation)
7. Fluctuation in cerebral circulation and intracranial pressure
8. Gastrointestinal disturbances

IV. Assessment of pain or distress

A. General

1. Acute distress: based largely on behavioral or physiologic measures
2. Sub-acute distress: difficult to assess
 - a. Increased activity or “thrashing”
 - b. “Frozen” or motionless; withdrawn behavior

B. Specific

1. Clinical tools
 - a. Approximately 40 pain assessment tools available
 - b. Designed for use in clinical practice and research
 - c. Uni-dimensional or multidimensional
 - d. Examples (Table 54.2)
 - (1) Neonatal facial coding system
 - (2) Premature Infant Pain Profile
2. Research tools
 - a. Neuro-endocrine markers (e.g., cortisol, adrenaline, endorphins)
 - b. Metabolic-biochemical markers of catabolism (e.g., 3-methylhistidine)
 - c. Computerized analysis of physiologic data (e.g., changes in vagal tone, heart rate variability)

Table 54.2 Validated pain assessment scores for use in the newborn
1. Neonatal facial coding system (NFCSS) (Grunau and Craig 1987)

Facial response to heel-stick (i.e., acute and obvious pain) in different sleep-wake states. 10 features scored:

1. Brow bulge
2. Eye squeeze
3. Nasolabial furrow
4. Open lips
5. Vertical stretch mouth
6. Horizontal mouth
7. Lip purse
8. Tongue taut
9. Chin quiver
10. Tone exaggeration with startling or twitching

2. Premature infant pain profile (PIPP) (Stevens et al. 1996)

Process	Indicator	0	1	2	3	Score
Chart	Gestational age	≥36 weeks	32–35 weeks	28–31 weeks	<28 weeks	
Observe infant 15 s	Behavioural state	Active/awake Eyes open Facial movements	Quiet/awake Eyes open No facial movements	Active/asleep Eyes closed Facial movements	Quiet/asleep Eyes closed No facial movements	
Observe baseline; Heart rate..... SaO ₂	Heart rate Max..... SaO ₂ Min.....	0–4 beats/min increase 0–2.4% decrease None	5–14 beats/min increase 2.5–4.9% decrease Minimum	15–24 beats/min increase 5.0–7.4% decrease Moderate	25 beats/min or more increase 7.5% or more increase decrease Maximum	
Observe infant 30 s	Brow bulge Eye squeeze Nasolabial furrow	0–9% of time None 0–9% of time	10–39% of time Minimum 10–39% of time	40–69% of time Moderate 40–69% of time	70% of time or more Maximum 70% of time or more	
		None 0–9% of time	Minimum 10–39% of time	Moderate 40–69% of time	Maximum 70% of time or more	
		None 0–9% of time	Minimum 10–39% of time	Moderate 40–69% of time	Maximum 70% of time or more	

C. Pain assessment in ventilated or preterm infants

1. Behavioral responses are influenced by:
 - a. Degree of prematurity
 - b. Behavioral state (level of arousal)
 - c. Severity of illness
2. Cry is inaudible in intubated infants
3. Presence and fixation of endotracheal tube or non-invasive respiratory support devices alter facial expression
4. Monitoring and infusions change posture and restrict limb movement
5. Agitation or distress may be secondary to a process other than pain (e.g., respiratory insufficiency, drug withdrawal)
6. Habituation to pain or stress can occur

V. Non-pharmacologic interventions to prevent or reduce distress

A. Environmental

1. Control of light, temperature, and noise
2. Positioning, swaddling, minimal handling, containment
3. Positive touch, especially from parents

B. Behavioral: non-nutritive sucking

VI. Indications for pharmacologic management (Table 54.3)

- A. Observed behavioral and physiologic indicators of pain
- B. Anticipated procedural pain
- C. Asynchronous respiration interfering with ventilation
- D. Physiologic instability
- E. Failure of non-pharmacological interventions
- F. Distress associated with therapeutic hypothermia

VII. Pharmacologic interventions

A. Sucrose

1. Reduces behavioral responses to minor painful stimuli
2. Effects mediated by sweet taste
3. Only effective by oral route
4. Administer 2 min before procedure onto anterior tongue
5. Dose 0.05–0.5 mL sucrose 24%

B. Opioids

1. Reduce endocrine stress response
2. Reduce asynchronous respiration during ventilation (sedative effect)

Table 54.3 Use of analgesics and sedatives

Relatively minor procedures		
Procedure	Comment	Suggested approach
Heel prick	Affected by technique <i>and heel perfusion</i> EMLA is not effective	Automated lancets Pacifier/sucrose Avoid EMLA
Vein and arterial puncture		Pacifier/sucrose/ Topical anesthetic cream
Suprapubic urine aspiration		Pacifier/sucrose/ Topical anesthetic cream
Insertion of nasogastric tube	Discomfort with gag Vagal reflex	Insert slowly
Moderate/major procedures		
Procedure	Issues	Suggested approach
Lumbar puncture	Pain or skin puncture Stress of restraint	Pacifier/sucrose/topical anesthetic Correct positioning/technique Lidocaine infiltration of skin (avoid deep infiltration as risk of spinal injection) Consider opiate if ventilated
Chest drain insertion	Skin, muscle, pleural pain	Opiate slow bolus Lidocaine infiltration of skin and pleura— if time
Chest drain (in situ)		Opiate infusion if distressed
Ventricular tap	Pain of skin penetration	Topical anesthetic Consider opiate if ventilated
Elective intubation	Discomfort Gag/cough Vagal reflex	Opiate slow bolus with muscle relaxant
Laser/cryotherapy for retinopathy of prematurity	Discomfort/restraint Eyeball pain Vagal reflex <i>(Reestablish full monitoring before procedure)</i>	Ventilation Oxybuprocaine eye drops Topical anesthesia Opiate loading and infusion or inhaled anesthetic before intubation Muscle relaxant to abolish eye and other movements (after intubation) Atropine to prevent bradycardia (intubation, oculocardiac reflex)
Persistent/ongoing pain or distress		
	Issues	Suggested approach
Mechanical ventilation/neonatal intensive care	Presence of ETT and fixation devices Ventilation asynchrony Possible associated muscle relaxation	Optimize environmental factors Minimal handling Opiate infusion if obvious distress continues despite environmental and behavioural interventions
Therapeutic hypothermia for hypoxic ischemic encephalopathy	Usually term infants May be distress associated with cooling and shivering	Opiate infusion if distressed

3. Side effects

- a. Hypotension
- b. Respiratory depression
- c. Bronchospasm (theoretical)
- d. Decreased gut motility
- e. Chest wall rigidity (caused by stimulation of excitatory pathways in spinal cord; give boluses slowly)
- f. Withdrawal. Wean gradually if given for more than 5 days. Late rebound respiratory depression may occur from enterohepatic recirculation or release from fat stores

4. Specific agents

a. Morphine sulfate

- (1) Most widely used
- (2) Loading dose: 100–150 mcg/kg over 30 min
- (3) Maintenance: 10–20 mcg/kg/h
- (4) Dose for procedures: 50–100 mcg/kg over 30 min (higher doses may be needed)

b. Fentanyl

- (1) Synthetic opioid
- (2) Less histaminic effect than morphine
- (3) Tends to reduce pulmonary vascular resistance; may be preferable in PPHN, CDH, CLD, during ECMO
- (4) Large doses tolerated without adverse hemodynamic effects
- (5) Chest wall rigidity if given quickly
- (6) Loading dose: 0.5–4 mcg/kg over 30 min
- (7) Maintenance: 1–5 mcg/kg/h

5. Weaning

a. Depends on duration of treatment

b. Signs of withdrawal

- (1) Irritability
- (2) Inconsolable cry
- (3) Tachypnea
- (4) Jitteriness
- (5) Hypertonicity
- (6) Vomiting
- (7) Diarrhea
- (8) Sweating
- (9) Skin abrasions
- (10) Seizures
- (11) Yawning
- (12) Nasal stuffiness

(13) Sneezing

(14) Hiccups

- c. If treatment <48 h, stop without weaning
- d. If 3–7 days, reduce by 25–50% of maintenance dose daily
- e. If >7 days, reduce by 10–20% every 6–12 h as tolerated

C. Non-opioids

1. Acetaminophen (Paracetamol)

- a. Analgesic and antipyretic. Analgesia is additive to opioid effect
- b. Newborn relatively resistant to liver toxicity with no respiratory or cardiovascular depression, G-I irritation, or platelet dysfunction
- c. Useful in inflammatory and postoperative pain
- d. Dose

(1) Oral: 10–15 mg/kg q4-6h (may load with 24 mg/kg)

(2) Rectal: 20–25 mg/kg q4-6h (maximum daily dose 60 mg/kg)

(3) Intravenous: 7.5 mg/kg q6h (maximum daily dose 30 mg/kg)

2. Ibuprofen

- a. Non-steroidal anti-inflammatory agent
- b. Recommended dose as for ductal closure (no information available regarding analgesic dose): 10 mg IV/PO, then 5–10 mg q24h

D. Sedative drugs

- 1. Adjuvant to analgesic, but no pain relief
- 2. May be useful for long-term ventilation
- 3. Useful when tolerance to opioids develops
- 4. May allow weaning from opioids
- 5. May help older babies with severe BPD
- 6. Specific agents
 - a. Midazolam
 - (1) Benzodiazepine
 - (2) Routine use not recommended
 - (3) IV bolus for procedures, infusion for background sedation, if required
 - (4) Respiratory depression and hypotension; synergistic with opioids
 - (5) Withdrawal (agitation, abnormal movements, depressed sensorium) after prolonged use
 - (6) Loading dose: 0.1 mg/kg over 15–30 min
 - (7) Maintenance: 10–60 mcg/kg/h

b. Chloral hydrate

- (1) Causes generalized neuronal depression
- (2) Does not appear to produce respiratory depression
- (3) May be given orally or rectally
- (4) Onset of action in 30 min., duration 2–4 h
- (5) Slow development of tolerance
- (6) Dose
 - (a) Sedation: 25–50 mg/kg
 - (b) Hypnosis: Up to 100 mg/kg

E. Local anesthetics

1. Lidocaine

- a. Infiltrate skin/mucous membranes
- b. Up to 3 mg/kg (0.3mL/kg of 1% solution)
- c. With overdosage, systemic absorption may cause sedation, cardiac arrhythmia, cardiac arrest, seizures

2. Topical anesthetic creams

- a. Apply pea-sized amount with occlusive dressing 30–60 min before procedure
- b. EMLA (eutectic mixture of Lidocaine and Prilocaine as 5% cream)
 - (1) Vasoconstrictor
 - (2) Minimal risk of methemoglobinemia
- c. Amethocaine (Ametop): less vasoconstriction

VIII. Assessing adequacy of analgesia and sedation

- A. Challenging because of lack of self-reporting
- B. Need for analgesia and sedation varies among infants
- C. Difficult to differentiate between analgesic and sedative effects of opiates
- D. Research is ongoing into emerging non-invasive technologies (e.g., near infra-red spectroscopy) that may provide more objective measures.

IX. Experience of pain in the newborn

A. The preterm infant

1. Increased sensitivity to pain (reduced pain threshold)
2. Hypersensitivity develops as a result of repeated tissue damage
3. Hyperalgesia
 - a. More pain neurotransmitters in spinal cord
 - b. Delayed expression of inhibitory neurotransmitters

4. Higher plasma concentrations of analgesic and anesthetic agents required to obtain clinical effects, compared to older age groups
5. Non-painful handling (e.g., care giving) may activate pain pathways and be experienced as pain

B. Sources of pain and distress

1. Painful conditions

a. Necrotizing enterocolitis

- (1) Low threshold for analgesia
- (2) Intravenous treatment needed
- (3) Non-steroidal anti-inflammatory agents contraindicated (G-I side effects)

b. Meningitis/osteomyelitis

- (1) Consider morphine if distressed
- (2) Acetaminophen/paracetamol to relieve pain, fever

2. Ventilation

- (1) Use environmental and behavioral measures and synchronized ventilation
- (2) Routine use of opiates not recommended for ventilation
- (3) Beware of hypotension with morphine use in extremely preterm infants

3. Medical/surgical procedures (Table 54.3)

C. Short-term consequences of pain and inadequate analgesia

1. Acute pain

- a. Physiologic and behavioral changes (Section “Potential Causes of Pain or Distress” steps A and B) to limit the duration of “protest” against painful experience
- b. These involve great energy expenditure

2. Continuing (i.e., chronic) pain: the body re-orientes its behavioral and physiologic expression of pain to conserve energy and expresses “despair”

- a. Passivity
- b. Little or no body movement
- c. Expressionless face
- d. Decreased variability in heart rate and respiration
- e. Decreased oxygen consumption

X. Clinical implications of pain or inadequate analgesia

- A. Responses to pain may be extreme enough to have an adverse effect on clinical state. Evidence from research:

1. Short term consequences

- a. Frequent invasive procedures soon after birth in the extremely immature infant may contribute to physiologic instability.
- b. Cardiac surgery causes extreme metabolic responses. Clinical outcome can be improved by analgesia—reduced incidence of post-operative sepsis, metabolic acidosis, disseminated intravascular coagulation, and death.
- c. Circumcision without analgesia in term boys causes increased irritability, decreased attentiveness and orientation, poor regulation of behavioral state and motor patterns, altered sleep and feeding patterns lasting for up to 7 days.
- d. Babies born at 28 weeks' gestation, compared to those born at 32 weeks' gestation, show reduced behavioral and increased cardiovascular responsiveness at 4 weeks of age. The magnitude of the changes correlates with the total number of invasive procedures experienced.

2. Long-term consequences

- a. Neonatal circumcision results in increased behavioral responses to vaccination at 4–6 months, which can be attenuated by the use of anesthetics.
- b. Stressful conditions at birth are associated with an increased cortisol response to vaccination at 4–6 months.
- c. Increased behavioral reactivity to heelstick sampling in term newborns correlates with increased distress to immunizations at 6 months.
- d. Former preterm infants showed increased somatization at 4½ years. The strongest predictor was duration of neonatal intensive care.

B. Therapeutic interventions and outcome

1. Analgesia

- a. Acute physiologic and behavioral changes can be attenuated with opioid analgesia.
- b. Routine use of morphine analgesia in preterm infants does not reduce the risk of intraventricular hemorrhage (IVH).

2. Individualized developmental care

- a. Aims to minimize stress and pain and support neurobehavioral development.
- b. Has been suggested to reduce the incidence of IVH and lead to improved developmental outcomes but further investigation is required to clarify potential benefits of developmental care.

Suggested Reading

- Anand KJS, Hall RW, Desai N, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet*. 2004;363:1673–82.
- Grunau RV, Johnston CC, Craig KD. Neonatal facial and cry responses to invasive and non-invasive procedures. *Pain*. 1990;42:295–305.
- Johnston CC, Fernandes AM, Campbell-Yeo M. Pain in neonates is different. *Pain*. 2011;152(3 Suppl):S65–73.
- Johnston CC, Stevens B, Craig KD. Developmental changes in pain expression in premature, full-term, two and four month old infants. *Pain*. 1993;52:201–8.
- Stevens B, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2010; 20(1):CD001069.
- Stevens BJ, Pillai Riddell RR, Oberlander TE, Gibbins S. Assessment of pain in neonates and infants. In: Anand KJS, Stevens BJ, McGrath PJ, editors. *Pain in neonates and infants, Pain Research and Clinical Management Series*. 3rd ed. Amsterdam: Elsevier Science Publishers BV; 2007. p. 67–90.
- Taddio A. Evidence for systemic morphine and fentanyl analgesia. In: Anand KJS, Stevens BJ, McGrath PJ, editors. *Pain in neonates and infants, Pain Research and Clinical Management Series*. 3rd ed. Amsterdam: Elsevier Science Publishers BV; 2007. p. 141–54.
- Grunau RV, Craig KD. Pain expression in neonates: facial action and cry. *Pain*. 1987;28(3):395–410.
- Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. *Clin J Pain* 1996;12(1):13–22.

Chapter 55

Inhaled Nitric Oxide Therapy

John P. Kinsella

I. Introduction

- A. Inhaled nitric oxide (iNO) therapy for the treatment of newborns with hypoxemic respiratory failure and pulmonary hypertension has dramatically changed management strategies for this critically ill population.
- B. iNO therapy causes potent, selective, and sustained pulmonary vasodilation and improves oxygenation in term newborns with severe hypoxemic respiratory failure and persistent pulmonary hypertension.
- C. Multicenter randomized clinical studies have demonstrated that iNO therapy reduces the need for extracorporeal membrane oxygenation (ECMO) treatment in term neonates with hypoxemic respiratory failure.
- D. The potential role of iNO in the preterm newborn is currently controversial and its use remains investigational in this population.

II. Rationale for iNO therapy

- A. The physiologic rationale for inhaled nitric oxide (iNO) therapy in the treatment of neonatal hypoxemic respiratory failure is based upon its ability to achieve potent and sustained pulmonary vasodilation without decreasing systemic vascular tone.
- B. Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome associated with diverse neonatal cardiac and pulmonary disorders that are characterized by high pulmonary vascular resistance (PVR) causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and/or foramen ovale (Chap. 64).
- C. Extrapulmonary shunting from high PVR in severe PPHN of the newborn can cause critical hypoxemia, which is poorly responsive to inspired oxygen or pharmacologic vasodilation.

J.P. Kinsella, MD (✉)
Children's Hospital of Colorado, Neonatology MS 8402,
13121 E. 17th Ave, Aurora, CO 80045, USA
e-mail: john.kinsella@ucdenver.edu

- D. Vasodilator drugs administered intravenously, such as tolazoline and sodium nitroprusside, are often unsuccessful because of systemic hypotension and an inability to achieve or sustain pulmonary vasodilation.
- E. The ability of iNO therapy to selectively lower PVR and decrease extrapulmonary venoarterial admixture accounts for the acute improvement in oxygenation observed in newborns with PPHN.
- F. Oxygenation can also improve during iNO therapy in some newborns who do not have extrapulmonary right-to-left shunting. Hypoxemia in these cases is primarily the result of intrapulmonary shunting caused by continued perfusion of lung units that lack ventilation (e.g., atelectasis), with variable contributions from ventilation/perfusion (V/Q) inequality. Low dose iNO therapy can also improve oxygenation by re-directing blood from poorly aerated or diseased lung regions to better aerated distal air spaces (“microselective effect”).
- G. The clinical benefits of low-dose iNO therapy may include reduced lung inflammation and edema, as well as potential protective effects on surfactant function, but these effects remain clinically unproven.
- H. The diagnostic value of iNO therapy is also important, in that failure to respond to iNO raises important questions about the specific mechanism of hypoxemia. Poor responses to iNO should lead to further diagnostic evaluation for “unsuspected” anatomic cardiovascular or pulmonary disease.

III. Evaluation of the term newborn for iNO therapy

A. The cyanotic newborn

1. History

- a. Assess the primary cause of hypoxemia. Marked hypoxemia in the newborn can be caused by lung parenchymal disease with intrapulmonary shunting, pulmonary vascular disease causing extrapulmonary right-to-left shunting, or anatomic right-to-left shunting associated with congenital heart disease.
- b. Assessment of risk factors for hypoxemic respiratory failure

(1) Prenatal ultrasound studies

- (a) Lesions such as diaphragmatic hernia and congenital cystic adenomatoid formation are frequently diagnosed prenatally.
- (b) Although many anatomic congenital heart diseases can be diagnosed prenatally, vascular abnormalities (e.g., aortic coarctation, total anomalous pulmonary venous return) are more difficult to diagnose.
- (c) A history of a structurally normal heart by fetal ultrasonography should be confirmed with echocardiography in the cyanotic newborn.

c. Maternal historical information

- (1) History of severe and prolonged oligohydramnios causing pulmonary hypoplasia.
- (2) Prolonged fetal brady- and tachyarrhythmias and marked anemia (caused by hemolysis, twin-to-twin transfusion, or chronic hemorrhage) may cause congestive heart failure, pulmonary edema, and respiratory distress.
- (3) Maternal illness (e.g., diabetes mellitus), medications (e.g., aspirin causing premature constriction of the ductus arteriosus, association of Ebstein's Anomaly with maternal lithium use), and drug use may contribute to disordered transition and cardiopulmonary distress in the newborn.
- (4) Risk factors for infection causing sepsis/pneumonia should also be considered, including premature or prolonged rupture of membranes, fetal tachycardia, maternal leukocytosis, uterine tenderness and other signs of intra-amniotic infection.

d. Events at delivery

- (1) If positive pressure ventilation is required in the delivery room, the risk of pneumothorax increases.
- (2) History of meconium stained amniotic fluid, particularly if meconium is present below the vocal cords, should raise the suspicion of meconium aspiration syndrome (Chap. 63).
- (3) Birth trauma (e.g., clavicular fracture and phrenic nerve injury) or acute fetomaternal/feto-placental hemorrhage may also cause respiratory distress in the newborn.

2. Physical examination

- a. The initial physical examination provides important clues to the etiology of cyanosis (Chap. 12).
- b. Marked respiratory distress in the newborn (retractions, grunting, nasal flaring) suggests the presence of pulmonary parenchymal disease with decreased lung compliance.
- c. Recognize that airways disease (e.g., tracheo-bronchomalacia) and metabolic acidemia can also cause severe respiratory distress.
- d. In contrast, the newborn with cyanosis alone ("non-distressed tachypnea") typically has cyanotic congenital heart disease (most commonly transposition of the great vessels) or idiopathic persistent pulmonary hypertension of the newborn.

3. Interpretation of pulse oximetry measurements

- a. Right-to-left shunting across the ductus arteriosus causes post-ductal desaturation.
- b. Interpretation of pre-ductal (right hand) and post-ductal (lower extremity) saturation by pulse oximetry provides important clues to the etiology of hypoxemia in the newborn.

- c. If the measurements of pre- and post-ductal SpO₂ are equivalent, this suggests either that the ductus arteriosus is patent and pulmonary vascular resistance is sub-systemic (i.e., the hypoxemia is caused by parenchymal lung disease with intrapulmonary shunting or cyanotic heart disease with ductal-dependent pulmonary blood flow), or that the ductus arteriosus is closed (precluding any interpretation of pulmonary artery pressure without echocardiography).
 - d. It is exceptionally uncommon for the ductus arteriosus to close in the first hours of life in the presence of suprasystemic pulmonary artery pressures.
 - e. When the post-ductal SpO₂ is lower than pre-ductal SpO₂ (>5%), the most common cause is suprasystemic pulmonary vascular resistance in PPHN, causing right-to-left shunting across the ductus arteriosus (associated with meconium aspiration syndrome, surfactant deficiency/dysfunction, congenital diaphragmatic hernia, pulmonary hypoplasia, or idiopathic).
 - f. Ductal-dependent systemic blood flow lesions (hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, and coarctation) may also present with post-ductal desaturation.
 - g. Anatomic pulmonary vascular disease (alveolar capillary dysplasia, pulmonary venous stenosis, and anomalous venous return with obstruction) can cause suprasystemic pulmonary vascular resistance with right-to-left shunting across the ductus arteriosus and post-ductal desaturation.
 - h. The unusual occurrence of markedly lower pre-ductal SaO₂ compared to post-ductal measurements suggests one of two diagnoses: transposition of the great vessels with pulmonary hypertension, or transposition with coarctation of the aorta.
4. Laboratory and radiologic evaluation
- a. One of the most important tests to perform in the evaluation of the newborn with cyanosis is the chest radiograph (CXR).
 - b. The CXR can demonstrate the classic findings of RDS (air bronchograms, diffuse granularity, and underinflation), meconium aspiration syndrome, and congenital diaphragmatic hernia.
 - c. The important question to ask when viewing the CXR is whether the severity of hypoxemia is out of proportion to the radiographic changes. Marked hypoxemia despite supplemental oxygen in the absence of severe pulmonary parenchymal disease radiographically suggests the presence of an extrapulmonary right-to-left shunt (idiopathic PPHN of the newborn or cyanotic heart disease).
 - d. Other essential measurements include an arterial blood gas analysis, a complete blood count to evaluate for infection, and blood pressure measurements in the right arm and a lower extremity to determine aortic obstruction (interrupted aortic arch, coarctation).

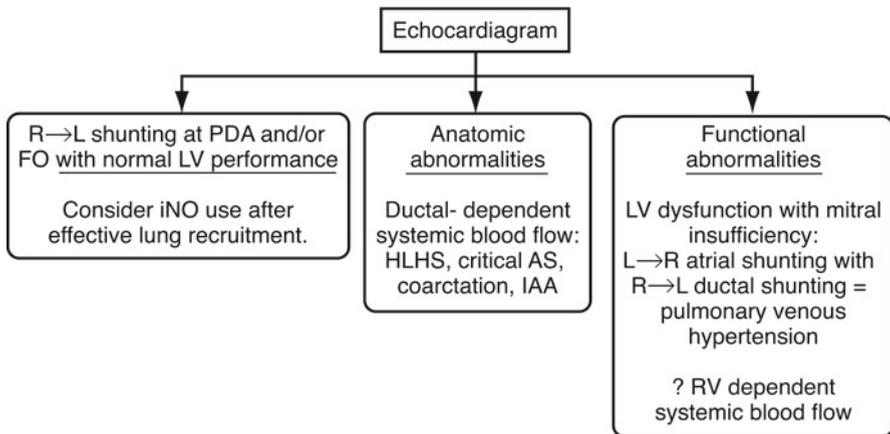


Fig. 55.1 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn

5. Response to supplemental oxygen (100% oxygen by hood, mask, or endotracheal tube)
 - a. Marked improvement in SpO_2 (increase to 100%) with supplemental oxygen suggests an intrapulmonary shunt (lung disease) or reactive PPHN of the newborn with vasodilation.
 - b. The response to mask CPAP is also a useful discriminator between severe lung disease and other causes of hypoxemia.
 - c. Most patients with PPHN of the newborn have at least a transient improvement in oxygenation in response to interventions such as high inspired oxygen and/or mechanical ventilation. If the pre-ductal SpO_2 never reaches 100%, the likelihood of cyanotic heart disease is high.
6. Echocardiography (Chap. 23)
 - a. The definitive diagnosis in newborns with cyanosis and hypoxemic respiratory failure often requires echocardiography. (Fig. 55.1)
 - b. The initial echocardiographic evaluation is important to rule-out structural heart disease causing hypoxemia (e.g., coarctation of the aorta, total anomalous pulmonary venous return).
 - c. It is critically important to diagnose congenital heart lesions for which iNO treatment would be contraindicated.
 - d. Additional congenital heart diseases that can present with hypoxemia unresponsive to high inspired oxygen concentrations (e.g., dependent on right-to-left shunting across the ductus arteriosus) include critical aortic stenosis, interrupted aortic arch, and hypoplastic left heart syndrome. Decreasing PVR with iNO in these conditions could lead to systemic hypoperfusion and delay definitive diagnosis.

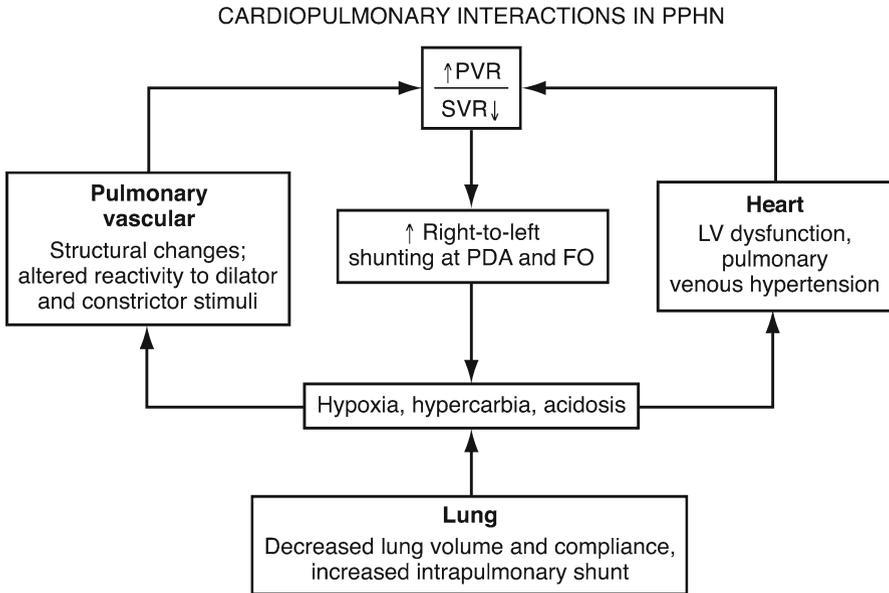


Fig. 55.2 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn (PPHN). *FO* Foramen ovale, *LV* left ventricular, *PDA* patent ductus arteriosus, *PVR* pulmonary vascular resistance, *SVR* systemic vascular resistance

- e. PPHN of the newborn is defined by the echocardiographic determination of extrapulmonary veno-arterial admixture (right-to-left shunting at the foramen ovale and/or ductus arteriosus), not simply evidence of increased PVR.
- f. Doppler measurements of atrial and ductal level shunts provide essential information when managing a newborn with hypoxemic respiratory failure.
- g. Left-to-right shunting at the foramen ovale and ductus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should be directed at optimizing lung inflation.
- h. In the presence of severe left ventricular dysfunction and pulmonary hypertension, pulmonary vasodilation alone may be ineffective in improving oxygenation. The echocardiographic findings in this setting include right-to-left ductal shunting (caused by suprasystemic pulmonary vascular resistance), and mitral insufficiency with *left-to-right* atrial shunting.

IV. Candidates for iNO therapy

- A. Several pathophysiologic disturbances contribute to hypoxemia in the newborn infant, including cardiac dysfunction, airway and pulmonary parenchymal abnormalities, and pulmonary vascular disorders (Fig. 55.2).

1. In some newborns with hypoxemic respiratory failure, a single mechanism predominates (e.g., extrapulmonary right-to-left shunting in idiopathic persistent pulmonary hypertension of the newborn), but more commonly, several of these mechanisms contribute to hypoxemia.
2. MAS represents the “perfect storm” of cardiopulmonary pathophysiology. Meconium may obstruct some airways decreasing V/Q ratios and increasing intrapulmonary shunting. Other lung segments may be over-ventilated relative to perfusion and cause increased physiologic dead space. Moreover, the same patient may have severe pulmonary hypertension with extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale, and LV dysfunction.
3. The effects of iNO may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease. Atelectasis and air space disease (pneumonia, pulmonary edema) will decrease effective delivery of iNO to its site of action in terminal lung units.
4. The effects of inhaled NO on ventilation-perfusion matching appear to be optimal at low doses (<20 ppm).
5. In cases complicated by homogeneous (diffuse) parenchymal lung disease and underinflation, pulmonary hypertension may be exacerbated because of the adverse mechanical effects of underinflation on pulmonary vascular resistance. In this setting, effective treatment of the underlying lung disease is essential (and sometimes sufficient) to cause resolution of the accompanying pulmonary hypertension.

B. Clinical criteria

1. Gestational and postnatal age
 - a. Available evidence from clinical trials supports the use of iNO in late preterm (>34 weeks’ gestation) and term newborns.
 - b. The use of iNO in infants <34 weeks’ gestation remains investigational (see below).
 - c. Clinical trials of iNO in the newborn have incorporated ECMO treatment as an endpoint. Therefore, most patients have been enrolled in the first few days of life.
 - d. Although one of the pivotal studies used to support FDA approval of iNO therapy included as an entry criterion a postnatal age up to 14 days, the average age at enrollment in that study was 1.7 days.
 - e. Currently, clinical trials support the use of iNO before treatment with ECMO, usually within the first week of life.
 - f. Clinical experience suggests that iNO may be of benefit as an adjunct treatment after ECMO therapy in patients with sustained pulmonary hypertension (e.g., congenital diaphragmatic hernia). Postnatal age alone should not define the duration of therapy in cases where prolonged treatment could be beneficial.

C. Severity of illness

1. Studies support the use of iNO in infants who have hypoxemic respiratory failure with evidence of PPHN requiring mechanical ventilation and high inspired oxygen concentrations.
2. The most common criterion employed has been the oxygenation index (OI). Although clinical trials commonly allowed for enrollment with $OI > 25$, the mean level at study entry in multicenter trials approximated 40.
3. There is no evidence that starting iNO therapy at a lower OI (i.e. < 25) reduces the need for treatment with ECMO.
4. Current multicenter studies suggest that indications for treatment with iNO may include an $OI > 25$ with echocardiographic evidence of extrapulmonary right-to-left shunting.

V. Treatment strategies

A. Dose

1. The first studies of iNO treatment in term newborns reported initial doses that ranged up to 80 ppm. Early laboratory and clinical studies established the boundaries of iNO dosing protocols for subsequent randomized, clinical trials in newborns.
2. Recommended starting dose for iNO in the term newborn in 20 ppm.
3. *Increasing the dose to 40 ppm does not generally improve oxygenation in patients who do not respond to the lower dose of 20 ppm.*
4. Although brief exposures to higher doses (40–80 ppm) appear to be safe, *sustained treatment with 80 ppm NO increases the risk of methemoglobinemia.*

B. Duration of treatment

1. In multicenter, clinical trials, the typical duration of iNO treatment has been < 5 days, which parallels the clinical resolution of persistent pulmonary hypertension.
2. Individual exceptions occur, particularly in cases of pulmonary hypoplasia.
3. If iNO is required for > 5 days, investigations into other causes of pulmonary hypertension should be considered (e.g., alveolar capillary dysplasia), particularly if discontinuation of iNO results in suprasystemic elevations of pulmonary artery pressure by echocardiography.
4. Discontinue iNO if the FiO_2 is < 0.60 and the PaO_2 is > 60 without evidence of rebound pulmonary hypertension or an increase in $FiO_2 > 15\%$ after iNO withdrawal.

C. Weaning

1. After improvement in oxygenation occurs with the onset of iNO therapy, strategies for weaning the iNO dose become important.

2. Numerous approaches have been employed, and few differences have been noted until final discontinuation of iNO treatment.
3. In one study, iNO was reduced from 20 ppm to 6 ppm after 4 h of treatment without acute changes in oxygenation. In another trial, iNO was reduced in a stepwise fashion to as low as 1 ppm without changes in oxygenation.

D. Monitoring

1. Early experience suggested that careful monitoring of NO and NO₂ levels should be done with chemiluminescence devices.
2. It has now become clear that NO₂ levels remain low at delivered iNO doses within the recommended ranges, and that electrochemical devices are reliable.
3. The currently available systems use electrochemical cells and appear to be reliable when used appropriately.
4. Methemoglobinemia occurs after exposure to high concentrations of iNO (80 ppm). This complication has not been reported at lower doses of iNO (≤ 20 ppm).
5. Because methemoglobin reductase deficiency may occur unpredictably, it is reasonable to measure methemoglobin levels by co-oximetry within 4 h of starting iNO therapy and subsequently at 24 h intervals.

E. Ventilator management

1. Along with iNO treatment, other therapeutic strategies have emerged for the management of the term infant with hypoxemic respiratory failure.
2. Considering the important role of parenchymal lung disease in specific disorders included in the syndrome of PPHN, pharmacologic pulmonary vasodilation alone should not be expected to cause sustained clinical improvement in many cases.
3. Patients not responding to iNO can show marked improvement in oxygenation with adequate lung inflation alone.
4. In newborns with severe lung disease, HFOV is frequently used to optimize lung inflation and minimize lung injury.
5. In clinical pilot studies using iNO, the combination of HFOV and iNO caused the greatest improvement in oxygenation in some newborns who had severe pulmonary hypertension complicated by diffuse parenchymal lung disease and underinflation (e.g. RDS, pneumonia).
6. A randomized, multicenter trial demonstrated that treatment with HFOV + iNO was often successful in patients who failed to respond to HFOV or iNO alone in severe pulmonary hypertension, and differences in responses were related to the specific disease associated with the various complex disorders.

VI. The preterm newborn

- A. Preliminary studies in human preterm infants with severe hypoxemic respiratory failure supported the potential role of low-dose iNO as adjuvant therapy.
 1. A pilot trial of iNO in preterm infants showed acute improvement in oxygenation after 60 min of treatment.
 2. Survival to discharge was 52% in the iNO group and 47% in controls. Total ventilator days for survivors were less for the iNO group.
 3. In contrast to uncontrolled pilot studies, there was no difference in the incidence of intracranial hemorrhage between the control and iNO treated groups.
 4. Low-dose iNO caused acute improvement in oxygenation in preterm newborns with severe hypoxemic respiratory failure, without increasing the risk of bleeding.
- B. Subsequently, four large multicenter trials were conducted to test the safety and efficacy of iNO in premature newborns.
 1. Van Meurs et al. enrolled 420 newborns (401–1,500 g birthweight) in a multicenter RCT. Overall, they found no difference in the incidence of death/BPD between the iNO and control groups.
 2. Ballard et al randomized 582 premature newborns with birth weights of 500–1,250 g who required ventilatory support between 7 and 21 days of age. The incidence of survival without BPD was increased in the iNO treatment group (43.9%) compared to controls (36.8%) ($P=0.042$). BPD reduction derived almost entirely from the subset of patients enrolled between 7 and 14 days, suggesting that early treatment is important to prevent BPD.
 3. Kinsella et al. randomized 793 premature newborns with birth weights of 500–1,250 g and requiring mechanical ventilation in the first 48 h of life to treatment with 5 ppm iNO versus placebo gas. Overall, there was no difference in the incidence of death or BPD between groups; however, iNO therapy reduced the incidence of BPD for infants with birth weight > 1,000 g by 50% ($P=0.001$). iNO reduced the incidence of PVL ($P=0.048$), as well as the combined end-points of ICH, PVL and ventriculomegaly for the entire study population ($P=0.032$).
 4. Mercier et al randomized 800 newborns (24–29 weeks' gestation) to treatment with 5 ppm iNO versus placebo gas. There were no differences in mortality, BPD, or brain injury.
- C. Current status of iNO treatment of premature newborns.
 1. An NIH consensus conference reviewed the currently available data and concluded that the routine use of iNO in premature newborns was not warranted based upon the available evidence. However, some subsets of premature newborns (e.g. pulmonary hypertension complicating pulmonary hypoplasia) may benefit from treatment with iNO.

2. Several trials of iNO treatment in premature newborns are ongoing. The consensus analysis will need to be re-evaluated if the results of these studies confirm the positive findings from individual trials (particularly, treatment of infants with evolving BPD after the first week).

Suggested Reading

- Antunes MJ, Greenspan JS, Holt WJ, et al. Assessment of lung function pre-nitric oxide therapy: a predictor of response? *Pediatr Res.* 1994;35:212A.
- Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med.* 2006;205:343–53.
- Clark RH. High-frequency ventilation. *J Pediatr.* 1994;124:661–70.
- Clark RH, Kueser TJ, Walker MW, et al. Low-dose inhaled nitric oxide treatment of persistent pulmonary hypertension of the newborn. *N Engl J Med.* 2000;342:469–74.
- Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. *Pediatrics.* 2011;127:363–9.
- Davidson D, Barefield ES, Kattwinkel J, et al. Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose–response, multicenter study. *Pediatrics.* 1998;101:325–34.
- Davidson D, Barefield ES, Kattwinkel J, et al. Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension. *Pediatrics.* 1999;104:231–6.
- Drummond WH, Gregory G, Heymann MA, Phibbs RA. The independent effects of hyperventilation, tolazoline, and dopamine on infants with persistent pulmonary hypertension. *J Pediatr.* 1981;98:603–11.
- Gerlach H, Rossaint R, Pappert D, Falke KJ. Time-course and dose–response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. *Eur J Clin Invest.* 1993;23:499–502.
- Gersony WM. Neonatal pulmonary hypertension: pathophysiology, classification and etiology. *Clin Perinatol.* 1984;11:517–24.
- Goldman AP, Tasker RC, Haworth SG, et al. Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics.* 1996;98:706–13.
- Hallman M. Molecular interactions between nitric oxide and lung surfactant. *Biol Neonate.* 1997;71:44–8.
- Kinsella JP, Abman SH. Clinical approach to inhaled nitric oxide therapy in the newborn. *J Pediatr.* 2000;136:717–26.
- Kinsella JP, Abman SH. Efficacy of inhalational nitric oxide therapy in the clinical management of persistent pulmonary hypertension of the newborn. *Chest.* 1994;105:92S–4.
- Kinsella JP, Abman SH. Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. *J Pediatr.* 1995;126:853–64.
- Kinsella JP, Abman SH. Clinical approach to the use of high frequency oscillatory ventilation in neonatal respiratory failure. *J Perinatol.* 1996;16:S52–5.
- Kinsella JP, Abman SH. Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. *J Pediatr.* 1995;126:853–64.
- Kinsella JP, Neish SR, Ivy DD, et al. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. *J Pediatr.* 1993;123:103–8.
- Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet.* 1992;340:819–20.
- Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe persistent pulmonary hypertension of the newborn. *J Pediatr.* 1997;131:55–62.

- Kinsella JP, Walsh WF, Bose CL, et al. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial. *Lancet*. 1999;354:1061–5.
- Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med*. 2006;205:354–64.
- Levin DL, Heymann MA, Kitterman JA, et al. Persistent pulmonary hypertension of the newborn. *J Pediatr*. 1976;89:626.
- Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med*. 1997;336:597–604.
- Roberts JD, Fineman JR, Morin FC, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. *N Engl J Med*. 1997;336:605–10.
- Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet*. 1992;340:818–9.
- Rossaint R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med*. 1993;328:399–405.
- Schreiber MD, Gin-Mestan K, Marks JD, et al. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med*. 2003;349:2099–107.
- Stevenson DK, Kasting DS, Darnall RA, et al. Refractory hypoxemia associated with neonatal pulmonary disease: the use and limitations of tolazoline. *J Pediatr*. 1979;95:595–9.
- Wessel DL, Adatia I, Van Marter LJ, et al. Improved oxygenation in a randomized trial of inhaled nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics*. 1997;100:e7.

Chapter 56

Extracorporeal Membrane Oxygenation

Robert E. Schumacher

I. Description

- A. Extracorporeal membrane oxygenation (ECMO) is a means, whereby an infant (usually, term or late preterm) with reversible lung failure is afforded a period of “lung rest” by use of an artificial lung. Such a period of rest may allow for lung recovery and ultimately survival of the infant. The circulation is diverted from the body and is pumped through a membrane oxygenator, which serves as an artificial lung.
- B. Oxygen delivery is determined by oxygen content and cardiac output (which is equivalent to “pump flow”). Venovenous (V-V) ECMO increases oxygen content (“intravenous O₂”). Venovenous (V-V) ECMO increases oxygen content and can increase cardiac output (pump flow).
- C. Ventilation is determined by gas flow through the artificial lung.

II. ECMO circuit

- A. For V-A bypass, venous blood is passively or actively (depending upon pump type) drained via the right atrium and passed via a pump to a venous capacitance reservoir (bladder box), an artificial lung, a heat exchanger, and an arterial perfusion cannula. The right internal jugular vein and common carotid artery are commonly used as access points and are often ligated as part of the bypass procedure.
- B. For V-V bypass, a double-lumen cannula is used. In this isovolemic procedure, blood is removed from and returned to the right atrium; the remainder of the circuit is the same as in V-A ECMO.
- C. To prevent thrombotic complications while on ECMO, the patient is treated with systemic heparinization.

R.E. Schumacher, MD (✉)

Department of Pediatrics, C.S. Mott Children’s Hospital, University of Michigan Health System, 8-621 Mott Hospital, 1549 East Hospital Drive, Ann Arbor, MI 48109-4254, USA

e-mail: neoschu@umich.edu

III. Patient selection

- A. For “standard” neonatal ECMO, the baby should:
1. Be of a gestational age such that the risk of intracranial hemorrhage is relatively low (≥ 35 weeks’ gestation is often used).
 2. Have a cranial sonogram with no IVH (grade I is a relative contraindication).
 3. Have no major bleeding problem (isolated pulmonary hemorrhage is not a contraindication).
 4. Have reversible respiratory failure.
 5. Be “failing” conventional medical management.
- B. Failure of conventional medical management is a definition that should be “individualized” for each ECMO center.
1. Guidelines (based on experience with populations) are used, but the ultimate decision is up to those caring for the individual infant. Cut-point values (i.e., ECMO/NO ECMO) should be chosen taking into account probabilities for mortality and long-term morbidity. Since different disease processes have different outcome probabilities, it is rational to take that into account when applying criteria. General criteria provide guidance.
 2. Oxygenation index (OI) criterion:
 - a.
$$OI = \frac{\text{Mean airway pressure} \times \text{FiO}_2}{\text{PaO}_2 \text{ (postductal)}} \times 100.$$
 - b. *After* stabilization, if the OI is ≥ 40 on three of five occasions (each value separated by >30 and <60 min), ECMO criteria have been met (University of Michigan “absolute” criterion; OI >25 is used as “consider” criterion).
 - c. V-V ECMO may not provide the same cardiac support that veno-arterial ECMO does.
 - (1) Infants with severe cardiac compromise may not tolerate V-V ECMO. How to identify such patients is difficult; results from the Extracorporeal Life Support Organization registry suggest that V-V ECMO is effective even in infants requiring substantial blood pressure support.
 - (2) Because the risk of carotid artery ligation is not present, consideration for V-V ECMO is sometimes made at a lower OI.
 3. Other criteria include A-aDO₂, “acute deterioration,” “intractable air leaks,” hemodynamic instability (refractory hypotension), and “unresponsive to medical management.”

IV. Management

A. Initial bypass problems

1. Hypotension:
 - a. Hypovolemia: ECMO circuit has high blood capacitance; treat this with volume. The technician/specialist may/should have blood or colloid available from circuit priming procedure.
 - b. Sudden dilution of vasopressors, especially with V-V ECMO; treat by having separate pressor infusion pumps to infuse into circuit.
 - c. Hypocalcemia from stored blood (sometimes an issue): Circuit can be primed with calcium to prevent this.
2. Bradycardia: From vagal stimulation by catheter(s).
3. Consequences of catheter misplacement: Correct catheter placement must be documented radiographically.
4. Once on initial bypass, there should be no blood squirting, no pumping air through circuit, and there should be “blue blood going in and red blood coming out.”

B. Initial management

1. V-A bypass: Wean ventilator rapidly (10–15 min) to “rest” settings (FiO_2 0.3, pressure 25/4 cm H_2O , rate 20 bpm, T_1 0.5–1.0 s). Use SvO_2 as guide. CPAP/high PEEP (10–12-cm H_2O) can often shorten bypass time. Inotropes can usually be quickly discontinued. (Caution: Avoid large swings in PaCO_2 and blood pressure; can be associated with unwanted rapid changes in cerebral blood flow).
2. V-V bypass: Wean with caution; infant is still dependent on innate myocardial function for O_2 delivery. SvO_2 is useful only for trends at same pump flow rate. Innate lung still provides gas exchange. High CPAP with V-V ECMO may impede cardiac output or pulmonary blood flow; if desired, use ETCO_2 to optimize PEEP. Inotropes must be weaned with caution.
3. Infants can self-decannulate; restraints are mandatory.
4. Head position is critical; head turned too far left functionally occludes the left jugular vein (right is already ligated). Such a scenario may lead to CNS venous hypertension.
5. Analgesia and sedation are usually required. Narcotic used for analgesia; if patient needs additional sedation, benzodiazepines are reasonable choices.
6. Heparin management:
 - a. Prior to cannulation, load with 100 U/kg.
 - b. Typical drip concentration is 50 U/mL (5 mL heparin [1,000 U/mL] in 95 mL D_5W).

- c. Usual consumption is 20–40 U/kg/h: Affected by blood–surface interactions in circuit, infant’s own clotting status, and heparin elimination (renal excretion).
- d. Titrate heparin to keep activated clotting time in desired range using activated clotting time (ACT).

C. Daily management, patient protocols, problems

1. Chest radiograph: Daily.
2. Cranial sonogram: Obtain the first day after cannulation, after every change in neurologic status, and regularly thereafter (every 2–3 days). Some centers prefer a daily study when on V-A ECMO.
 - a. Brain hemorrhage: Includes both typical and atypical (including posterior fossa) hemorrhages. If seen and patient is able to come off ECMO, do so. If patient is likely to die if removed from bypass, has stable hemorrhage, or is neurologically stable, consider staying on bypass with strict attention to lower ACT values, and keeping platelet counts higher (e.g., 125,000–200,000/mm³).
 - b. Cranial sonography is not as good as CT for demonstrating peripheral/posterior fossa lesions.
3. Fluids: Follow I/O, weights; the membrane lung provides an additional area for evaporative losses.
 - a. Total body water (TBW) is high: A common problem, etiology probably multifactorial. A problem arises when TBW is high but intravascular volume is low (capillary leak); early vigorous attempts at diuresis in this instance usually do not help and can be harmful. Some argue that vigorous attempts at diuresis can hasten lung recovery; others state that spontaneous diuresis is a marker for improvement and attempts to hasten it are of no avail. If diuresis is deemed advisable, use diuretics first and mechanical support (e.g., hemofilter) last. (Furosemide in combination with theophylline may be helpful). Expect decreased urine output when a hemofilter is used.
 - b. K⁺: Serum values are often low and require replacement; check for alkalosis. (Low K⁺ may be related to the use of washed RBCs).
 - c. Pump is primed with banked blood; depending upon the preservative, ionized Ca²⁺ can be low. Checking and correcting the circuit can prevent this.
4. Hemostasis/hemolysis:
 - a. Obtain appropriate lab studies (e.g., fibrinogen, fibrin degradation products, serum hemoglobin) and platelet counts daily.
 - b. Clots are common, especially in venous capacitance reservoir (bladder). Pre-lung clots are usually left alone. Those post-lung are handled by ECMO specialist/technician. When clots appear, review platelet/heparin consumption, FDP, etc.

c. Bleeding:

- (1) From neck wound: Treated with cannula manipulation, light pressure, or fibrin glue.
 - (2) Hemothorax/pericardium present with decreased pulse pressure and decreased pump filling. Treated by drainage first (a more common problem if previous surgery has been done, e.g., CDH, thoracostomy tube).
 - (3) Treat with blood replacement, keep platelet counts high ($>150,000/\text{mm}^3$), lower target ACT values.
5. TPN: A *major* benefit of ECMO can be the immediate provision of TPN and adequate caloric/low volume intake (use high dextrose concentrations).
 6. Blood products:
 - a. Minimize donor exposures, give only when indicated.
 - b. Excessive PRBC's administration without increasing pump flow (V-A ECMO) leads to lower aortic PO_2 greater oxygen delivery.
 7. Hypertension is a known complication. The final mechanism by which it occurs is usually high total body water. It is almost always transient and resolves near the end of a run. Use population norms for blood pressure (a useful working definition for hypertension is $\text{MAP} >75$ mmHg.). Initial treatment is usually with diuretics.
 8. WBC is often low, probably from peripheral migration of WBCs.
 9. Infection is not a common problem. Suspect infection if unanticipated increase in ECMO support is required.
 10. Bilirubin can be elevated, especially with sepsis or long ECMO runs. A cholestatic picture is typical; phthalate in plastic tubing may be hepatotoxic. Hepatosplenomegaly is common.
 11. Cardiac stun: Once on ECMO, a dramatic decrease in cardiac performance is seen in up to 5% of patients. Seen more in V-A patients, and may be ECMO induced from increased afterload and decreased coronary artery oxygen content. The stun phenomenon usually resolves, but patients with it do have higher overall mortality rates. Treatment is supportive.

D. Circuit problems (selected more common problems)

1. Air in circuit: Treatment depends upon location, and can often be aspirated.
2. Pump cutouts: Kinked tube, malposition, low volume, low filling pressure (pneumothorax, hemopericardium), agitated infant.
3. Pump:
 - a. Electric failure: Can be cranked by hand.
 - b. With roller pumps: If occlusion set too loose: false high-flow readings; if set too tight: hemolysis.

4. Lung pathophysiology: The membrane lung can get “sick,” and have pulmonary embolus, edema, etc. Treatment depends upon specific problem.

E. Weaning

1. Use serial measures of oxygen content (on V-A ECMO, easiest to follow SvO_2) and wean by preset parameters.
2. Chest radiograph is very helpful.
 - a. Usually shows initial complete opacification.
 - b. Starts to clear prior to “reventilating” the lungs and serves as a marker for lung recovery. Anticipate a trial off with this early sign.
3. Pulmonary mechanics tests: Compliance becomes poor hours after going on and improvement is an early marker of lung recovery.
4. $ETCO_2$: Increasing exhaled CO_2 indicative of return of lung function.

F. Trial off

1. Lung conditioning: Lungs are periodically (hourly) inflated using a long (≥ 5 s), sustained inflation.
2. Turning up the ventilator FiO_2 and following SvO_2 give a feel for whether or not there is any effective pulmonary gas exchange.
3. Increased ventilator settings to achieve adequate tidal volumes 30–60 min before trial off appear to allow for recruitment of lung units.
4. V-A: Obtain blood gas frequently to assess ventilation. Wean FiO_2 aggressively per oximetry.
5. V-V: Halt gas flow to membrane lung, and keep pump flowing. Since infant is still on bypass but with no effective gas exchange through membrane, use venous line SvO_2 to wean FiO_2 as it is now a true venous saturation. Residual O_2 in membrane lung may falsely elevate O_2 content for 20–30 min.
6. A successful trial off depends upon the individual patient. In general, patient should be stable on $FiO_2 \leq 0.4$ and reasonable ventilator settings.

G. Inability to wean from ECMO (non-CDH)

1. With prolonged need for bypass (e.g., 7 days) and little to no improvement, consideration for an underlying “rare” lung disease must be made.
2. Bronchoscopy and lavage and/or biopsy may allow for the diagnosis of rare lung disease (e.g., surfactant protein deficiencies, alveolar capillary dysplasia).

H. Decannulation

1. Notify surgeon as soon as possible.

2. Give skeletal muscle relaxant.
3. Need for repair of carotid artery or jugular vein controversial.

V. Post-ECMO follow-up

- A. Neck: Sutures removed in 7 days.
- B. Platelets will continue to fall post-ECMO. Serial counts are necessary until stable (24–48 h).
- C. CNS:
 1. EEG is a sensitive screening test for acute functional CNS problems.
 2. CT/MRI: Obtained because of relative insensitivity of sonography for posterior fossa and near-field parenchymal lesions.
 3. BAER: Because of high incidence of sensorineural hearing loss with PPHN, hearing screening is recommended. Delayed onset loss has been described and repeated screening advised.
- D. Airway: Vocal cord paresis seen in approximately 5% of infants post-ECMO; acute respiratory deterioration has occurred. If persistent stridor is noted, flexible bronchoscopy is recommended. Hoarseness has always resolved clinically (days to months).
- E. Long-term follow-up
 1. Neurodevelopmental follow-up should be provided: 10–20% show major problems.
 2. Medical problems include lower respiratory tract infections in many.

Suggested Reading

- Bartlett RH. Extracorporeal life support for cardiopulmonary failure. *Curr Prob Surg.* 1990; 27:7–705.
- Elbourne D, Field D, Mugford M. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. *Cochrane Database Syst Rev.* 2002;1:CD001340.
- Glass P, Wagner AE, Papero PH, et al. Neurodevelopmental status at age five years of neonates treated with extracorporeal membrane oxygenation. *J Pediatr.* 1995;127:447–557.
- Kim ES, Stolar CJ. ECMO in the newborn. *Am J Perinatol.* 2000;17:345–56.
- Schumacher RE, Baumgart S. Extracorporeal membrane oxygenation 2001: the odyssey continues. *Clin Perinatol.* 2001;28:629–53.
- Zwischenberger JB, Steinhorn RH, Bartlett RH, editors. *ECMO: extracorporeal cardiopulmonary support in critical care.* 2nd ed. Ann Arbor: Extracorporeal Life Support Organization; 2000.

Chapter 57

Liquid Ventilation for Neonatal Respiratory Failure

Ronald B. Hirschl

- I. Description: Liquid ventilation refers to the process of enhancing pulmonary function through the instillation of perfluorocarbon (PFC) liquid into the lungs.
 - A. Partial liquid ventilation (PLV): The achievement of gas exchange through the delivery of gas tidal volumes to lungs which have been filled with PFC liquid.
 - B. Total liquid ventilation (TLV): The achievement of gas exchange through the delivery of tidal volumes of PFC liquid to the lungs using a specialized mechanical liquid ventilator.
- II. Physiology of perfluorocarbon ventilation.
 - A. PFCs: Inert liquids which are produced by the fluorination of common organic hydrocarbons. The carbon chain length and any additional atom give unique properties to each PFC molecule.
 - B. Physical properties of PFCs:
 1. Density: Denser than hydrocarbon counterparts with levels approaching twice that of water (1.75–1.95 g/mL at 25°C).
 2. Surface tension: Have weak intermolecular forces and remarkably low surface tensions (15–20 dynes/cm at 25°C).
 3. Respiratory gas solubility: Solubilities of the respiratory gases in PFCs are significantly greater than their corresponding solubilities in water or nonpolar solvents.
 - a. O₂ solubility at 37°C = 44–55 mL gas/100 mL liquid
 - b. CO₂ solubility at 37°C = 140–210 mL gas/100 mL liquid

R.B. Hirschl, MD (✉)
Department of Pediatric Surgery, C.S. Mott Children's Hospital,
1500 E Medical Center Dr., F3970 Pediatric Surgery, Ann Arbor, MI 48109-5245, USA
e-mail: rhirschl@med.umich.edu

4. An ideal PFC for respiratory application should have the properties of high gas solubility and moderate vapor pressure and viscosity. These properties, however, might not be found in a single pure PFC. Thus, recent studies are focusing on PFC combinations that may optimize the fluid properties to better suit a particular application.
 5. Vapor pressure: PFCs are relatively volatile (vapor pressure ranges from 11 to 85 Torr at 37°C). This property is important because it governs the evaporation rate of PFCs from the lungs during and after both types of liquid ventilation: high vapor pressure liquid would need more frequent supplementation than a low vapor pressure one.
- C. Basis for the use of liquid ventilation in neonatal ventilator-dependent respiratory failure:
1. Gas exchange
 - a. Dependent portion of the lungs tends to be collapsed or filled with inflammatory exudate during severe pulmonary inflammation leading to ventilation–perfusion mismatching and hypoxemia.
 - b. The high densities of PFC liquids facilitate their distribution to the dependent portions of the lungs, where atelectatic lung appears to be recruited.
 - c. PFCs have also been shown to redistribute pulmonary blood flow to the better-inflated, nondependent segments.
 - d. These effects, combined with the high respiratory gas solubilities of PFCs, lead to improvements in ventilation–perfusion matching and arterial oxygenation.
 2. Pulmonary compliance
 - a. PFCs lead to an increase in pulmonary compliance secondary to their density-related recruiting effect on collapsed, inflamed alveoli. However, during partial liquid ventilation, an increase in the PFC dose can be associated with a reduction in compliance. This is related to the heterogeneous distribution of the gas in the partially liquid-filled lungs.
 - b. PFCs act as an artificial surfactant and increase the stability of small airways.
 - c. The regions of the lung that are filled with PFC liquid (all regions for TLV, the dependent regions for PLV) exhibit a reduction of the gas–liquid interface in the distal airway which also reduces surface-active forces favoring alveolar collapse.
 - d. The result of these effects is enhanced alveolar recruitment at lower inflation pressures.
 3. Reduction of lung injury
 - a. Effects may relate to improved alveolar inflation and better displacement and lavage of inflammatory mediators and debris from the affected portions of the lungs or to a limitation of excessive ventilator pressures from improvements in compliance.

- b. PFCs have been shown to have in vitro anti-inflammatory activities, such as reduction in neutrophil chemotaxis and nitric oxide production, as well as decreased LPS-stimulated macrophage production of cytokines. Neutrophil infiltration also appears to be reduced following lung injury in liquid-ventilated animals. In vivo evaluation has shown a reduction in the release of TNF- α , IL-1, and IL-6 in human alveolar macrophages in PFC-exposed lungs.

D. Uptake, biodistribution, elimination, and toxicology

1. Uptake: Absorbed in small quantities from the lungs during liquid ventilation, reaching a steady state at 15–30 min of liquid breathing.
2. Biodistribution: Have preferential distribution to tissues with high lipid content. These compounds are cleared most quickly from vascular, lipid-poor tissues, such as muscle.
3. Elimination: Do not undergo significant biotransformation or excretion. PFCs are primarily eliminated by evaporation from the lungs and are scavenged by macrophages in both the lungs and other tissues.
4. Toxicology: Pulmonary, metabolic, hematologic, and clinical effects of liquid ventilation have been studied extensively in laboratory animals with no significant pulmonary or systemic toxicity noted. Clinical studies have identified transient hypoxemia during PFC dosing and the development of pneumothorax as potential short-term complications of partial liquid ventilation in humans.

III. Partial liquid ventilation.

- A. A hybrid method of gas exchange, achieved through the delivery of conventional gas tidal volumes to PFC-filled lungs.

1. Methods

- a. Lungs are filled to an estimated fraction of FRC (approximately 5–30 mL/kg, depending on disease process, age, and weight) with PFC liquid and conventional ventilation superimposed to achieve gas exchange.
- b. Adequate filling of the lungs is judged by the presence of a fluid meniscus in the endotracheal tube at zero PEEP by the opacification of the dependent portions of the lungs on lateral chest radiography and by the adequacy of gas tidal volumes. Fluid may be added or withdrawn.

2. Theoretical basis for use of PLV in RDS

- a. PLV has relative simplicity as the need for a complex mechanical liquid ventilator is eliminated.
- b. The presence of dense PFC fluid in the dependent regions of the lungs allows the recruitment of severely inflamed airways for the purpose of gas exchange. Oxygenation during PLV can occur either by the gas ventilation of these airways directly or the oxygenation of the liquid as it equilibrates with the inspired gas.

- c. Carbon dioxide elimination is enhanced by increased gas tidal volumes.
 - d. Compliance is enhanced secondary to alveolar recruitment and the surfactant-like activity of the PFCs. Because the gas–liquid interface is not completely eliminated during PLV, compliance improvement is not as dramatic as that seen during TLV and can actually deteriorate if the lungs are overfilled with PFC liquid.
- B. Clinical studies of PLV in neonatal ventilator-dependent respiratory failure.
1. Leach reported significantly improved gas exchange and pulmonary compliance during PLV in 13 premature infants (24–34 weeks' gestation at birth) with refractory RDS as part of a multicenter, noncontrolled trial. Significant complications occurring during the trial were limited to the development of Grade IV intracranial hemorrhage (IVH) in one patient. Of the ten patients completing at least 24 h of PLV, survival to a corrected gestational age of 36 weeks was 60%.
 2. Pranikoff evaluated the use of PLV in four newborn patients maintained with extracorporeal life support for respiratory failure secondary to congenital diaphragmatic hernia (CDH). During 5–6 days of PLV therapy, patients exhibited significant increases in arterial oxygen tension and static pulmonary compliance compared to pretreatment values. The therapy was well-tolerated and significant complications were limited to the development of pulmonary hemorrhage in one patient 4 days after the final dose of PFC.
 3. Migliori et al. evaluated the use of high-frequency partial liquid ventilation in two infants with chronic lung disease and severe respiratory failure. Both patients showed improved gas exchange with reduction in oxygen indices.
- IV. Total liquid ventilation.
- A. Lungs are completely filled with PFC and a liquid tidal volume is perfused into and drained from the lungs for the purpose of gas exchange using a specialized mechanical liquid ventilator.
- B. Clinical studies of TLV.
1. The feasibility and potential of liquid ventilation as treatment for severe respiratory distress was reported in 1990 by Greenspan.
 2. Liquid ventilation was performed in three preterm neonates in whom conventional treatment had failed.
 3. Improvement of pulmonary mechanics without hemodynamic impairment was reported in all the three neonates.
 4. The severity of pulmonary injury before the initiation of liquid ventilation precluded a successful outcome.

V. Perfluorocarbon-induced lung growth.

- A. Different studies have demonstrated the effectiveness of PFC to induce lung growth in neonates with CDH on ECMO.
- B. A multicenter, prospective, randomized pilot study showed a higher mortality for the PFC-induced lung growth (PILG) group (75%) compared to patients treated with conventional ventilations (40%), though the number of patients in the study was very small.

VI. *At present, liquid ventilation is not yet an approved therapy for clinical use and remains investigational.*

Suggested Reading

- Furhman BP, Paczan PR, DeFancis M. Perfluorocarbon-assisted gas exchange. *Crit Care Med.* 1991;19:712–22.
- Greenspan JS, Wolfson MR, Rubenstein SD, et al. Liquid ventilation of human preterm neonates. *J Pediatr.* 1990;117:106–11.
- Hirschl RB, Croce M, Gore D. et al for the Adult PLV study group: prospective, randomized controlled pilot study evaluating the safety and efficacy of partial liquid ventilation in adult patients with the acute respiratory distress syndrome (ARDS). *Am J Respirat Crit Care Med.* 2002;165(6):781–7.
- Hirschl RB, Pranikoff T, Gauger P, et al. Liquid ventilation in adults, children and neonates. *Lancet.* 1995;346:1201–2.
- Ivascu FA, Hirschl RB. New approaches to managing congenital diaphragmatic hernia. *Semin Perinatol.* 2004;28(3):185–98.
- Leach CL, Greenspan JS, Rubenstein SD, et al. Partial liquid ventilation with perflubron in infants with severe respiratory distress syndrome. *New Engl J Med.* 1996;335:761–7.
- Migliori C, Bottino R, Angeli A, et al. High frequency partial liquid ventilation in two infants. *J Perinatol.* 2004;24(2):118–20.
- Pranikoff T, Gauger P, Hirschl RB. Partial liquid ventilation in newborn patients with congenital diaphragmatic hernia. *J Pediatr Sur.* 1996;31:613–8.
- Shaffer TH, Douglas PR, Lowe CA, et al. The effects of liquid ventilation on cardiopulmonary function in preterm lambs. *Pediatr Res.* 1983;17:303–6.
- Shaffer TH, Moskowitz GD. Demand-controlled liquid ventilation of the lungs. *Appl Physiol.* 1974;36:208–13.
- Shaffer TH, Wolfson MR, Clark C. Liquid ventilation (state of the art review). *Pediatr Pulmonol.* 1992;14:102–9.
- Tredici S, Komori E, Funakubo A, et al. A prototype of a liquid ventilator using a novel hollow fiber oxygenator in a rabbit model. *Crit Care Med.* 2004;32:2104–9.
- Wolfson MR, Shaffer TH. Liquid ventilation: an adjunct for respiratory management. *Pediatr Anesth.* 2004;14:15–23.
- Wolfson MR, Shaffer TH. Liquid ventilation during early development: theory, physiologic processes and application. *J Appl Physiol.* 1990;13:1–12.
- Wolfson MR, Tran N, Bhutani VK, et al. A new experimental approach for the study of cardiopulmonary physiology during early development. *J Appl Physiol.* 1998;65:1436–43.

Part X
Management of Common Neonatal
Respiratory Diseases

Chapter 58

Mechanisms of Respiratory Failure

Anne Greenough and Anthony D. Milner

- I. Respiratory failure is present when there is a major abnormality of gas exchange.
 - A. In an adult, the limits of normality are a PaO₂ of >60 Torr (8 kPa).
 - B. In the newborn, the oxygen tension needed to maintain the arterial saturation above 90% varies between 40 and 60 Torr (5.3–8 kPa) depending upon the proportion of hemoglobin that is fetal and the arterial pH (a drop in pH of 0.2 eliminates the left shift produced by 70% of the hemoglobin being fetal). Thus, in the newborn period, respiratory failure is best defined in terms of oxygen saturation. There are, however, no agreed criteria (see below).
 - C. Hypoxia may be associated with hypercarbia (PaCO₂>6.7 kPa or 55 Torr)

$$\text{PaCO}_2 \approx \frac{\text{CO}_2 \text{ production}}{\text{Alveolar ventilation}}$$

$$\text{Alveolar ventilation} = (\text{tidal volume} - \text{dead space} \times \text{frequency})$$

- D. Respiratory failure associated with hypercarbia occurs, therefore, in situations associated with reduction in tidal volume and/or frequency.
 - E. Respiratory failure in the neonatal period may be defined as:
PaO₂<50 Torr (6.7 kPa) in an inspired oxygen of at least 50% with/without PaCO₂>50 Torr (6.7 kPa).
- II. Hypoxemia in the neonatal period can result from multiple causes.
 - A. Ventilation/perfusion (V/Q) mismatch
 - 1. Distinguished by a good response to supplementary oxygen (intrapulmonary shunting).

A. Greenough, MD (✉) • A.D. Milner, MD
Division of Asthma, Allergy and Lung Biology, King's College London,
London SE5 9RS, UK
e-mail: anne.greenough@kcl.ac.uk

2. Increased physiologic dead space.
 3. Found in the following conditions:
 - a. Respiratory distress syndrome
 - b. Pneumonia
 - c. Meconium aspiration syndrome
 - d. Bronchopulmonary dysplasia
 - B. Extrapulmonary (right-to-left) shunts are distinguished by relatively little improvement with supplementary oxygen and are found in:
 1. Pulmonary hypertension*
 2. Cyanotic congenital heart disease*
 - C. Methemoglobinemia*
 - D. Inadequate inspired oxygen*

**Note:* Although these situations produce cyanosis, this is not from respiratory failure. Cyanosis appears when the reduced hemoglobin concentration of the blood in the capillaries is >5 g/dL. Cyanosis, therefore, does not occur in severe anemic hypoxia (hypoxia is oxygen deficiency at the tissue level).
- III. Hypoventilation (reduced alveolar ventilation, reduction in tidal volume, and/or frequency) distinguished by a high PaCO_2 in association with hypoxemia.
- A. Reduced respiratory compliance found in the following conditions:
 1. RDS
 2. Pneumonia
 - B. Reduced lung volume found in the following conditions:
 1. RDS
 2. Pulmonary hypoplasia
 - C. Compressed lung found in the following conditions:
 1. Pneumothorax
 2. Congenital diaphragmatic hernia
 3. Pleural effusion
 4. Lobar emphysema
 5. Cystic adenomatoid malformation
 6. Asphyxiating thoracic dystrophy
- IV. Ventilatory pump failure
- A. Reduced central drive found in:
 1. Maternal opiate treatment (high levels of sedation)
 2. Cerebral ischemia
 3. Intracerebral hemorrhage
 4. Apnea of prematurity
 5. Central alveolar hypoventilation syndrome

- B. Impaired ventilatory muscle function found in:
1. Drugs (corticosteroids, paralytics—synergism with aminoglycosides).
 2. Disuse atrophy (first signs occur after 1–2 days of mechanical ventilation).
 3. Protein calorie malnutrition.
 4. Disadvantageous tension–length relationship, e.g., hyperinflation—diaphragm must contract with a much higher than normal tension. When completely flat, contraction of the diaphragm draws in the lower rib cage, producing an expiratory rather than inspiratory action.
 5. Neuromuscular disorders (Werdnig–Hoffman disease, myotonic dystrophy, etc.).
 6. Diaphragmatic problems (e.g., hernia, eventration).
 7. Phrenic nerve palsy (traumatic birth, with Erb’s palsy).
- C. Increased respiratory muscle workload found in:
1. Chest wall edema (hydrops)
 2. Upper airway obstruction/endotracheal tube with insufficient compensatory ventilatory support
 3. Pulmonary edema, pneumonia
 4. Intrinsic (inadvertent) PEEP
- V. Disorders affecting the alveolar–capillary interface, distinguished, if incomplete, by a good response to increased supplementary oxygen.
- A. Diffusion abnormalities (interstitial lung disease), e.g., pulmonary lymphangiectasia (Noonan syndrome)
 - B. Anemia
 - C. Alveolar capillary dysplasia

Suggested Reading

- Aldrich TK, Prezant DJ. Indications for mechanical ventilation. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw-Hill Inc; 1994. p. 155–89.
- Bazzy-Asaad A. Respiratory muscle function: implications for ventilatory failure. In: Haddad GG, Abman SH, Chernick V, editors. Basic mechanisms of pediatric respiratory disease. 2nd ed. Hamilton: BC Decker; 2002. p. 250–71.
- Greenough A, Milner AD. Pulmonary disease of the newborn; Part 1 Physiology. In: Rennie JM, Robertson NRC, editors. Textbook of neonatology. 5th ed. Edinburgh: Churchill Livingstone; 2005.
- Marini JJ, Slutsky AS. Physiological basis of ventilatory support. In: Lenfant C, editor. Lung biology in health and disease, vol. 188. New York: Marcel Dekker Inc; 1988.
- Roussos C, Macklem PT. The respiratory muscles. *N Engl J Med*. 1982;307:786–97.

Chapter 59

Tissue Hypoxia

Anne Greenough and Anthony D. Milner

I. Definition

- A. Tissue hypoxia occurs when oxygen transport is reduced below a critical level (i.e., below the metabolic demand), at which point either metabolism must be maintained anaerobically or tissue metabolic rate must be reduced.
- B. Under experimental conditions, if demands are kept constant, there is a biphasic response in oxygen consumption as oxygen transport is progressively reduced.
 - 1. Initially, oxygen consumption is independent of oxygen transport.
 - 2. Subsequently, oxygen consumption becomes dependent on oxygen transport and declines in proportion (physiologic supply dependency).

II. Evaluating tissue oxygenation

- A. Mixed venous saturation identifies global tissue hypoxia, but tissue hypoxia can exist with a normal, mixed-venous saturation.
- B. Blood lactate levels; elevation can be present in the absence of tissue hypoxia, particularly in patients with sepsis.
- C. Fractional oxygen extraction increases as oxygen transport is progressively compromised. Fractional oxygen extraction (FOE) can be measured by near-infrared spectroscopy (NIRS). Using spatially resolved spectroscopy, a new NIRS method, it is possible to measure regional tissue oxygen saturation in different organs (e.g., brain, kidney, liver, muscle or body regions, preductal and postductal peripheral tissue).

A. Greenough, MD (✉) • A.D. Milner, MD
Division of Asthma, Allergy and Lung Biology, King's College London,
London SE5 9RS, UK
e-mail: anne.greenough@kcl.ac.uk

III. Oxygen transport

A. Determinants

1. Cardiac output
2. Hemoglobin concentration
3. Hemoglobin saturation (to a lesser extent)

B. Oxygen–hemoglobin dissociation curve (Fig. 19.1)

1. The quaternary structure of hemoglobin determines its affinity for oxygen. By shifting the relationship of its four component polypeptide chains, and hence a change in the position of the heme moieties, it can assume:
 - a. A relaxed (R) state—favors O_2 binding
 - b. A tense (T) state—decreases O_2 binding
2. When hemoglobin takes up a small amount of the oxygen, the R state is favored and additional O_2 uptake is facilitated.
3. The oxygen–hemoglobin dissociation curve (which relates percentage oxygen saturation of hemoglobin to PaO_2) has a sigmoidal shape.

C. Factors affecting the affinity of hemoglobin for oxygen are as follows:

1. Temperature
2. pH
3. 2,3-Diphosphoglycerate (2,3-DPG)
 - a. A rise in temperature, a fall in pH (Bohr effect, elevated $PaCO_2$), or an increase in 2,3-DPG all shift the curve to the right, liberating more oxygen.
 - b. The P_{50} is the PaO_2 at which the hemoglobin is half saturated with O_2 ; the higher the P_{50} , the lower the affinity of hemoglobin for oxygen.
 - c. A right shift of the curve means a higher P_{50} (i.e., a higher PaO_2 is required for hemoglobin to bind a given amount of O_2).

D. 2,3-DPG

1. Formed from 3-phosphoglyceride, a product of glycolysis.
2. It is a high-charged anion, which binds to the β chains of deoxygenated hemoglobin, but not those of oxyhemoglobin.
3. 2,3-DPG concentration:
 - a. Increased by:
 - (1) Thyroid hormones
 - (2) Growth hormones
 - (3) Androgens
 - (4) Exercise
 - (5) Ascent to high altitude (secondary to alkalosis)

b. Decreased by:

- (1) Acidosis (which inhibits red blood cell glycolysis).
- (2) Fetal hemoglobin (HbF) has a greater affinity for O_2 than adult hemoglobin (HbA); this is caused by the poor binding of 2,3-DPG to the δ chains of HbF. Increasing concentrations of 2,3-DPG have much less effect on altering the P_{50} if there is HbF rather than HbA.

IV. Response to reduced oxygen transport

- A. From low cardiac output; if chronic, 2,3-DPG increases unless there is systemic acidemia.
 - B. From anemia
 1. Cardiac output and oxygen extraction increase.
 2. If chronic, the HbO_2 dissociation curve shifts to the right.
 - C. From alveolar hypoxemia
 1. Increased cardiac output and oxygen extraction
 2. Increased hemoglobin
- V. Oxygen extraction increases progressively as oxygen transport is reduced if oxygen consumption remains constant
- A. Alterations in vascular resistance with adjustments to the microcirculation—opening of previously closed capillaries. This has three positive effects.
 1. The increase in capillary density decreases the distance for diffusion between the blood and site of oxygen utilization.
 2. It increases the lateral surface area for diffusion.
 3. The increase in cross-sectional area of the capillaries reduces the blood linear velocity and increases the transit time for diffusion.
 - B. Changes in hemoglobin–oxygen affinity
 1. Increase in hydrogen (H^+) concentration results in a right shift of the dissociation curve.
 2. Changes in the 2,3-DPG concentration.
 3. The concentration of 2,3-DPG is regulated by red blood cell H^+ concentration (as the rate-limiting enzyme is pH sensitive)—a high pH stimulates 2,3-DPG synthesis.
 4. Deoxyhemoglobin provides better buffering than oxyhemoglobin and thereby raises red cell pH; thus, low-venous oxygen promotes DPG synthesis. (*Note:* This adaptive mechanism is less prominent in young infants with high levels of HgF, as HbF binds 2,3-DPG poorly and its synthesis is inhibited by unbound DPG).

VI. Consequences of tissue hypoxia

- A. Reduced oxidative phosphorylation.
- B. Electron transport chain slows.
- C. Reduced phosphorylation of adenosine-5'-diphosphate (ADP) to adenosine-5'-triphosphate (ATP).
- D. Increased adenosine-5'-monophosphate (AMP), which is rapidly catabolized to inosine and hypoxanthine during hypoxia.
- E. Creatinine phosphate acts as a “supplementary” energy reservoir if creatinine kinase is available, but becomes rapidly depleted.
- F. ADP can be phosphorylated anaerobically, but this is much less efficient than aerobic metabolism. During aerobic glycolysis, production of ATP is 19 times greater than it is under anaerobic conditions (i.e., production of 38 vs. 2 mmol of ATP). Lactic acid accumulates.
- G. Adverse effect on immune function and inflammation.
 - 1. Increased neutrophil sequestration
 - 2. Increased vascular permeability
 - 3. Decreased cellular immune function

Suggested Reading

- Lister G. Oxygen transport and consumption. In: Gluckman PD, Heymann MA, editors. *Pediatrics and perinatology - the scientific basis*. 2nd ed. London: Edward Arnold; 1996. p. 778–90.
- Lister G, Farhey J. Oxygen transport. In: Haddad GG, Abman SH, Cherick V, editors. *Basic mechanisms of pediatric respiratory disease*. 2nd ed. Hamilton: BC Decker Inc.; 2002. p. 184–99.
- Van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. *Neonatology*. 2008;94:237–44.
- Victor S, Weindling MA. Near-infrared spectroscopy and its use for the assessment of tissue perfusion in neonates. In: Kleinman CS, Seri L, editors. *Haemodynamics and cardiology*. Philadelphia: Elsevier Health Sciences; 2008. p. 111–30.

Chapter 60

Indications for Mechanical Ventilation

Anne Greenough and Anthony D. Milner

I. Absolute indications

A. In the delivery room

1. Failure to establish adequate spontaneous respiration immediately after delivery despite adequate face mask ventilation.
2. A large diaphragmatic hernia: Affected infants should be intubated and ventilated. In some centers, infants are paralyzed from birth to stop them from swallowing, which can increase the dimensions of the bowel and worsen respiratory failure.

B. In the neonatal intensive care unit (NICU)

1. Sudden collapse with apnea and bradycardia, with failure to establish satisfactory ventilation after a short period of face mask ventilation.
2. Massive pulmonary hemorrhage: Such infants should be intubated, and ventilated with high positive end-expiratory pressure (PEEP).

II. Relative indications

A. In the delivery room

1. Infants of extremely low gestational age may be electively intubated to receive prophylactic surfactant therapy; in some centers, infants are immediately extubated to CPAP. In other centers, continuous positive airway pressure is used as an alternative to elective intubation and mechanical ventilation and surfactant is given as “rescue” therapy.

A. Greenough, MD (✉) • A.D. Milner, MD
Division of Asthma, Allergy and Lung Biology, King’s College London,
London SE5 9RS, UK
e-mail: anne.greenough@kcl.ac.uk

B. In the NICU

1. Worsening respiratory failure—the criteria depend upon the gestational age of the infant.
 - a. <28 weeks' gestation: Arterial carbon dioxide tension (PaCO_2) >45–55 Torr (6.0–7.3 kPa), the lower limit if associated with a pH <7.25 and/or arterial oxygen tension (PaO_2) <50–60 Torr (6.7–8 kPa) in a fractional inspired oxygen (FiO_2) of greater than 0.40, although if the infants only have poor oxygenation nasal CPAP may be tried first.
 - b. 28–32 weeks' gestation: PaCO_2 >45–55 Torr (6.0–7.0 kPa), the lower limit being used if the pH is <7.25 and/or PaO_2 <50–60 Torr (6.7–8 kPa) in an FiO_2 of greater than 0.6, if nasal CPAP has failed to improve blood gas tensions.
 - c. ≥ 33 weeks' gestation: If the PaCO_2 exceeds 60 Torr (8 kPa) with a pH below 7.25 and/or PaO_2 <45 Torr (6 kPa) in an FiO_2 of >0.80. CPAP is usually less well-tolerated in mature infants. (N.B.: In centers which prefer to use CPAP rather than intubation and mechanical ventilation, more severe blood gas abnormalities may be used as criteria for intubation).
2. Stabilization of infants at risk for sudden collapse
 - a. Small preterm infants with recurrent apnea unresponsive to nasal CPAP and administration of methylxanthines
 - b. Severe sepsis
 - c. Need to maintain airway patency
3. To maintain control of carbon dioxide tension

Suggested Reading

- Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal–perinatal medicine: diseases of the fetus and infant. 8th ed. St. Louis: Elsevier/Mosby; 2011. p. 1116–40.
- Greenough A, Milner AD. Acute respiratory disease. In: Rennie JM, editor. Robertson's textbook of neonatology. 4th ed. Edinburgh: Elsevier Churchill Livingstone; 2005. p. 468–553.

Chapter 61

Respiratory Distress Syndrome

Steven M. Donn and Sunil K. Sinha

(Case Study by Brooke D. Vergales and Jay P. Goldsmith)

I. Description

- A. Respiratory distress syndrome (RDS) is a primary pulmonary disorder that accompanies prematurity, specifically immaturity of the lungs, and to a lesser extent the airways. It is a disease of progressive atelectasis, which in its most severe form can lead to severe respiratory failure and death.
- B. The incidence and severity of RDS are generally inversely related to gestational age. Approximate incidence:
 - 1. 24 weeks—>80%
 - 2. 28 weeks—70%
 - 3. 32 weeks—25%
 - 4. 36 weeks—5%

II. Pathophysiology

A. Biochemical abnormalities

- 1. The major hallmark is a deficiency of surfactant, which leads to higher surface tension at the alveolar surface and interferes with the normal exchange of respiratory gases.

S.M. Donn, MD, FAAP (✉)

Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

S.K. Sinha, MD, PhD, FRCP, FRCPC

Department of Neonatal Medicine, The James Cook University Hospital, University of Durham,
Marton Road, Marton-in-Cleveland, Middlesbrough TS4 3BW, UK
e-mail: sunil.sinha@tees.nhs.uk

2. The higher surface tension requires greater distending pressure to inflate the alveoli, according to LaPlace's law:

$$P = 2T / r,$$

where P =pressure, T =surface tension, and r =radius of curvature.

3. As the radius of the alveolus decreases (atelectasis) and as surface tension increases, the amount of pressure required to overcome these forces increases.

B. Morphologic/anatomic abnormalities

1. The number of functional alveoli (and thus the surface area available for gas exchange) decreases with decreasing gestational age.
2. With extreme prematurity (23–25 weeks), the distance from the alveolus or terminal bronchiole to the nearest adjacent capillary increases, thus increasing the diffusion barrier and interfering with oxygen transport from lung to blood.
3. Septal wall thickness is also inversely proportional to gestational age.
4. The airways of the preterm infant are incompletely formed and lack sufficient cartilage to remain patent. This can lead to collapse and increased airway resistance.
5. The chest wall of the preterm newborn is more compliant than the lungs, tending to collapse when the infant attempts to increase negative intrathoracic pressure.

C. Functional abnormalities

1. Decreased compliance
2. Increased resistance
3. Ventilation/perfusion abnormalities
4. Impaired gas exchange
5. Increased work of breathing

D. Histopathologic abnormalities

1. The disorder was originally referred to as hyaline membrane disease as a result of the typical postmortem findings in nonsurvivors.
2. Macroscopic findings.
 - a. Decreased aeration
 - b. Firm, rubbery, "liver-like" lungs
3. Microscopic findings.
 - a. Air spaces filled with an eosinophilic-staining exudate composed of a proteinaceous material, with and without inflammatory cells
 - b. Edema in the air spaces
 - c. Alveolar collapse
 - d. Squamous metaplasia of respiratory epithelium
 - e. Distended lymphatics
 - f. Thickening of pulmonary arterioles

III. Clinical manifestations of RDS

- A. Tachypnea: The affected infant breathes rapidly, attempting to compensate for small tidal volumes by increasing respiratory frequency to maintain minute ventilation.
- B. Flaring of the ala nasi: This increases the cross-sectional area of the nasal passages and decreases upper airway resistance.
- C. Grunting: This is an attempt by the infant to produce positive end-expiratory pressure (PEEP) by exhaling against a closed glottis. Its purpose is to maintain some degree of alveolar volume (distention) so that the radius of the alveolus is larger and the amount of work needed to expand it further is less than if the radius were smaller.
- D. Retractions: The infant utilizes the accessory muscles of respiration, such as the intercostals, to help overcome the increased pressure required to inflate the lungs.
- E. Cyanosis: This is a reflection of impaired oxygenation, when there is >5 g/dL of deoxygenated hemoglobin.

IV. Radiographic findings

- A. The classic description is a “ground glass” or “reticulo-granular” pattern with air bronchograms (Chap. 21).
- B. Severe cases with near-total atelectasis may show complete opacification of the lung fields (“white out”).
- C. Extremely preterm infants with a minimal number of alveoli may actually have clear lung fields.
- D. Most cases show diminished lung volumes (unless positive pressure is being applied).

V. Laboratory abnormalities

- A. Arterial oxygen tension is usually decreased.
- B. Arterial carbon dioxide tension may be initially normal if the infant is able to compensate (tachypnea), but it is usually increased.
- C. Blood pH may reflect a respiratory acidosis (from hypercarbia), metabolic acidosis (from tissue hypoxia), or mixed acidosis.

VI. Diagnosis

- A. Clinical evidence of respiratory distress
- B. Radiographic findings
- C. Laboratory abnormalities from impaired gas exchange

VII. Differential diagnoses

- A. Sepsis/pneumonia, especially Group B streptococcal infection, which can produce a nearly identical radiographic picture
- B. Transient tachypnea of the newborn

- C. Pulmonary malformations (e.g., cystic adenomatoid malformation, congenital lobar emphysema, diaphragmatic hernia)
- D. Extrapulmonary abnormalities (e.g., vascular ring, ascites, abdominal mass)

VIII. Treatment

A. Establish adequate gas exchange

1. If the infant is only mildly affected and has reasonable respiratory effort and effective ventilation, only an increase in the FiO_2 may be necessary. This can be provided by an oxygen hood or nasal cannula.
2. If the infant is exhibiting evidence of alveolar hypoventilation ($\text{PaCO}_2 > 50$ Torr or 6.7 kPa) or hypoxemia ($\text{PaO}_2 < 50$ Torr or 6.7 kPa in $\text{FiO}_2 \geq 0.5$), some form of positive pressure ventilation is indicated.
 - a. Consider the use of continuous positive airway pressure (CPAP) if the infant has reasonable spontaneous respiratory effort and has only minimal hypercapnia (Chap. 26). A level of 4–8 cm H_2O should be used.
 - b. Consider endotracheal intubation and mechanical ventilation (Chap. 60) if there is:
 - (1) Hypercapnia ($\text{PaCO}_2 > 60$ Torr or 8 kPa)
 - (2) Hypoxemia ($\text{PaO}_2 < 50$ Torr or 6.7 kPa)
 - (3) Decreased respiratory drive or apnea
 - (4) Need to maintain airway patency
 - (5) Plan to administer surfactant replacement therapy
 - c. Mechanical ventilation
 - (1) The goal is to achieve adequate pulmonary gas exchange while decreasing the patient's work of breathing.
 - (2) Either conventional mechanical ventilation or high frequency ventilation can be used.
 - (3) RDS is a disorder of low lung volume, so the approach should be one that delivers an appropriate tidal volume while minimizing the risks of complications (see below).

B. Surfactant replacement therapy (Chap. 51)

1. The development and use of surfactant replacement therapy have revolutionized the treatment of RDS.
2. Numerous preparations (natural, synthetic, and semisynthetic) are now available.
3. Types of intervention
 - a. Prophylaxis—infant is immediately intubated and given surfactant as close to the first breath as possible.

- (1) One option is intubation, administration of surfactant, and continued mechanical ventilation until the baby is ready for extubation.
 - (2) Another option is to intubate, administer surfactant, and extubate to CPAP. The evidence supporting this practice in the more pre-term baby is not convincing.
- b. Rescue—infant is not treated until the diagnosis is established.
4. Dose and interval are different for each preparation.
 5. Although there is little doubt as to efficacy, the treatment is still very expensive.

C. Adjunctive measures

1. Maintain adequate blood pressure (and hence pulmonary blood flow) with judicious use of blood volume expanders and pressors.
2. Maintain adequate oxygen carrying capacity (Hgb) in infants with a high oxygen ($\text{FiO}_2 > 0.4$) requirement.
3. Maintain physiologic pH, but do not give sodium bicarbonate if hypercarbia is present.
4. Maintain adequate sedation/analgesia (Chap. 54), but avoid respiratory depression, which delays weaning.
5. Provide adequate nutrition (Chap. 50), but avoid excessive non-nitrogen calories, which can increase CO_2 production and exacerbate hypercapnia.
6. Observe closely for signs of complications, especially infection.

IX. Complications

A. Respiratory

1. Air leaks
 - a. Pneumomediastinum
 - b. Pulmonary interstitial emphysema
 - c. Pneumothorax
 - d. Pneumopericardium
 - e. Pneumoperitoneum (trans-diaphragmatic)
 - f. Subcutaneous emphysema
2. Airway injury
3. Pulmonary hemorrhage (Chap. 74)
4. Bronchopulmonary dysplasia (Chaps. 69–71).

B. Cardiac

1. Patent ductus arteriosus (Chap. 73)
2. Congestive heart failure

3. Pulmonary hypertension (Chap. 64)
 4. Cor pulmonale
- C. Neurologic (Chap. 76)
1. Relationship to intraventricular hemorrhage
 2. Relationship to periventricular leukomalacia
 3. Neurodevelopmental impact
- D. Infectious
1. Nosocomial and acquired pneumonia (Chap. 62)
 2. Sepsis
- X. Prenatal treatments and conditions which impact RDS
- A. Antenatal treatment of the mother with corticosteroids has been demonstrated to reduce the incidence and severity of RDS, particularly if given between 28 and 32 weeks' gestation.
1. Betamethasone
 2. Dexamethasone
- B. Other agents have been explored, but results are thus far unconvincing.
1. Thyroid hormone
 2. Thyrotropin
- C. Accelerated pulmonary (i.e., surfactant system) maturation is seen in:
1. Intrauterine growth retardation
 2. Infants of substance-abusing mothers
 3. Prolonged rupture of the membranes
- D. Delayed pulmonary maturation is seen in:
1. Infants of diabetic mothers
 2. Rh-sensitized fetuses
 3. Infants of hypothyroid mothers
 4. Infants with hypothyroidism

Suggested Reading

- Cotton RB. Pathophysiology of hyaline membrane disease (excluding surfactant). In: Polin RA, Fox WW, editors. *Fetal and neonatal physiology*. 2nd ed. Philadelphia: Saunders; 1998. p. 1165–74.
- Donn SM. Neonatal ventilators: how do they differ? *J Perinatol*. 2009;29:s73–8.
- Greenough A, Dixon AK, Robertson NR. Pulmonary interstitial emphysema. *Arch Dis Child*. 1984;59:1046.
- Hamvas A. Pathophysiology and management of Respiratory Distress Syndrome. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Neonatal-perinatal medicine. Diseases of the fetus and infant*. 9th ed. St Louis: Elsevier Mosby; 2011. p. 1106–16.
- Kattwinkel J. Surfactant: evolving issues. *Clin Perinatol*. 1998;25:17–32.
- Kezler M. State of the art in conventional mechanical ventilation. *J Perinatol*. 2009;29:1–14.
- Keszler M, Donn SM, Bucciarelli RL, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. *J Pediatr*. 1991;119:85–93.
- Martin GI, Sindel BD. Neonatal management of the very low birth weight infant: the use of surfactant. *Clin Perinatol*. 1992;19:461–8.
- Nelson M, Becker MA, Donn SM. Basic neonatal respiratory disorders. In: Donn SM, editor. *Neonatal and Pediatric pulmonary graphics: principles and clinical applications*. Armonk, NY: Futura; 1998. p. 253–78.
- Phatek RS, Paireudeau CF, Smith CJ, Paireudeau PW, Klonin H. Heliox with inhaled nitric oxide: a novel strategy for severe localized interstitial pulmonary emphysema in preterm neonatal ventilation. *Resp Care*. 2008;53:12.
- Robertson B, Halliday HL. Principles of surfactant replacement. *Biochim Biophys Acta*. 1998;1408:346–61.
- Walsh MC, Carlo WA, Miller MJ. Respiratory diseases of the newborn. In: Carlo WA, Chatburn RL, editors. *Neonatal respiratory care*. 2nd ed. Chicago: Year Book Medical; 1988. p. 260–88.
- Verma RP, Chandra S, Niwas R, Komaroff E. Risk factors and clinical outcomes of pulmonary interstitial emphysema in extremely low birth weight infants. *J Perinatol*. 2006;26:197–200. II.

Ventilatory Case Study

Brooke D. Vergales, MD
Jay P. Goldsmith, MD

A. Prenatal data

1. Mother: 24 year-old G2 P1→2 with intractable advanced preterm labor at 25 weeks' gestation despite magnesium sulfate tocolysis.
2. One dose of betamethasone given 2 h before delivery; no clinical evidence of infection.

B. Patient data

1. 680 g male born by spontaneous vaginal delivery, vertex presentation
2. Apgar scores of 3 (1 min) and 5 (5 min)
3. Intubated at 2 min of life, stiff lungs requiring high ventilatory pressures in delivery room
4. Surfactant given at 14 min of age in delivery room

C. Physical findings

1. Severe respiratory distress: Retractions, poor air exchange, wet rales bilaterally
2. Hypotonia
3. Fused eyelids, poor skin integrity, visible veins

D. Clinical course

1. Conventional mechanical ventilation (CMV): Increasing ventilatory support up to peak inspiratory pressure (PIP) 26 cm H₂O, rate to 60 breaths per minute (bpm), FiO₂ 0.6–1.0. Switched to high-frequency oscillatory ventilation (HFOV).
2. Dopamine to support blood pressure.
3. Increasing CO₂ retention despite increasing delta P and mean airway pressure (P_{aw}).
4. Repeat surfactant given via endotracheal tube at 6 and 12 h of age.

E. Chest radiographs

1. Fig. 61.1. Chest X-ray (CXR) 1 h after birth showing severe respiratory distress syndrome (RDS) with ground glass appearance, air bronchograms, and decreased lung volume.
2. Fig. 61.2. CXR taken at 15 h of life showing microradio-lucencies throughout all lung fields with areas of large bullae and hyperinflation.

(continued)

(continued)

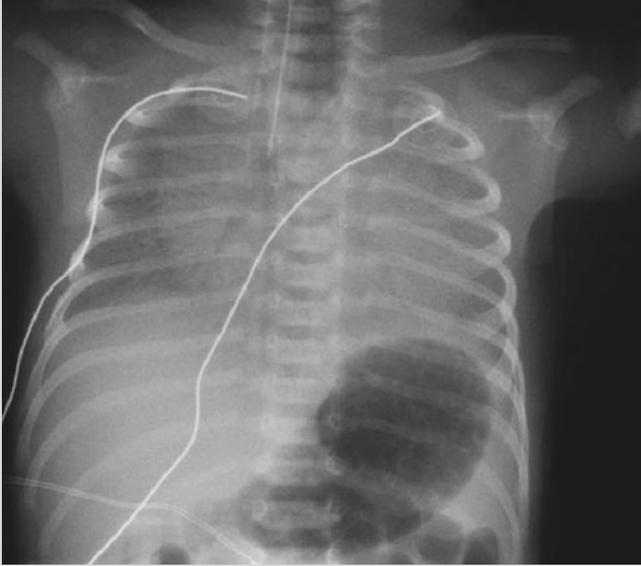


Fig. 61.1 Chest radiograph 1 h after birth showing ground glass appearance, air bronchograms, and decreased lung volume consistent with respiratory distress syndrome (RDS)

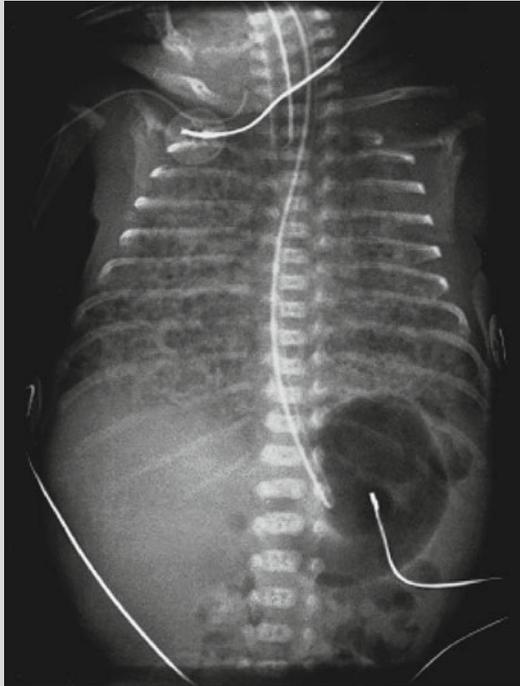


Fig. 61.2 Chest radiographs taken at 15 h of life showing microradiolucencies throughout all lung fields with areas of bullae and hyperinflation

(continued)

(continued)

F. Laboratory values

1. Normal CBC, CRP < 0.3
2. Increasing hypercapnia and acidosis with increased base deficit over first 15 h of life

G. Diagnosis

1. Severe RDS complicated by pulmonary interstitial emphysema (PIE)
2. Concern for necrotizing pneumonitis (doubt, too early)
3. Possible lobar emphysema or cystic adenomatoid malformation of the lung (doubt, disease process too generalized)

H. Potential therapies

1. Change to high-frequency jet ventilation (HFJV)—low volume strategy
2. Start inhaled heliox as a strategy to control rising PaCO₂ and acidosis (although at present FiO₂ is too high and use in preterm infants is unestablished)
3. Linear pleurotomies or scarification of lungs with creation of pneumothoraces and placement of chest tubes
4. Positional therapy or single lung inflation with selective intubation (works best with unilateral PIE)

I. Denouement

1. Conservative therapy and high-frequency ventilation not successful
2. Patient developed spontaneous pneumothoraces which were relieved with bilateral chest tubes
3. Prolonged ventilatory support with the development of bronchopulmonary dysplasia and grade 3 intraventricular hemorrhage (IVH)
4. Discharged on oxygen at 3 months of age

Chapter 62

Pneumonia

Elvira Parravicini and Richard A. Polin

I. Background

- A. An estimated 800,000 deaths occur worldwide from respiratory infections in newborn infants.
- B. Four varieties of pneumonia occur in newborn infants (differ in pathogens and routes of acquisition).
 - 1. Congenital pneumonia: acquired by transplacental transmission of infectious agents (usually one manifestation of a generalized infection).
 - 2. Intrauterine pneumonia: associated with intrauterine bacterial infection (chorioamnionitis/choriodecidualitis); may be noninfectious and associated with fetal asphyxia.
 - 3. Pneumonia acquired during birth: caused by organisms colonizing the genital tract.
 - 4. Pneumonia acquired after birth: in the nursery (health-care-associated infection) or at home.
- C. Lung host defenses.
 - 1. Local and systemic host defenses are diminished in newborn infants.
 - a. Lack of secretory IgA in the nasopharynx and upper airway.
 - b. Developmental differences in expression of toll-like receptors.

E. Parravicini, MD (✉)

Division of Neonatology, Department of Pediatrics, NY Presbyterian Morgan Stanley Children's Hospital, 3959 Broadway, Room CHN 1213, 10032, New York, NY, USA
e-mail: ep127@columbia.edu

R.A. Polin, MD

Division of Neonatology, Department of Pediatrics, NY Presbyterian Morgan Stanley Children's Hospital, 3959 Broadway, Room CHN 1201, 10032, New York, NY, USA

- c. Reduced expression of β -defensins
[Absence of protective antibody for common bacterial pathogens (e.g., group B streptococcus (GBS)].
 - d. Lower complement levels.
 - e. Diminished phagocyte function (chemotaxis, phagocytosis, and killing) especially in stressed neonates.
 - f. Slower development of inflammatory responses.
2. Endotracheal tubes promote colonization of the trachea and injure the mucosa (portal for entry); oxygen interferes with ciliary function and mucosal integrity.

II. Congenital pneumonia

A. Toxoplasmosis

1. Transmission: result of primary maternal infection during pregnancy
2. Pathology
 - a. Widened and edematous alveolar septa infiltrated with mononuclear cells.
 - b. Walls of small blood vessels are infiltrated with lymphocytes and mononuclear cells.
 - c. Parasites may be found in endothelial cells and the epithelium lining small airways.
3. Manifestations
 - a. Infected infants may be asymptomatic (>80%), exhibit neurologic findings (chorioretinitis, hydrocephalus, and calcification), or demonstrate a generalized systemic illness (IUGR, hepatosplenomegaly, pneumonia, etc.).
 - b. Pneumonia is observed in 20–40% of infants with generalized disease. Infants exhibit signs of respiratory distress/sepsis along with other manifestations of systemic disease (e.g., hepatosplenomegaly).
 - c. Respiratory distress may result from superinfection with other pathogens.
4. Diagnosis
 - a. Infants with a suspected infection from *Toxoplasma* should have ophthalmologic, auditory, and neurologic examinations including lumbar puncture and cranial imaging.
 - b. Demonstration of tachyzoites in tissue (placenta, umbilical cord, or blood specimen from the infant) by mouse inoculation is definitive.
 - c. Peripheral white blood cells, CSF, and amniotic fluid specimens can be assayed by PCR in a reference laboratory.
 - d. Detection of *Toxoplasma* specific IgM or IgA antibodies is diagnostic; however, any infant with a positive titer should be retested at 10 days of age to exclude placental leak.
 - e. Persistence of IgG titers to *T. gondii* beyond 6–12 months is highly suggestive.

- f. There is a high incidence of false negative results with the IgM indirect immunofluorescent antibody (IFA) test.
- g. The double-sandwich IgM capture ELISA and the IgM immunosorbent agglutination assay (ISAGA) have a sensitivity of 75–80% and a lower incidence of false positive reactions.

5. Treatment and prognosis

- a. Pyrimethamine and sulfidiazene (plus folinic acid).
- b. Most infants survive with good supportive care; however, up to 30% of treated infants with ophthalmologic or neurologic manifestations at birth exhibit neurologic sequelae.

B. Cytomegalovirus

1. Transmission

- a. CMV transmission can occur *during pregnancy* by transplacental viral passage, *at birth* by exposure to CMV in cervical secretions, or *postnatally* by ingestion of contaminated breast milk. The latter two modalities of transmission usually do not result in a symptomatic infection.
- b. CMV transmission to preterm infants, by any route, including exposure to CMV-positive blood products, can be associated with systemic infections, including pneumonia.

2. Pathology

- a. Pneumocytes contain characteristic intranuclear inclusions.
- b. Minimal inflammatory reaction.

3. Manifestations

- a. Most common congenital infection (~1% of all newborns).
- b. Only 10% of congenitally infected newborns have clinically apparent disease.
- c. A diffuse interstitial pneumonitis occurs in <1% of congenitally infected, symptomatic infants.
- d. Common signs of congenital infection at birth include intrauterine growth restriction, microcephaly, intracerebral calcifications, retinitis, hepatosplenomegaly, jaundice, and purpura.
- e. Common sequelae include developmental delay and hearing loss.

4. Diagnosis

- a. Virus isolation from urine or other infected fluids is best.
- b. Anti-CMV IgM is suggestive, but antibody assays vary in accuracy for identification of primary infection.
- c. A presumptive diagnosis can be made on the basis of a fourfold antibody titer increase and by detection of viral DNA in tissues and body fluids.

5. Treatment and prognosis

- a. There are limited data on the use of Ganciclovir in neonates with CNS involvement.
- b. Symptomatic preterm infants (pneumonitis and hepatitis) can be treated, although no efficacy data exist.

C. Herpes simplex virus

1. Transmission

- a. Infants can acquire HSV through an infected maternal genital tract or by an ascending infection with intact membranes. The risk of transmission is 25–50% for infants born to mothers with primary infection, but only 1–2% with viral reactivation.
- b. Transmission by contact (hands) in the nursery is unlikely.

2. Pathology: Diffuse interstitial pneumonitis, which progresses to a hemorrhagic pneumonitis

3. Manifestations

- a. Most HSV infections in the neonate are symptomatic, but 20% of infants never develop vesicles.
- b. Three varieties: localized disease (skin, eye, or mouth), encephalitis with or without localized disease, or disseminated infection (mainly liver and lungs).
- c. Half the infants are born prematurely. *RDS must always be a consideration.*
- d. Infants with disseminated infection usually present between the first and second week of life, with signs of bacterial sepsis or shock, liver dysfunction (hepatitis), and respiratory distress.
- e. Infants with CNS involvement typically present in the second or third week of life, but occasionally up to 6 weeks.

4. Diagnosis

- a. Positive viral cultures (oropharyngeal and respiratory secretions, conjunctiva and rectum, skin vesicles, blood, and CSF), obtained 12–24 h after birth, are suggestive of infection.
- b. Direct immunofluorescence of skin lesion specimens and PCR assay on cerebrospinal fluid are useful.

5. Treatment and prognosis

- a. Intravenous acyclovir and supportive care.
- b. Mortality is highest with disseminated infection, but is improved with acyclovir.

D. *Treponema pallidum*

1. Transmission

- a. Vertical transmission can happen at any time during pregnancy or during delivery.
- b. The rate of transmission increases with advancing gestation.
- c. Transmission rates are highest for early primary syphilis (60–100%) and lowest for late, latent infections.
- d. Untreated maternal syphilis can result in abortion, hydrops fetalis, fetal demise, stillbirth, prematurity, congenital infection, or perinatal death.

2. Pathology

- a. “Pneumonia alba” is characterized grossly as heavy, firm, yellow-white enlarged lungs.
- b. Marked increase in connective tissue in the interalveolar septa and the interstitium with collapse of the alveolar spaces.

3. Manifestations

- a. Infants with early congenital syphilis present between birth and 3 months of age.
- b. Two-thirds of infected infants are asymptomatic at birth.
- c. Early congenital syphilis should be suspected in any infant with unexplained prematurity, hydrops, or an enlarged placenta.
- d. Pneumonia is an uncommon manifestation.
- e. Common manifestations of “early congenital syphilis” include hepatosplenomegaly, anemia, leukopenia or leukocytosis, generalized lymphadenopathy, rhinitis, nephrotic syndrome, maculopapular rash, bony abnormalities, and leptomeningitis.

4. Diagnosis

- a. Confirmation of *T. pallidum* by dark-field microscopy.
- b. Antibody titers (VDRL/RPR) from infant that are fourfold greater than maternal titers *or* a positive VDRL in a spinal fluid specimen *or* a positive VDRL in an infant with clinical findings consistent with syphilis.
- c. IgM by FTA-ABS is not recommended (20–39% incidence of false negative and 10% incidence of false positive results).
- d. PCR tests have been developed, but are not widely available.

5. Treatment and prognosis

- a. All symptomatic newborn infants with a positive RPR should be treated as if they have congenital infection.

- b. Penicillin is the drug of choice.
- c. The earlier the treatment is initiated, the greater the likelihood of a good outcome (prevention of stigmata).

III. Pneumonia acquired before, during, or after birth

A. Background: Time of presentation varies

1. The onset of respiratory distress immediately after birth suggests aspiration of infected amniotic fluid in utero.
2. A “delayed” presentation (1–3 days) results from colonization of mucoepithelial surfaces and seeding of the blood stream.

B. Pathology

1. Dense cellular exudate, congestion, hemorrhage, and necrosis.
2. *Staphylococcus aureus* and *Klebsiella* may cause microabscesses and pneumatoceles.
3. Hyaline membranes are common (especially in preterm infants), and bacteria may be seen within the membranes.

C. Pathophysiology of lung injury

1. Direct invasion of lung tissue by bacteria (bacterial pathogens secrete microbial enzymes and toxins that disrupt cell membranes, disturb metabolism, and interfere with the supply of nutrients).
2. Indirect injury secondary to the host inflammatory response [mediated by phagocytes and the inflammatory cascade (cytokines, complement, and coagulation)].
3. Airway obstruction from inflammatory debris.
4. Alteration in surfactant composition and function (secondary to leak of proteinaceous material or presence of meconium).

D. Disturbances in lung function

1. Increased airway resistance from inflammatory debris and airway smooth muscle constriction.
2. Decreased lung compliance (atelectasis and parenchymal inflammation).
3. Ventilation–perfusion (V/Q) abnormalities (intrapulmonary shunts).
4. Pulmonary hypertension secondary to release of vasoactive mediators.
5. Alveolar diffusion barriers.

E. Epidemiology

1. Identical to that for early-onset bacterial sepsis
2. Risk factors
 - a. Prematurity and low birth weight
 - b. Low socioeconomic status
 - c. Male gender
 - d. Colonization with a known pathogen (e.g., GBS)

- e. Prolonged rupture of membranes >18 h
- f. Galactosemia; increased susceptibility to infections with gram-negative organisms
- g. Preterm premature rupture of membranes
- h. Signs of chorioamnionitis (maternal fever >38°C, abdominal tenderness, foul-smelling or cloudy amniotic fluid)
 - (1) Chorioamnionitis can be subclinical or clinical
 - (2) Subclinical chorioamnionitis may be a risk factor for BPD (see “Ureaplasma” below)

F. Pathogenesis

1. Infection begins with colonization of the maternal genital tract.
2. Organisms that colonize the cervix, vagina, or rectum spread upward into the amniotic cavity through intact or ruptured membranes (causing amnionitis).
3. The fetus either inhales infected amniotic fluid (and exhibits immediate onset of respiratory distress) or becomes colonized and becomes symptomatic after an asymptomatic interval.

G. Bacterial pathogens

1. *Streptococcus agalactiae* (group B streptococcus-GBS)
 - a. Most common bacterial pathogen in term infants.
 - b. 15–40% of women are colonized with GBS.
 - c. Women who are “culture positive” are more than 25 times likely to deliver an infant with early-onset sepsis than “culture negative” women.
 - d. Intrapartum antibiotics have reduced the incidence of early-onset GBS sepsis by 80%.
 - e. In the absence of intrapartum antibiotics, the vertical transmission rate is ~50% and the risk of infection (sepsis and pneumonia) in colonized infants is 1–2%.
2. *Escherichia coli*
 - a. Most common pathogen in preterm infants (6.8/1,000 live births).
 - b. Most strains causing sepsis are resistant to ampicillin.
 - c. Associated with a higher mortality than infection from gram-positive organisms.
3. *Listeria monocytogenes*
 - a. Most infections are caused by three serotypes (1a, 1b, and 4b).
 - b. Almost all cases originate from ingestion of contaminated food.
 - c. May cause acute bacterial sepsis (when acquired during labor and delivery), a widely disseminated granulomatous infection (when acquired in utero), or late-onset disease (frequently meningitis).

- d. *Listeria* can be transmitted to the fetus transplacentally or via an ascending infection.
 - e. Commonly results in preterm delivery.
 - f. Maternal “influenza-like” infection precedes delivery in 50% of cases.
 - g. Two-thirds of infants who survive delivery to a woman with Listeriosis will develop neonatal infection.
4. Other pathogens: *Staphylococcus aureus*, *Haemophilus* species, *Enterococcus*, *Streptococcus viridans*, *Klebsiella*, *Enterobacter* species, Group A *Streptococcus*, and Coagulase negative *Staphylococcus*

H. Clinical history (suggestive of sepsis/pneumonia)

- 1. Prolonged rupture of membranes >18 h
- 2. Maternal signs and symptoms of chorioamnionitis
- 3. Colonization with GBS (adequate intrapartum therapy lowers the risk of infection by 85–90%)
- 4. Maternal urinary tract infection
- 5. Preterm premature rupture of membranes
- 6. Preterm labor
- 7. Unexplained fetal tachycardia
- 8. Meconium (decreases the antibacterial properties of amniotic fluid)

I. Clinical manifestations

- 1. Signs of sepsis/pneumonia can be subtle (tachypnea) or overt (grunting flaring, retracting)
- 2. Pulmonary findings
 - a. Tachypnea (respiratory rate >60/min)
 - b. Grunting
 - c. Flaring
 - d. Retractions
 - e. Rales or rhonchi
 - f. Cyanosis
 - g. Change in the quality of secretions (serosanguinous or purulent)
- 3. Systemic findings (nonpulmonary)
 - a. Apnea
 - b. Lethargy
 - c. Irritability
 - d. Hypothermia, hyperthermia, or temperature instability
 - e. Poor perfusion or hypotension (manifest as oliguria or metabolic acidosis)
 - f. Pulmonary hypertension
 - g. Abdominal distention

J. Diagnosis

1. General concepts

- a. Laboratory testing (in general) is not useful for identifying infants that are likely to have bacterial sepsis/pneumonia (i.e., most laboratory tests have a low positive predictive value).
- b. Testing is helpful in deciding which infants are *not likely* to be infected and who do not require antibiotics (high negative predictive value).
- c. In infants with proven sepsis/pneumonia, laboratory tests (e.g., white blood count, neutrophil indices, acute phase reactants) obtained at birth are frequently normal. Tests obtained 8–12 h following birth have a higher likelihood of being abnormal.
- d. The only absolute way to make the diagnosis of bacterial sepsis/pneumonia is to recover an organism from a normally sterile site (blood, urine, cerebrospinal fluid, pleural fluid). The presence of bacteria from a tracheal aspirate obtained *immediately after intubation* is presumptive evidence of infection.
- e. Infants with evolving sepsis/pneumonia can be asymptomatic at the time of birth.
- f. All symptomatic infants should be cultured and treated. Some infants exhibit transient signs and symptoms that resolve quickly (within a few hours of birth), and these infants may not require treatment.
- g. Figure 62.1 summarizes the 2010 recommendation by the Center for Disease Control for the evaluation of infants at risk for early-onset GBS sepsis.

2. Cultures

- a. A positive blood culture is the “gold standard” for detection of bacteremia in the newborn.
- b. Urine cultures are rarely positive in infants with early-onset bacterial sepsis and should not be routinely obtained.
- c. A lumbar puncture should be performed in all infants with a positive blood culture *or* in symptomatic infants with a high probability of infection based on adjunct laboratory studies, *or* infants with a poor response to conventional antimicrobial treatment. The lumbar puncture should be deferred in any infant who is clinically unstable or who has an uncorrected bleeding diathesis.

3. Adjunct laboratory tests

- a. Neutrophil indices (absolute neutrophil count, absolute band count, and immature-to-total neutrophil (I/T ratio)) are more useful than total leukocyte counts.
- b. The most sensitive index is the I/T ratio, and the most specific index is neutropenia.

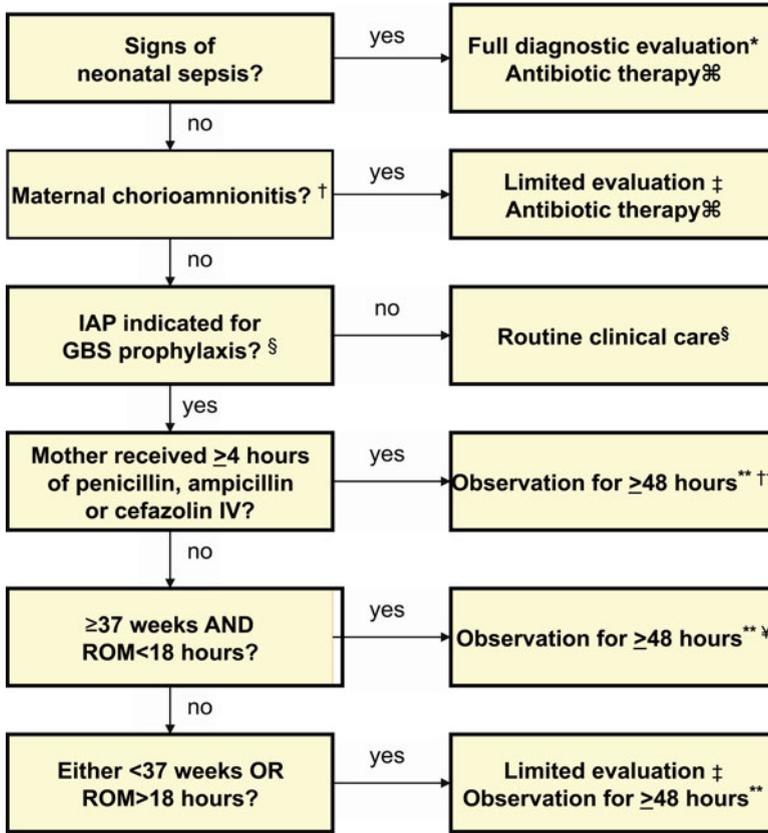


Fig. 62.1 *Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell and platelet counts, chest radiograph (if respiratory abnormalities are present), and LP (if patient stable enough to tolerate procedure and sepsis is suspected). †Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are non specific. ®Antibiotic therapy should be directed toward the most common causes of neonatal sepsis including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance pattern. §Limited evaluation includes blood culture (at birth) CBC with differential and platelets (at birth and/or 6–12 h of life). §GBS prophylaxis indicated if one or more of the following: (1) positive GBS vaginal rectal culture in late gestation, (2) GBS status unknown with one or more intrapartum risk factors including <37 weeks gestation, ROM ≥ 18 h or temperature ≥100.4°F (38.0°C), GBS bacteriuria during the current pregnancy, (4) history of a previous infant with GBS disease. **If signs of sepsis develop, a full diagnostic evaluation should be done and antibiotic therapy initiated. ††If >37 weeks gestation, observation may occur at home after 24 h if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 h and until discharge criteria have been achieved. ¥Some experts recommend a CBC with differential and platelets at 6–12 h of age

- c. There is no consensus on the neutrophil indices suggestive of infection; however, an absolute band count $\geq 2,000/\text{mm}^3$ or an I/T ratio ≥ 0.2 are both suggestive of neonatal sepsis.
- d. Lower limits for the absolute neutrophil count vary with gestational age (suggested cutoff values at 8–12 h of postnatal age are $< 8,000/\text{mm}^3$ in late preterm and term infants and $< 2,200/\text{mm}^3$ in very low birth weight infants).
- e. Infants delivered by cesarean section without labor have lower total neutrophil counts and infants delivered at high altitude may have higher absolute neutrophil counts.
- f. C-reactive protein (CRP) (an acute phase reactant) is a useful adjunctive test.
 - (1) Values rise slowly in infected infants (therefore, a CRP obtained at birth is not as useful as one obtained at 8–12 h of life).
 - (2) A CRP determination obtained 12–24 h following birth has a high negative predictive accuracy and is most useful for excluding the diagnosis of sepsis.
 - (3) A CRP value of ≥ 1 mg/dL is considered positive.
- g. *Sepsis Screens*: Suggested algorithms for the management of *asymptomatic infants* (< 37 weeks or ≥ 37 weeks) are shown below. These algorithms use physical examination in combination of laboratory tests [neutrophil indices (I/T ratio, absolute neutrophil count, and absolute band count) and CRP] to help with decisions about antibiotics.
 - (1) Sepsis screens are most useful for identifying infants with a low probability of infection (i.e., who do not require antibiotics or who no longer require antibiotics).
 - (2) Sepsis screens are not very useful for identifying infected infants (the positive predictive value is $< 40\%$).
 - (3) In applying these algorithms, major risk factors for sepsis are (Fig. 62.2a–c):
 - (a) Prematurity
 - (b) Prolonged rupture of membranes > 18 h
 - (c) Maternal signs and symptoms of chorioamnionitis (fever $\geq 100.4^\circ\text{F}$, uterine tenderness, foul-smelling or cloudy amniotic fluid)
 - (d) Colonization with GBS (GBS is not a risk factor if there has been adequate intrapartum treatment or the infant is delivered by elective cesarean section with intact membranes and no labor)

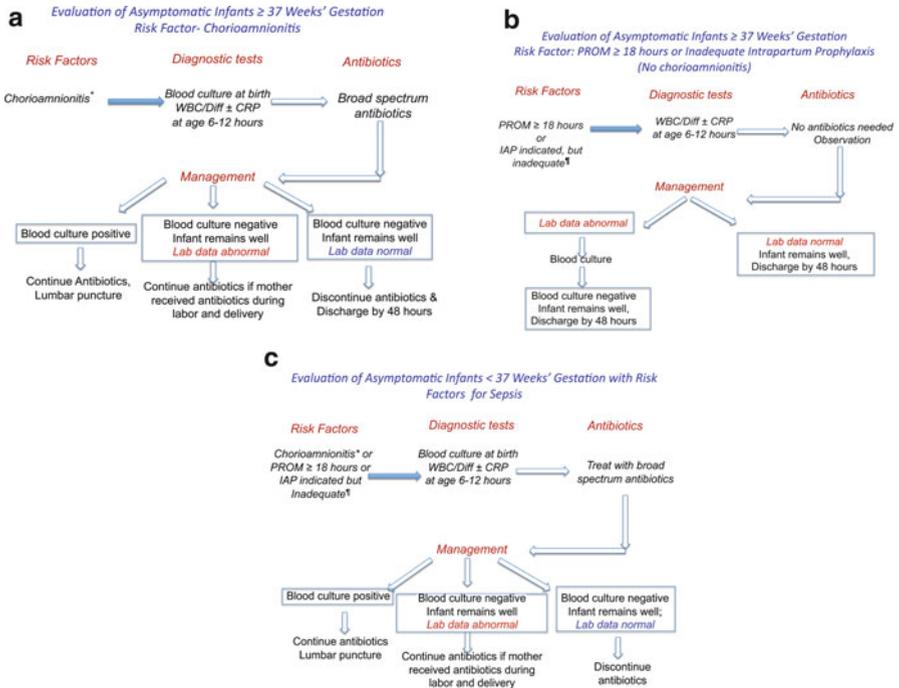


Fig. 62.2 (a) Evaluation of asymptomatic infants ≥37 weeks' gestation risk factor—chorioamnionitis. (b) Evaluation of asymptomatic infants ≥37 weeks' gestation risk factor: PROM ≥ 18 h or inadequate intrapartum prophylaxis (no chorioamnionitis). (c) Evaluation of asymptomatic infants <37 weeks' gestation with risk factor for sepsis

4. Chest radiographs

- a. In preterm infants the radiographic appearance of pneumonia may be indistinguishable from RDS (i.e., ground glass appearance and air bronchograms).
- b. In term infants, pneumonia more commonly causes hyperinflation with increased central peribronchial infiltrates and scattered subsegmental atelectasis.
- c. Other findings include effusions/empyema, hyperinflation, pneumatoceles (suggestive of *S. aureus*).

K. Management

1. Broad-spectrum antibiotics

- a. Choice depends on the predominant pathogen causing sepsis and the antibiotic sensitivity patterns for the microorganisms causing early-onset sepsis in a given NICU.

- b. Empiric therapy must cover both gram-positive and gram-negative organisms.
 - c. The most commonly used combination is ampicillin and an aminoglycoside (frequently gentamicin). Ampicillin and cefotaxime is an effective alternative, but resistance to cefotaxime develops quickly; therefore, cefotaxime should be reserved for infants with gram-negative meningitis.
 - d. None of the third generation cephalosporins are active against *L. monocytogenes* or *Enterococcus*.
 - e. After an organism has been identified the antibiotic therapy should be tailored according to the sensitivities.
 - (1) *Listeria monocytogenes* is treated with ampicillin. If meningitis is present ampicillin should be administered in combination with an aminoglycoside antibiotic.
 - (2) Enterococci are treated either with ampicillin and an aminoglycoside or vancomycin and an aminoglycoside depending on sensitivities.
 - (3) *Streptococcus agalactiae* is treated with penicillin or Ampicillin (Group B streptococci are demonstrating increasing resistance to erythromycin and clindamycin).
 - (4) *Staphylococcus aureus* is treated with penicillinase resistant penicillins (e.g., methicillin) or cephalosporins. Methicillin resistant organisms are treated with vancomycin. Bacterial resistance must be considered whenever *Staphylococcus aureus* is recovered.
 - (5) *Pseudomonas aeruginosa* infections are commonly treated with ticarcillin or carbenicillin and an aminoglycoside, but most are also sensitive to ceftazidime.
 - (6) Most other gram-negative infections can be treated with aminoglycoside antibiotics or cefotaxime.
 - f. Duration of therapy usually 7–10 days (3 weeks or longer for a pneumonia secondary to *S. aureus*).
2. Supportive care
- a. Hemodynamic support (volume and pressors) to assure adequate systemic perfusion.
 - b. Nutritional support; parenteral nutrition for any infant who will not be able to tolerate enteral feedings.
 - c. Respiratory support
 - (1) Oxygen to maintain saturation 88–94%.
 - (2) Use the least invasive form of respiratory support to achieve adequate oxygenation and ventilation.
 - (3) Chest physiotherapy (vibration and percussion) once the infant is clinically stable.

- (4) Judicious use of suctioning.
 - (5) Drainage of pleural effusions if lung function is compromised.
- d. Nitric oxide for term and late preterm infants with persistent hypoxemia despite maximal ventilatory support.
 - e. ECMO for term and late preterm infants unresponsive to above measures if criteria are met.
 - f. Surfactant treatment improves oxygenation and reduces the need for ECMO in neonates with pneumonia.

L. Prevention

1. The incidence of early-onset sepsis/pneumonia due to GBS can be diminished by intrapartum administration of antibiotics. The following “high risk” women should be treated:
 - a. Previous infant with invasive disease
 - b. GBS bacteriuria during pregnancy
 - c. Positive GBS screening culture during pregnancy
 - d. Unknown GBS status (culture not done, incomplete, or results unknown) and any of the following:
 - (1) Delivery at <37 weeks’ gestation
 - (2) Amniotic membrane rupture ≥ 18 h
 - (3) Intrapartum temperature $\geq 100.4^{\circ}\text{F}$ ($\geq 38^{\circ}\text{C}$)

IV. Atypical pneumonia: *Ureaplasma urealyticum*

A. Transmission

1. Although *U. urealyticum* is a frequent member of the lower genital tract of asymptomatic women, isolation of *U. urealyticum* from the chorion or amnion has been associated with premature labor and chorioamnionitis.
2. The vertical transmission rate ranges from 18% to 88% and is highest in preterm infants.
3. Transmission occurs in utero by ascending infection, even with intact membranes, by hematogenous route through placental infection, or at delivery by contact with a colonized vaginal canal.

B. Pathology

1. Patchy exudate of polymorphonuclear cells and swollen vacuolated macrophages are found in bronchioles and alveoli.
2. Prominent interstitial fibrosis of lung tissue (possible association with chronic lung disease).

C. Manifestations

1. *U. urealyticum* infection of the newborn is associated with pneumonia, meningitis, and hydrops fetalis.

2. Radiographs: radiating streakiness, coarse patchy infiltrates, subtle haziness, or diffuse granularity indistinguishable from RDS.

D. Diagnosis

1. Cultures (blood, urine, nasopharyngeal secretions, endotracheal aspirates) require special media and long incubation times.
2. PCR has a better sensitivity than culture and results are available in less than 24 h.
3. Serologic tests (*U. urealyticum* IgG and IgM) have limited value.

E. Treatment and prognosis

1. Prophylactic treatment of colonized women in preterm labor does not decrease mortality or morbidity and is not recommended.
2. Erythromycin is the drug of choice for infections that do not involve the CNS (a risk of hypertrophic pyloric stenosis has been reported with use of erythromycin).
3. Long-term morbidities include increased stay in the NICU and a possible association with BPD.

V. *Chlamydia trachomatis*

A. Transmission

1. In women colonized with *Chlamydia trachomatis*, 50% of offspring become colonized at the time of delivery, of which 30% develop conjunctivitis and 5–20% develop pneumonia between 1 and 3 months of life.
2. Systematic screening and treatment of Chlamydial infection during pregnancy markedly decreases perinatally acquired infections.

B. Pathology

1. Intra-alveolar inflammation with a mild degree of interstitial reaction.
2. Alveolar lining cells contain intracytoplasmic inclusions.

C. Manifestations

1. *C. trachomatis* pneumonia in newborn presents between 2 and 19 weeks of age with repetitive staccato cough, tachypnea, rales, and rarely wheezing or fever. Purulent conjunctivitis can be observed.
2. Significant laboratory findings include eosinophilia and elevated serum immunoglobulins. Chest radiography demonstrates hyperinflation and bilateral diffuse nonspecific infiltrates.

D. Diagnosis

1. Definitive diagnosis is made by culture (conjunctiva, nasopharynx, vagina, or rectum) or by nucleic acid amplification on nasopharyngeal or endotracheal aspirates. Because *Chlamydia* is an obligate intracellular organism, culture specimens must contain epithelial cells.

2. In infants with pneumonia the detection of specific IgM ($\geq 1:32$) is diagnostic.

E. Treatment and prognosis: Erythromycin is the treatment of choice (risk of hypertrophic pyloric stenosis)

VI. Ventilator-associated pneumonia

A. General concepts

1. In the absence of mechanical ventilation, pneumonia is an uncommon presentation for hospital-acquired infections.
2. Pneumonia in the hospitalized newborn infant results either from dissemination of microorganisms from colonized mucosal sites or aspiration of food or gastric contents.
 - a. Oropharyngeal colonization plays a critical role in the pathogenesis of ventilator-associated pneumonia (VAP).
 - b. Endotracheal tubes and suctioning can disrupt mucosal integrity and promote dissemination.
 - c. Microaspiration of secretions commonly occurs.
 - d. Contaminated oral and gastric secretions can leak around uncuffed endotracheal tubes.
 - e. On rare occasions, microorganisms may be transmitted from contaminated equipment.
3. VAP accounts for 6.8–32.2% of health-care-associated infections.
4. The diagnosis of VAP requires new and persistent focal radiographic infiltrates occurring >48 h after NICU admission in a ventilated infant.

B. Epidemiology of nosocomial sepsis/pneumonia: risk factors for nosocomial sepsis/pneumonia include:

1. Prematurity (most important)
2. Parenteral nutrition and central venous catheters (general risk factor for a healthcare associated infection)
3. Mechanical ventilation
4. Frequent endotracheal tube suctioning
5. Reintubation
6. Treatment with opiates
7. Use of H_2 blockers and antacids

C. Bacterial and fungal pathogens

1. VAP is frequently polymicrobial.
2. *Staphylococcus aureus* and enteric organisms (*Escherichia coli*, *Serratia marcescens*, *Klebsiella* sp., *Enterobacter cloacae*, *Citrobacter diversus*, and *Pseudomonas aeruginosa*) are most common.
3. *Candida* sp.

D. Diagnosis

1. Pneumonia should be suspected in any hospitalized newborn infant who exhibits a deterioration in respiratory status unexplained by other events or conditions.
2. A change in the characteristics of the tracheal secretions may be an early clinical sign.
3. Sepsis may be suspected because of increased apnea, hypothermia, hyperthermia, feeding intolerance, or abdominal distention.
4. Blood cultures may or may not be positive in infants with VAP.
5. Tracheal aspirates for culture are not helpful because they merely identify microorganisms colonizing the airway (not necessarily those causing disease). Knowledge of antimicrobial sensitivity may be useful in targeting therapy.
6. The value of quantitative cultures or the presence of intracellular bacteria has not been adequately studied in neonates.
7. Chest radiographs may indicate new or focal infiltrates, but in infants with chronic lung changes, the distinction from atelectasis is difficult.
8. Adjunctive laboratory studies are not generally helpful; however, infants with serious bacterial or fungal infections commonly exhibit an increase in total white blood count, an increased percentage of immature forms, and thrombocytopenia.
9. Bronchoscopy (used in the adult population) is not recommended for neonates with suspected VAP.

E. Management

1. Broad-spectrum antibiotics targeting gram-positive and gram-negative organisms (including *Pseudomonas* and *Staphylococcus*) are commonly used (e.g., piperacillin-tazobactam or ticarcillin-clavulanate).
2. If extended spectrum beta-lactamase producing organisms are identified, carbapenems may be more appropriate.
3. When there is an outbreak of pneumonia from a resistant microorganism, empiric therapy should target those pathogens. *Any cluster of infections or an infection secondary to an unusual pathogen (e.g., Citrobacter) should be investigated by the infection control service.*
4. Amphotericin or fluconazole are used for fungal infections.
5. Hemodynamic and respiratory support as noted above.

F. Prevention

1. Avoidance of mechanical ventilation.
2. Minimize days of ventilation.
3. Suctioning oropharyngeal secretions before an endotracheal tube is removed or repositioned (unproven).
4. Good hand hygiene practices and using gloves when in contact with secretions.

5. Change ventilator circuit only when visibly soiled or malfunctioning.
6. Remove condensate from the ventilator circuit.

VII. Respiratory syncytial virus

A. Background

1. Although respiratory syncytial virus (RSV) infections are rare in the first weeks of life, epidemics in newborns have been described.
2. RSV pneumonia and bronchiolitis constitute the leading cause of infant hospitalization and are the most common viral cause of death in children in the first year of life.
3. RSV is spread by direct or close contact with infected secretions. The virus can live up to 7 h on countertop, gloves, and clothes, and up to 30 min on skin.
4. Risk factors for severe RSV infection in infants include prematurity, BPD, and congenital heart disease.

B. Pathology: Necrosis of the bronchiolar epithelium and peribronchiolar infiltrate of lymphocytes and mononuclear cells

1. Filling of alveolar spaces with fluid
2. Multinucleated giant cells circumscribed by large syncytia

C. Manifestations

1. Upper respiratory tract infection, pneumonia, bronchiolitis.
2. Clinical signs of RSV infection include lethargy, irritability, poor feeding, apnea, and respiratory distress with tachypnea and wheezing.
3. RSV infection increases the infant's risk for wheezing or asthma up to 7 years and has been associated with sudden infant death syndrome.

D. Diagnosis

1. Rapid diagnostic assays (immunofluorescence and enzyme immunoassay) using nasopharyngeal specimens are reliable.
2. Viral isolation in cell culture (3–5 days) on nasopharyngeal specimens using specific methods of collection and transport.
3. Serologic tests cannot be relied on for confirmation.
4. PCR assay can be used, but is not widely available.

E. Prevention

1. In absence of a safe and effective vaccine, passive immunization has been licensed for prevention of RSV infection. Palivizumab, a humanized monoclonal antibody, is the product of choice.
2. Palivizumab is not approved for *treatment* of the disease.
3. Palivizumab is recommended for RSV prophylaxis by the AAP for all high-risk infants including:

- a. Premature infants with GA ≤ 32 weeks without BPD may benefit from RSV prophylaxis.
 - (1) Infants born at < 28 weeks' gestation may benefit from RSV prophylaxis during the RSV season whenever that occurs during the first 12 months of life.
 - (2) Infants born at 29–32 weeks' gestation may benefit from prophylaxis up to 6 months of age.
 - b. Prophylaxis is recommended for all infants with BPD requiring medical therapy. Not more than five doses are recommended; however, patients with severe chronic lung disease may receive prophylaxis during the following RSV season.
 - c. Prophylaxis is recommended for all infants with hemodynamically significant cyanotic or acyanotic congenital heart disease (CHD). Highest risk groups include infants with cyanotic CHD, those requiring medications for congestive heart failure, and infants with pulmonary hypertension.
4. Prophylaxis should be considered for infants born with GA 32–35 weeks, who are born less than 3 months before or during RSV season, and when supplemental risk factors are present. These patients should not receive more than three doses.
 5. Administration is given monthly throughout the RSV season.
 6. Other guidelines differ from those of the AAP and are less restrictive.
- F. Treatment and prognosis
1. Primary treatment is supportive (hydration, oxygen, ventilatory support as needed).
 2. Ribavirin has antiviral activity in vitro; however, it has not been shown to decrease the need for mechanical ventilation or length of hospitalization.

VIII. Human metapneumovirus

A. Background

1. Paramyxovirus discovered in 2001: recognized only recently because of new diagnostic methods
2. Affects all age groups, but most children are infected by age 5 years
3. Seasonal distribution similar to RSV (greatest number in early late winter or early spring)
4. May coinfect with RSV, possibly increasing the severity of the disease

B. Pathology

1. Primarily affects airway epithelium leading to cell degeneration or necrosis
2. Pathological findings similar to RSV

C. Manifestations

1. Causes both upper and lower respiratory infections: rhinopharyngitis, bronchiolitis, bronchitis, and pneumonia

D. Diagnosis

1. Human metapneumovirus (hMPV) replicates poorly in traditional cell cultures
2. RT-PCR is the method of choice for diagnosis
3. Serologic tests permit only a retrospective diagnosis

E. Treatment and prevention: None

Suggested Reading

- AAP – Committee on Infectious Diseases. Policy statement modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6). doi:10.1542/peds.2009-2345.
- Ablow RC, Gross I, Effman EL, et al. The radiographic features of early-onset group B streptococcal neonatal sepsis. *Radiology*. 1977;127:771–7.
- Barker JA, McLean SD, Jordan GD, et al. Primary neonatal Herpes simplex virus pneumonia. *Pediatr Infect Dis J*. 1990;9:285–9.
- Barton L, Hodgman JE, Pavlova Z. Causes of death in the extremely low birth weight infant. *Pediatrics*. 1999;103:446–51.
- Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. *Clin Perinatol*. 2010;37(2):421–38.
- Benjamin Jr DK, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics*. 2010;126(4):e865–73.
- Bertsche A, Wagner MH, Bollmann R, Obladen M, Felderhoff-Mueser U. An unusual manifestation of a neonatal Chlamydia. *J Child Neurol*. 2008;23:948–9.
- Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. *Arch Dis Child Fetal Neonatal Ed*. 2006;91(3):F208–12.
- Britt W. Cytomegalovirus. In: Remington JS, Klein JO, editors. *Infectious diseases of the fetus newborn*. Philadelphia: WB Saunders; 2011. p. 706–55.
- Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA 98109, USA. *N Engl J Med*. 2009;361(14):1376–85.
- Edell DS, Davidson JJ, Mulvihill DM, Majure M. A common presentation of an uncommon cause of neonatal respiratory distress: Pneumonia alba. *Pediatr Pulmonol*. 1993;15:376–9. *Epidemiol Infect*. 2010;138(10):1503–9.
- Fitzgerald DA. Preventing RSV. bronchiolitis in vulnerable infants: the role of palivizumab. *Paediatr Respir Rev*. 2009;10:143–7.
- Garland JS. Strategies to prevent ventilator-associated pneumonia in neonates. *Clin Perinatol*. 2010;37(3):629–43.
- Gronek P, Schmale J, Soditt V, et al. Bronchoalveolar inflammation following airway infection in preterm infants with chronic lung disease. *Pediatr Pulmonol*. 2001;31:331–8.
- Hammerschlag MR. Chlamydia Trachomatis and Chlamydia Pneumoniae infection in children and adolescents. *Pediatr Rev*. 2004;25:43–51.
- Jackson KA, Iwamoto M, Swerdlow D. Pregnancy-associated listeriosis. *Epidemiol Infect*. 2010;138(10):1503–9. Epub 2010 Feb 17.

- Langlet C, Gaugler C, Castaing M, et al. An uncommon case of disseminated neonatal herpes simplex infection presenting with pneumonia and pleural effusions. *Eur J Pediatr*. 2003;162:532–3.
- Larsen JW, Sever JL. Group B Streptococcus and pregnancy: a review. *Am J Obstet Gynecol*. 2008;198:440–50.
- Lau YL, Hey E: Sensitivity and specificity of daily tracheal aspirate cultures in predicting organisms causing bacteremia in ventilated neonates. *Pediatr Infect Dis J*. 1991;10:290–4.125(5): 1031–41.
- Mishra UK, Jacobs SE, Doyle LW, Garland SM. Newer approaches to the diagnosis of early onset neonatal sepsis. *Am J Obstet Gynecol*. 2008;198(4):440–8; discussion 448–50.
- Nissen MD. Congenital and neonatal pneumonia. *Paediatr Respir Rev*. 2007;8:195–203.
- Numazaki K, Asanuma H, Niida Y. Chlamydia Trachomatis infection in early neonatal period. *BMC Infect Dis*. 2003;3:2.
- Principi N, Bosos S, Esposito S. Human metapneumovirus in paediatric patients. *Clin Microbiol Infect*. 2006;12:301–8.
- Resch B, Paes B. Are late preterm infants as susceptible to RSV infection as full term infants? *Early Hum Dev*. 2011;87S (2011):S47–9.
- Romero R, Gotsch F, Pineles B, Kusanovic JP. *Nutr Rev*. 2007;65(12 Pt 2):S194–202. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. *Pediatr Res*. 2009;65(5 Pt 2):84R–90R.
- Skevaki C, Kafetzis DA. Ureaplasma Urealyticum airway colonization and pulmonary outcome in neonates. *Expert Rev Anti Infect Ther*. 2003;1:183–91.
- Stoll BJ, Hansen N, Fanaroff AA, Wright LL, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. *N Engl J Med*. 2002;347(4):240–7.
- Verani JR, McGee L, Schrag SJ. Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010; 19(59(RR-10)):1–36.
- Verani JR, Schrag SJ. Group B streptococcal disease in infants: progress in prevention and continued challenges. *Clin Perinatol*. 2010;37(2):375–92.
- Vicencio AG. Susceptibility to bronchiolitis in infants. *Curr Opin Pediatr*. 2010;22:302–6.
- Viscardi RM, Hasday JD. Role of Ureaplasma species in neonatal chronic lung disease: epidemiologic and experimental evidence. *Pediatrics*. 2005;116(3):595–602.
- Viscardi RM, Manimtim WM, Sun CJ, et al. Lung pathology in premature infants with Ureaplasma Urealyticum infection. *Pediatr Dev Pathol*. 2002;5:141–50.
- Waites KB, Katz B, Schelonka RL. Mycoplasmas and Ureaplasmas as neonatal pathogens. *Clin Microbiol Rev*. 2005;18:757–89.
- Waites KB, Schelonka RL, Xiao L, Grigsby PL, Novy MJ. Congenital and opportunistic infections: Ureaplasma species and Mycoplasma hominis. *Semin Fetal Neonatal Med*. 2009;14:190–9.
- Weiss LM, Dubey JP. Toxoplasmosis: a history of clinical observations. *Int J Parasitol*. 2009;39(8): 895–901.
- Woods CR. Congenital syphilis—persisting pestilence. *Pediatr Infect Dis J*. 2009;28:536–7.
- Wynn J, Cornell TT, Wong HR, Shanley TP, Wheeler DS. The host response to sepsis and developmental impact. *Pediatrics*. 2010;125(5):1031–41.

Chapter 63

Meconium Aspiration Syndrome

Thomas E. Wiswell

(Case Study by Brooke D. Vergales and Jay P. Goldsmith)

I. Overview

A. Meconium-stained amniotic fluid (MSAF).

1. Occurs in approximately 10–15% of all deliveries.
2. Meconium passage may be a marker of antepartum or intrapartum compromise (such as hypoxemia or umbilical cord compression).
3. Passage of meconium is likely more often a maturational event. MSAF is rarely noted before 37 weeks' gestation, but may occur in 35% or more of pregnancies ≥ 42 weeks' gestation.

B. Meconium aspiration syndrome (MAS).

1. Definition: Respiratory distress in an infant born through MSAF whose signs cannot be otherwise explained.
2. MAS occurs in 2–6% of newborns born through MSAF.
3. Aspiration most commonly occurs in utero. Aspiration with the initial postnatal breaths appears to be decidedly less common.
4. The thicker the MSAF consistency, the greater the likelihood of MAS.
5. The more depressed a baby is (as reflected by the need for positive pressure ventilation or low Apgar scores), the greater the likelihood of MAS.
6. Of those with MAS, 30–60% require mechanical ventilation, 10–25% develop pneumothoraces, and 2–7% die.
7. 50–70% of infants with persistent pulmonary hypertension of the newborn (PPHN) have MAS as an underlying disorder.

T.E. Wiswell, MD (✉)

Department of Pediatrics, Florida Children's Hospital,
2718 North Orange Avenue, Suite B, Orlando, FL 32804, USA
e-mail: Thomas.Wiswell.MD@FLHOSP.org

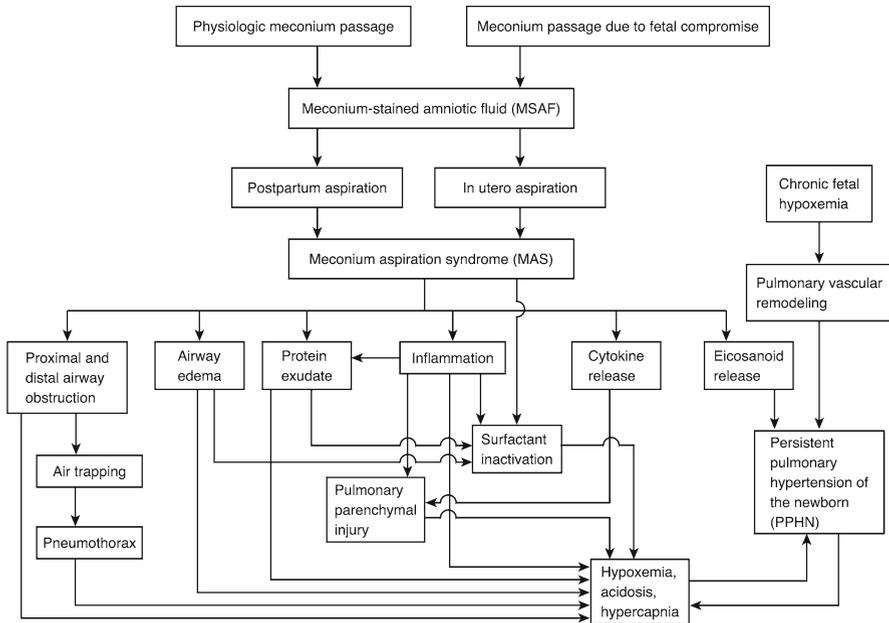


Fig. 63.1 Pathophysiology of the meconium aspiration syndrome (MAS)

II. Pathophysiology

- A. Complex mechanisms involved (Fig. 63.1).
- B. At any given moment, several of these mechanisms may be influencing the degree of respiratory distress.

III. Prevention of MAS

- A. Amnioinfusion: the recent very large, international, randomized, controlled trial indicated that this therapy does not reduce the risk of MAS.
- B. Oropharyngeal suctioning: the recent large, international, randomized, controlled trial indicates that intrapartum naso- and oropharyngeal suctioning does not reduce the incidence of MAS.
- C. Potentially dangerous maneuvers of no proven benefit.
 1. Cricoid pressure: application of pressure to the infant's airway to prevent intratracheal meconium from descending into the lungs.
 2. Epiglottal blockage: insertion of 1–3 fingers into the child's airway to manually "close" the epiglottis over the glottis to prevent aspiration.
 3. Thoracic compression: encircling the infant's chest and applying pressure in an attempt to prevent deep inspiration prior to endotracheal cleansing.
 4. None of these maneuvers has ever been scientifically validated and all are potentially dangerous (trauma, vagal stimulation, or induction of deep inhalation with chest recoil upon removing encircling hands).

D. Endotracheal intubation and intratracheal suctioning in the delivery room.

1. A large trial indicated that endotracheal intubation is of no benefit in the apparently vigorous infant born through any consistency MSAF (apparent vigor was defined within the first 10–15 s of life by a heart rate >100 beats/min, spontaneous respirations, and reasonable tone).
2. Endotracheal intubation and suctioning should still be performed in infants born through MSAF if they are depressed, if they need positive pressure ventilation, or if they are initially apparently vigorous, but subsequently manifest any respiratory distress within the first minutes of life.

E. Gastric suctioning.

1. Theoretically, postnatal suctioning of the gastric contents in meconium-stained infants could prevent postnatal reflux or emesis and frank aspiration of meconium-stained amniotic fluid.
2. No studies to date have assessed this approach.

IV. Radiographic findings (Chap. 20)

A. Radiographic findings among infants with MAS are diverse and include the following:

1. Diffuse, patchy infiltrates
2. Consolidation
3. Atelectasis
4. Pleural effusions
5. Air leaks (pneumothorax, pneumomediastinum)
6. Hyperinflation
7. “Wet-lung” appearance similar to findings seen with transient tachypnea of the newborn
8. Hypovascularity
9. Apparently clear, virtually normal appearance

B. Correlation of radiographic findings with disease severity:

1. One early study indicated direct correlation between severity of MAS and the degree of radiographic abnormalities.
2. Other studies found no such correlation. Patients with minimal signs may have a strikingly abnormal chest radiograph, while the sickest infant may have a virtually normal chest radiograph.
3. As with other aspiration syndromes, the radiographic appearance usually lags behind the clinical. Inflammation takes time to become radiographically apparent.

V. Conventional management of MAS

A. Chest physiotherapy (CPT)

1. Objectives of CPT are to prevent accumulation of debris, improve mobilization of airway secretions, and improve oxygenation.

2. CPT consists of postural drainage, percussion, vibration, saline lavage, and suctioning (oropharyngeal and intratracheal).
3. Although commonly performed in both the delivery room (DR) and the newborn intensive care unit (NICU), CPT for MAS has never been studied scientifically and its “benefits” are unproven.

B. Oxygen

1. The goal is to maintain acceptable systemic oxygenation. Generally, this consists of sustaining peripheral oxygen saturation between 92% and 97% or arterial partial pressure of oxygen (PaO_2) between 60 and 80 Torr (8 and 10.7 kPa).
2. Because of the potential for gas trapping and air leaks, some advocate increasing the fraction of inspired oxygen (FiO_2) to 1.0 before implementing more aggressive therapy (mechanical ventilation, etc.). Typically, however, once FiO_2 requirements exceed 0.60, more aggressive therapy [continuous positive airway pressure (CPAP) or mechanical ventilation] is indicated.
3. Oxygen is also a pulmonary vasodilator. Since aberrant pulmonary vasoconstriction frequently accompanies MAS, clinicians often attempt to maintain higher than usual oxygenation early in the course of the disorder [saturation 98–100% or PaO_2 100–120 Torr (13.3–16 kPa)] or even higher. However, this practice has not been validated in clinical trials. Moreover, high oxygen concentrations have the potential to adversely affect neonates (Chap. 6).
4. Supplemental oxygen is used in conjunction with more aggressive therapy.

C. Nasal cannula

1. This is a noninvasive method of administering oxygen and providing a degree of positive pressure (Chap. 25).
2. Both low (1–2 L/min) and high (3–7 L/min) flow rates have been used therapeutically.
3. No clinical trials have been performed to assess the use of nasal cannula flow for MAS.

D. Continuous positive airway pressure (CPAP) (Chap. 26)

1. CPAP is often begun once FiO_2 requirements exceed 0.50–0.60 or if the patient exhibits substantial respiratory distress. Some clinicians, however, prefer to move directly to mechanical ventilation without a trial of CPAP.
2. CPAP is provided most commonly in newborns intranasally via prongs inserted into the nostrils. CPAP may also be administered via a face-mask or via an endotracheal tube.
3. Major potential complications of CPAP are gas trapping, hyperinflation, and increased functional residual capacity. These factors could contribute to gas leaks or to decreased venous return to the heart, further compromising the infant.

4. There is limited published information concerning the use of CPAP in MAS.

E. Conventional mechanical ventilation

1. Typically provided with time-cycled, pressure-limited mechanical ventilators. Some clinicians avoid volume-targeted ventilators because of an unsubstantiated fear of air leaks. Others avoid pressure control because of high flow rates and the propensity for gas trapping.
2. Multiple strategies have been advocated.
 - a. Use of any settings (pressure, rate, I:E ratio, FiO_2 , etc) that will maintain arterial blood gases within normal ranges.
 - b. Hyperventilation to achieve respiratory alkalosis in an attempt to achieve pulmonary vasodilation.
 - c. "Gentle" ventilation allows for higher PaCO_2 and lower pH and PaO_2 in an attempt to prevent lung injury (from barotrauma or volutrauma) and potential side effects from hypocapnia and alkalosis.
3. To date, there have been no prospective, randomized trials comparing any of the various mechanical ventilator strategies in the management of MAS. Hence, no single approach can be considered optimal.

F. Other conventional therapies

1. Sedation.
2. Paralysis.
3. Systemic alkalosis from parenteral administration of sodium bicarbonate.
4. Use of pressors (dopamine, dobutamine) or fluid boluses to maintain high systemic blood pressure.
5. None of these therapies have been rigorously investigated in infants with MAS; some are potentially harmful.

VI. Nonconventional management

A. High-frequency ventilation

1. Includes both high-frequency jet ventilation and high-frequency oscillatory ventilation.
2. Trials in animal models of MAS have generally indicated no additional benefit.
3. Limited human anecdotal experience has been touted as indicating efficacy.
4. To date, there are no published prospective human trials that have documented either form of high-frequency ventilation to be more efficacious than conventional ventilation in the management of MAS.

B. Bolus exogenous surfactant (Chap. 51)

1. Rationale.
 - a. Meconium produces a concentration-dependent direct inactivation of a newborn's endogenous surfactant.

- b. Meconium has a direct cytotoxic effect on the type II pneumocyte.
 - c. Meconium causes decreased levels of surfactant proteins A and B.
 2. In the largest randomized, controlled trial assessing bolus surfactant use in term-gestation infants with respiratory failure (51% of whom had MAS), surfactant-treated infants with MAS had a decreased need for extracorporeal membrane oxygenation (ECMO). However, there were no differences in mortality, duration of mechanical ventilation or oxygen therapy, or total hospital days.
 3. An alternative approach is the use of dilute surfactant to *lavage* the lungs of infants with MAS.
 - a. Several different techniques have been used, as have several different surfactants.
 - b. Two randomized, controlled trial have assessed lung lavage with dilute surfactant. Infants receiving this therapy had more favorable outcomes, such as more rapid and sustained improvement in oxygenation, a shorter ventilator course, and decreased need for ECMO.
 4. Currently, no commercially available surfactant is FDA-approved for either bolus or lavage use in MAS in the USA.
 5. Further trials are necessary to assess this therapy.
- C. Inhaled nitric oxide (iNO) (Chap. 55)
 1. Results of several trials in newborns with hypoxemic respiratory failure have been published. Approximately half of the babies in these trials had MAS.
 2. Among MAS babies in the various nitric oxide trials, there has been a slight decrease in the need for ECMO. However, there have been no significant differences in mortality, length of hospitalization, or duration of mechanical ventilation.
 3. Currently, inhaled nitric oxide should be considered in infants with concomitant persistent pulmonary hypertension who are not responding to conventional therapy.
- D. Steroid therapy
 1. Rationale is to counter the profound inflammation occurring within hours of aspiration.
 2. Steroids could be administered either systemically or via the inhalation route.
 3. Animal data are intriguing; limited human data show some benefit.
 4. Additional clinical trials are warranted involving infants with substantial MAS who require mechanical ventilation.

E. Extracorporeal membrane oxygenation (ECMO) (Chap. 56)

1. ECMO is the therapy of last resort and is used when mortality is estimated to be very high, 50–80%.
2. Of more than 18,000 newborns treated with ECMO since the mid-1980s, approximately a third had MAS as their underlying respiratory disorder.
3. Compared to ECMO-treated infants with other disorders, those with MAS have the shortest duration of cardiopulmonary bypass and the highest survival rates, approaching 95%.
4. V-A bypass is still the most commonly used form of ECMO in infants with MAS. In most centers, this requires permanent ligation of the right common carotid artery and the right internal jugular vein.
5. ECMO survivors have morbidity rates of 20–40%. It is unknown how much of this morbidity is from pre-existing conditions versus how much is from ECMO.

VII. Summary

- A. MAS remains a common cause of respiratory distress among newborns.
- B. Of the various therapies used in the management of MAS, few have been adequately investigated.
- C. Further work is needed to elucidate optimal management of MAS.

Suggested Reading

- Bhutani VK, Benitz WE. Pulmonary function and graphics (Chapter 18). In: Goldsmith JP, Karotkin EH, editors. *Assisted ventilation of the neonate*. 5th ed. Philadelphia: Elsevier; 2010. p. 306–20.
- Cleary GM, Wiswell TE. Meconium-stained amniotic fluid and the meconium aspiration syndrome: An update. *Pediatr Clin N Am*. 1998;45:511–29.
- Dargaville PA. Copnell, for the Australian and New Zealand Neonatal Network: the epidemiology of meconium aspiration syndrome: incidence, risk factors, therapies and outcome. *Pediatrics*. 2006;117:1712–21.
- Dargaville PA, Copnell B, Mills JF, et al. Randomized controlled trial of lung lavage with dilute surfactant for meconium aspiration syndrome. *J Pediatr*. 2011;158:383–9.
- Donn SM. *Neonatal and pediatric pulmonary graphics: principles and clinical applications*. Armonk, NY: Futura Publishing; 1997.
- Fraser W, Hofmeyr J, Lede R, et al. Amnioinfusion for prevention of the meconium aspiration syndrome. *N Engl J Med*. 2005;353:909–17.
- Kääpä PO. Meconium aspiration syndrome (MAS): where do we go? Research perspectives. *Early Hum Dev*. 2009;85:627–9.
- Kezler M, Abubakar MK. Physiologic principles (Chapter 2). In: Goldsmith JP, Karotkin EH, editors. *Assisted ventilation of the neonate*. 5th ed. Philadelphia: Elsevier; 2010. p. 19–46.
- Moses D, Holm B, Spitale P, et al. Inhibition of pulmonary surfactant function by meconium. *Am J Obstet Gynecol*. 1991;164:477–81.

- Singh BS, Clark RH, Powers RJ, Spitzer AR. Meconium aspiration syndrome remains a significant problem in the NICU: outcomes and treatment patterns in term neonates admitted for intensive care during a ten-year period. *J Perinatol.* 2009;29:497–503.
- The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med.* 1997;336:597–604.
- Vain N, Szylid E, Prudent L, Wiswell TE, et al. Oro- and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: results of the international, multicenter, randomized, controlled trial. *Lancet.* 2004;364:597–602.
- Wiswell TE. Advances in the management of the meconium aspiration syndrome. *Acta Paediatr Scand.* 2001;90(Suppl. 436):28–30.
- Wiswell TE. Extended use of surfactant therapy. *Clin Perinatol.* 2001b;28:695–711.
- Wiswell TE, Gannon M, Jacob JJ, et al. Delivery room management of the apparently vigorous meconium-stained neonate: Results of the multicenter, international collaborative trial. *Pediatrics.* 2000;105:1–7.
- Wiswell TE, Knight GR, Finer NN, Donn SM, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics.* 2002;109:1081–7.

Ventilatory Case Study

Brooke D. Vergales, MD
Jay P. Goldsmith, MD

A. Prenatal data

1. Mother: 18-year-old G2 P1 → 2 at term
2. Pregnancy reported as uncomplicated

B. Patient data

1. 3,510 g female infant born by precipitous vaginal delivery; vertex presentation
2. Thick meconium-stained amniotic fluid
3. Infant was limp and not breathing at delivery and brought to warming table
4. Intubated and suctioned below the cords for meconium
5. Stimulated and dried with warm towels after tracheal suctioning
6. Apgar scores 4 (1 min), 9 (5 min)

C. Initial course

1. Oxygen by hood ($FiO_2=0.4$)
2. First arterial blood gas at 30 min of age: pH 7.19; $PaCO_2=54$ Torr; $PaO_2=29$ Torr
3. Intubation; placed on conventional mechanical ventilation: PIP 20 cm H_2O , rate 30 breaths per minute, PEEP 4 cm H_2O
4. Sepsis workup → antibiotics started

(continued)

(continued)

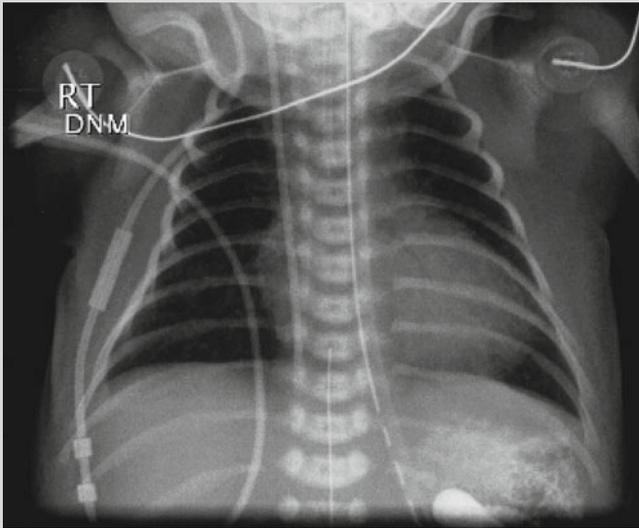


Fig. 63.2 Initial chest radiograph showing bilateral alveolar filling and mild cardiomegaly

D. Initial CXR (Fig. 63.2)

1. Bilateral alveolar filling
2. Mild cardiomegaly
3. Hyperinflation—flattened diaphragms

E. Clinical course

1. Patient treated for meconium aspiration syndrome, PPHN
2. Oxygen saturations fell to less than 60% when patient agitated → patient started on fentanyl drip at 1 mcg/kg/h
3. Increased respiratory settings on time-cycled, pressure-limited ventilator up to PIP 30 cm H₂O, FiO₂ to 1.0

F. Further clinical testing

1. 2D Echocardiogram revealed normal structural heart anatomy and no right-to-left shunting
2. Pulmonary waveform graphic analysis (Fig. 63.3)

G. Therapeutic options

1. HFV
2. Surfactant

(continued)

(continued)

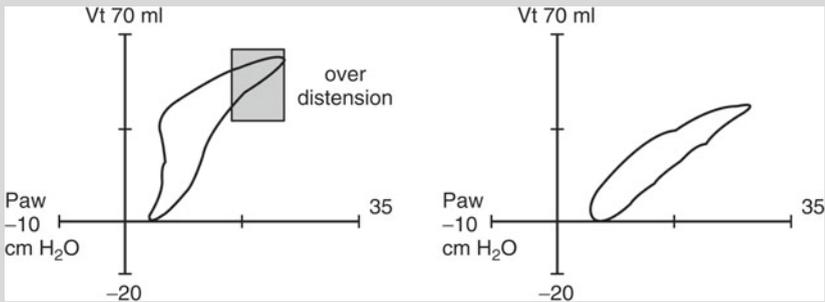


Fig. 63.3 Pressure–volume loop demonstrating flattening of inspiratory curve (“beaking”) indicative of no significant increase in lung volume despite increasing inspiratory pressure (adapted from Wiswell TE. *Advances in the management of the meconium aspiration syndrome.* *Acta Paediatr Scand.* 2001; 436(Suppl):28–30)

3. iNO
4. Intravenous or inhaled eprostenol
5. Allow patient to wake up, normalize blood gases, and wean ventilator rapidly using pulmonary graphics and blood gases to monitor gas trapping and ventilation–perfusion match

H. Denouement

1. Normal 2D echocardiogram and pulmonary graphics revealed normal pulmonary arterial pressure and was being iatrogenically overventilated
2. Patient allowed to wake up and breathe on her own
 - a. Ventilation–perfusion normalized
 - b. Ventilator settings weaned quickly
3. Patient extubated in next 24 h and discharged home 6 days later

Chapter 64

Persistent Pulmonary Hypertension of the Newborn

Robert E. Schumacher and Steven M. Donn
(Case Study by Brooke D. Vergales and Jay P. Goldsmith)

I. Description

- A. Persistent pulmonary hypertension of the newborn (PPHN) is a condition in which pulmonary vascular resistance (PVR) is elevated, usually from a failure of its normal postbirth decline. This leads to a variable degree of right-to-left shunting through persistent fetal channels, the foramen ovale and ductus arteriosus, and severe hypoxemia. A similar clinical picture can arise from decreased systemic vascular resistance or any condition where the PVR:SVR ratio is >1 . Originally, a diagnosis reserved for term babies with “clear” lungs, profound cyanosis, and a structurally normal heart, so-called secondary PPHN now occurs in babies with primary pulmonary parenchymal disease or with left ventricular dysfunction.
- B. PVR may be elevated as a result of an “appropriate” response to an underlying acute pathologic state (e.g., alveolar hypoxia), where decreased perfusion would serve to match decreased ventilation (an appropriate response for a functioning lung). In addition, increases in PVR can occur with acute pneumothorax or as a result of structural abnormalities of the pulmonary vascular bed.
- C. Although the disorder is also referred to as persistent fetal circulation (“PFC”), this is a misnomer, since the fetal organ of respiration, the placenta, has been removed, and the infant is dependent upon the lungs for gas exchange.

R.E. Schumacher, MD (✉)

Department of Pediatrics, C.S. Mott Children’s Hospital, University of Michigan Health System,
8-621 Mott Hospital, 1549 East Hospital Drive, Ann Arbor, MI 48109-4254, USA
e-mail: neoschu@umich.edu

S.M. Donn, MD, FAAP

Division of Neonatal–Perinatal Medicine, C.S. Mott Children’s Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

II. Pulmonary vascular development

- A. Alveolar development is primarily a postbirth event. Intra-acinar vascular development is thus also a postbirth phenomenon. As a consequence, at birth, at the acinar level, there is a decreased cross-sectional area available for pulmonary blood flow and obligate high vascular resistance.
- B. In the newborn, complete vascular smooth muscle development does not extend to the level of the acinus, theoretically making increases in PVR more difficult. Abnormally large amounts of in utero pulmonary blood flow (such as in premature closure of the ductus arteriosus) may contribute to structural/muscular changes in the pulmonary vascular system and increased PVR. (Muscular hypertrophy may be the most long-term energy efficient way to deal with pathologic increases pulmonary blood flow).
- C. Some increase in pulmonary vascular muscle mass occurs at the end of gestation, and thus true structurally based PPHN is uncommon in the preterm infant.
- D. A number of nonstructural (and hence more reversible) factors may significantly impact pulmonary vascular reactivity and pressure, including arterial oxygen and carbon dioxide tensions, and pH. Hypoxia, hypercapnia, and acidosis cause vasoconstriction and elevate pulmonary artery pressure, and their presence may lead to maladaptation from fetal to neonatal (adult-type) circulation.

III. Pathogenesis

- A. Normal pulmonary vascular morphology with myocardial dysfunction or increased vascular reactivity from vasoconstrictive stimuli
 1. Associated with asphyxia
 - a. Vasoconstrictive effects of hypoxia, hypercapnia, acidosis
 - b. Myocardial dysfunction (especially left ventricular) leading to pulmonary venous hypertension and subsequent PPHN with right-to-left shunting through the ductus arteriosus
 2. Associated with meconium aspiration syndrome
 - a. Alveolar hypoxia results in vasoconstriction.
 - b. Gas trapping and lung overdistention contribute to increased PVR at the acinar level.
 - c. Concomitant effects of severe parenchymal lung disease.
 - d. Some infants will also have morphological changes in pulmonary vasculature (see below).
 3. Sepsis/pneumonia
 - a. Infection initiates an inflammatory response.
 - b. Release of cytokines and other vascular mediators increases PVR.
 - c. Severe parenchymal lung disease aggravates hypoxemia and hypercapnia.

4. Thrombus or microthrombus formation with release of vasoactive mediators
5. Hyperviscosity syndrome, although in some newborn models using fetal hemoglobin one cannot elevate PVR/SVR

B. Morphologically or “functionally” abnormal pulmonary vasculature

1. Abnormal extension of vascular smooth muscle, with thickening and increased resistance deeper into the pulmonary vascular tree. May be related to chronic intrauterine hypoxia.
 - a. Some cases of meconium aspiration syndrome
 - b. In utero closure of the ductus arteriosus
 - c. Alveolar capillary dysplasia
 - d. Idiopathic PPHN
2. Abnormally small lungs with decreased cross-sectional area of the pulmonary vascular bed *and* muscular thickening and distal extension.
 - a. Pulmonary hypoplasia (either primary or secondary)
 - b. Congenital diaphragmatic hernia
 - c. Congenital cystic adenomatoid malformation
3. Hypoxia-induced functional abnormalities of the pulmonary vasculature.
 - a. Hypoxia downregulates endothelin NO resulting in reduced NO production (causing pulmonary vasoconstriction).
 - b. Hypoxia affects upregulation of NO synthase, impairing NO release.
 - c. Hypoxia also induces vascular myocyte dysfunction.

C. Structurally abnormal heart disease

1. Left ventricular outflow tract obstruction
2. Anomalous pulmonary venous return
3. Ebstein’s anomaly
4. Left ventricular cardiomyopathy
5. Any structural abnormality which results in an obligatory right-to-left shunt

IV. Diagnosis

A. Differential diagnoses of hypoxemia in the term or late preterm infant

1. Primary pulmonary disease
2. Cyanotic congenital heart disease
3. PPHN, with or without lung disease

B. Initial work-up

1. History.
 - a. Evidence of infection
 - b. Meconium-stained amniotic fluid

- c. IUGR/uteroplacental insufficiency (e.g., postmaturity, dysmaturity)
 - d. Maternal aspirin use (premature ductal closure)
2. Physical examination (findings are nonspecific, but may help to suggest etiologic considerations).
 - a. Murmur
 - b. Abnormal breath sounds
 - c. Inequality of pulses
 - d. Scaphoid abdomen
 - e. Potter's facies
 3. Chest radiograph (again, nonspecific, but may suggest or exclude associated conditions).
 4. Arterial blood gas determination. Attempt to correct ventilation and acid–base abnormalities before attributing hypoxemia to PPHN.
- C. The hyperoxia test
1. Expose infant to 1.0 FiO₂ for 10–15 min.
 2. Expected responses:
 - a. Parenchymal lung disease: PaO₂ should rise
 - b. Cyanotic congenital heart disease: no change in PaO₂
 - c. PPHN: PaO₂ may rise slightly, but usually does not
- D. Simultaneous evaluation of pre- and postductal oxygenation
1. Obtain simultaneous arterial blood gas samples from pre- (right radial artery) and postductal (umbilical or posterior tibial artery) sites.
 2. If there is a gradient (20 Torr or 2.7 kPa higher in the pre-ductal PaO₂), a right-to-left ductal shunt may be inferred. Low values from both sites do not rule out PPHN; shunting may still be occurring at the level of the foramen ovale. If both values are high and essentially equal, PPHN is unlikely to be present.
- E. The hyperoxia–hyperventilation test
1. Hypoxemia and acidosis augment pulmonary vasoconstriction.
 2. Alkalosis and hyperoxia decrease PVR.
 3. Method:
 - a. Hyperventilate the infant (either mechanically or manually) using 1.0 FiO₂ for 10–15 min.
 - b. Attempt to decrease PaCO₂ (usually to the range of 25–30 Torr or 3.3–4.0 kPa), and increase pH to 7.5 range.
 - c. Obtain arterial blood gas.
 - d. *Profound prolonged changes in PaCO₂ may alter cerebral blood flow. Use this test with caution.*

4. Result:

- a. A *dramatic* response (increase in PaO₂) along with marked lability generally suggests PPHN.
- b. Must differentiate whether increase in PaO₂ came from induced alkalosis and hyperoxia vs. increased mean airway pressure during test.

F. Echocardiography (Chap. 23)

1. Will rule out congenital heart disease
2. Evaluates myocardial function
3. May enable direct visualization of shunting (Doppler blood flow)
4. Estimates pulmonary artery pressure from regurgitant tricuspid jet

V. Treatment

A. Prenatal

1. Pregnancies found to be complicated by conditions associated with PPHN (e.g., congenital diaphragmatic hernia, prolonged oligohydramnios) should be referred to a high-risk center capable of caring for the infant following delivery.
2. Identification and appropriate obstetrical management of other at-risk pregnancies (e.g., meconium staining, chorioamnionitis, postdatism).

B. Postnatal

1. Adequate resuscitation
2. Avoidance of hypothermia, hypovolemia, hypoglycemia
3. Avoidance of acidosis, hypoxia, and hypercarbia
4. Prompt treatment of suspected sepsis, hypotension, or other problems

C. Establish the diagnosis

D. General supportive measures

1. Use an appropriate ventilatory strategy, mode, and modality
2. Assure adequate systemic blood pressure
3. Maintain adequate oxygen carrying capacity (hemoglobin >15 mg/dL)
4. *Treat the underlying disorder*
 - a. Surfactant replacement for RDS
 - b. Antibiotics, if indicated
 - c. Correct mechanical problems (e.g., ascites, pleural effusions, air leaks)

E. Mechanical ventilation

1. Initial approach should be to establish adequate normal ventilation while correcting the underlying pulmonary disease, if present. Both conventional mechanical ventilation and high-frequency ventilation have been utilized.

2. There is a paucity of literature to define an optimal approach to the ventilatory management of PPHN. Two diametrically opposite approaches have been suggested, but have not been compared by adequate clinical investigation.
 - a. Conservative ventilation uses the least amount of support possible to achieve gas exchange and pH which are marginally acceptable (by conventional standards). The philosophy is to decrease the level of ventilatory support to the lowest possible, so that lung hyperexpansion (which contributes to PVR) and barotrauma are avoided. PaO₂ levels of 40–45 Torr (5.7–6.0 kPa), PaCO₂ levels of 55–60 Torr (7.7–8.0 kPa), and pH levels of 7.25 are tolerated. In usual clinical practice, oxygen saturation values better reflect blood oxygen content; hence, many clinicians opt to follow these values rather than PaO₂ values. Additionally, while PVR is responsive to alveolar oxygen concentration, there is a paucity of human evidence to suggest that it is PaO₂ responsive. From this perspective, keeping PaO₂ greater than “X” seems an unhelpful approach.
 - b. Modest hyperventilation and alkalosis. This approach attempts to take advantage of the vasodilatory effects of alkalosis and hypocapnia on the pulmonary vasculature. Decrease the PaCO₂ to the “critical” value, below which there is a sharp rise in PaO₂. Alkalosis can be augmented by infusion of sodium bicarbonate (although recent evidence suggests that this increases morbidity, and is thus no longer recommended). If used, pH levels are usually kept above 7.5. However, cerebral blood flow also responds to PaCO₂ (decreased flow at low PaCO₂), and there is epidemiologic evidence associating low values with long-term motor disability in children. Hence, this approach has fallen out of favor.
 - c. Prudence should dictate that many clinicians favor a “middle of the road” or an “avoid acidosis and hypercapnia approach,” where physiologically normal blood gases and pH are targeted by using ventilator support which is somewhere in between those described above.
3. Maintain adequate lung volume. In normal lungs, study of basic mechanics/physiology suggests PVR is lowest at functional residual capacity (FRC). In diseased lungs, there will be a volume where PVR is lowest (probably near FRC) but the exact volume is unknown. Following pulmonary mechanics may be a useful technique in this regard.
4. No matter which approach is chosen, remember that some infants with PPHN demonstrate extreme lability. It is usually better to attempt several small ventilator/FiO₂ changes than one large one.
5. A transitional phase of PPHN occurs at 3–5 days of age. Vascular reactivity diminishes and support can be decreased at a faster rate.

F. Pharmacotherapy (Chaps. 49, 52, 54, and 55)

1. Maintain adequate cardiac output and systemic blood pressure. The degree of right-to-left shunting depends upon the pulmonary-to-systemic gradient. Avoidance of systemic hypotension is critical. CVP monitoring may be of benefit.
 - a. Correct hypovolemia by administering volume expanders.
 - b. Cardiotonic/vascular agents: Dopamine, Dobutamine, Epinephrine, Norepinephrine, Milrinone. All have differing effects on PVR, SVR, and contractility. There is a paucity of evidence guiding one to “the” correct medicine and dose.
2. Correct acidosis.
 - a. Sodium bicarbonate may be given as a bolus (1–3 mEq/kg) or as a continuous infusion (≤ 1.0 mEq/h). *Avoid hypernatremia; assure adequate ventilation.*
 - b. Tris-hydroxyaminomethane (THAM, 0.3 M) can be given even if PaCO₂ is elevated. Dose: 4–8 mL/kg. Observe for hypokalemia, hypoglycemia, and respiratory depression.
3. Pulmonary vasodilating agents.
 - a. Inhaled nitric oxide (Chap. 55). Inhaled nitric oxide has been successful in the treatment of PPHN. Given by inhalational route. Potential toxicities include methemoglobinemia and lung injury from metabolites formed during the oxidation of NO.
 - b. Other agents which have been tried and reported to have efficacy in series or case reports, but which are still investigational include the following:
 - (1) Prostacyclin/Epoprostenol
 - (2) Bosentan
 - (3) Sildenafil

G. Extracorporeal membrane oxygenation (ECMO) (Chap. 56)

1. Rescue modality generally used when predicted mortality from PPHN is high (generally 80–85%).
2. Overall survival approximates 70–80% and is dependent upon underlying disease; lower rates are noted for congenital diaphragmatic hernia and pulmonary hypoplasia.
3. Long-term sequelae in about 20%, which is equivalent to that reported in infants surviving PPHN treated by conventional means.

Suggested Reading

- Arensman RA, Short BL. Extracorporeal membrane oxygenation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: Elsevier; 2010.
- Kelly LK, Porta NFM, Goodman DM, et al. Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr.* 2002;141:6.
- Kinsella JP, Abman SH. Special ventilation techniques III: inhaled nitric oxide therapy (Chapter 14). In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: Elsevier; 2010.
- Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr.* 1997;131:55–62.
- Kinsella JP, Shaffer E, Neish SR, et al. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet.* 1992;340:818–22.
- Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. *Pediatr Clin N Am.* 2009;56:579–600.
- Lapointe AJ, Barrington KG. Pulmonary hypertension and the asphyxiated newborn. *J Pediatr.* 2011;158(2 Suppl 1):19–24.
- Peckham GJ, Fox WW. Physiological factors affecting pulmonary artery pressures in infants with persistent pulmonary hypertension. *J Pediatr.* 1978;93:1005–110.
- Roberts Jr JD, Fineman JR, Morin III FC, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. *N Engl J Med.* 1997;336:605.
- Roberts JD, Polaner DM, Lang P, et al. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet.* 1992;340:818–21.
- UK Collaborative ECMO Trial Group. UK Collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet.* 1996;384:75.
- Walsh MC, Stork EK. Persistent pulmonary hypertension of the newborn. Rational therapy based on pathophysiology. *Clin Perinatol.* 2001;28:609.
- Wung JT, James LS, Kilchevsky E, et al. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics.* 1985;76:488–93.

Ventilatory Case Study

Brooke D. Vergales, MD

Jay P. Goldsmith, MD

A. Prenatal data

1. Mother: 37-year-old G4 P3 → 4 induced at 41 weeks' gestation
2. Postdates and decreased fetal movement for 2 days

B. Patient data

1. 3,810 g female born vaginally, vertex presentation assisted by vacuum extraction under epidural anesthesia
2. Tight nuchal cord
3. Apgar scores 4 (1 min), 6 (5 min)
4. Initial arterial blood gas at 1 h in oxyhood ($FiO_2=0.4$): pH=7.12, $PaCO_2=83$ Torr, $PaO_2=44$ Torr
5. Intubated, placed on time-cycled, pressure-limited ventilator
6. Umbilical artery catheter placed for blood pressure and blood gas monitoring, double lumen umbilical venous catheter placed for access

C. Physical findings

1. Dysmature, peeling skin, decreased subcutaneous tissue, long nails
2. Increased anterior/posterior diameter of chest, coarse inspiratory rales, tachypnea
3. Acrocyanosis, hypotonia

D. Chest radiograph/laboratory results

1. CXR: Fluffy lung fields, diaphragm flat, no air leaks (Fig. 64.1)
2. White blood count 27,200 with left shift; platelets 110,000
3. Glucose and calcium normal
4. Normal metabolic profile at 12 h of life

E. Clinical course

1. Placed on antibiotics, maintenance IV fluids at 80 mL/kg/day.
2. Sedated
3. Received normal saline bolus × 2, then started dopamine for hypotension
4. 2-D Echo: increased PVR with right-to-left shunt at foramen ovale and ductus arteriosus
5. Repeat CXR showed flattened diaphragms, interstitial fluid, small heart, no air leaks (Fig. 64.2)
6. FiO_2 increased to 1.0, ventilatory settings increased to $P_{\text{aw}}=16$ cm H_2O . Unable to adequately oxygenate (PaO_2 less than 50 Torr)

(continued)

(continued)

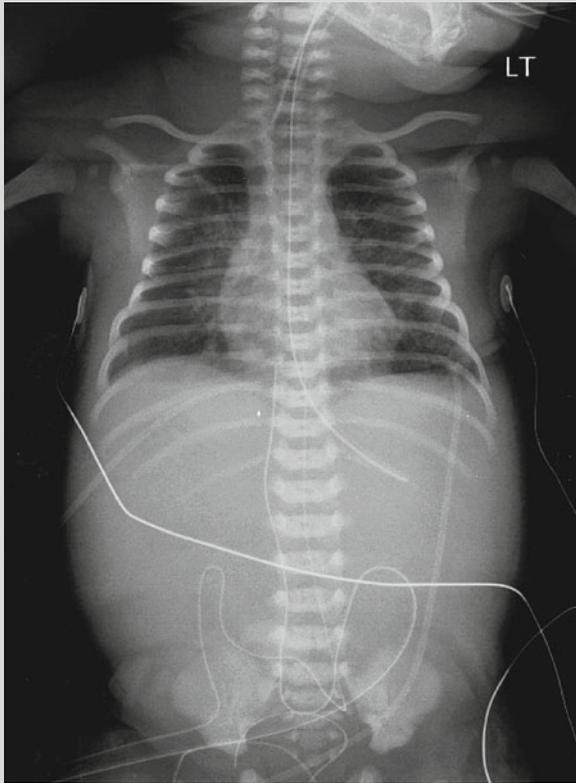


Fig. 64.1 Chest radiograph on admission showing fluffy lung fields, flat diaphragms, no air leaks

F. Diagnosis

1. Persistent pulmonary hypertension of the newborn (PPHN)
2. Suspected total anomalous pulmonary venous return or other congenital heart anomaly (doubt with normal cardiac anatomy seen on 2-D Echo)

G. Potential therapies

1. Switch to HFOV
2. Inhaled nitric oxide (iNO)
3. Surfactant
4. Inhaled or continuous IV flolan (Epoprostenol)
5. Extracorporeal membrane oxygenation (ECMO)

(continued)

(continued)

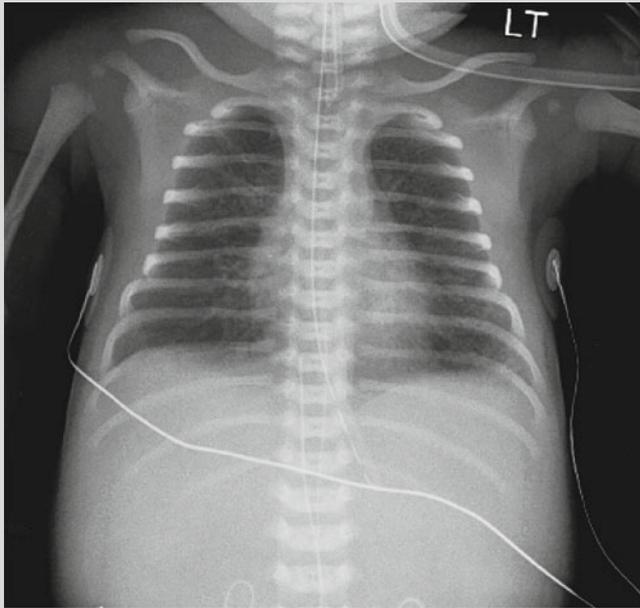


Fig. 64.2 Chest radiograph at 24 h showing hyperinflation, small heart, no air leaks

H. Failure of mechanical ventilation

1. Inability to adequately oxygenate (unacceptably low PaO_2 , high oxygenation index)
2. Inability to adequately ventilate (unacceptably high PaCO_2)
3. Toxic ventilatory settings (will cause unacceptable pulmonary sequelae) or ventilator parameters predictive of poor outcome
4. Inadequate pulmonary blood flow

I. Predictive indices of poor outcome (babies greater than 34 weeks gestational age): indications for ECMO

1. Alveolar/arterial oxygen gradient (AaDO_2)

- a. $(\text{AaDO}_2) = (760 - 47) - \text{PaCO}_2 - \text{PaO}_2$

760 mmHg = atmospheric pressure

47 mmHg = water vapor

$\text{AaDO}_2 > 610 \text{ mmHg} \times 8 \text{ h}$ or $> 605 \text{ mmHg} \times 4 \text{ h}$, if $\text{PIP} > 38 \text{ cm H}_2\text{O}$

(continued)

(continued)

2. Oxygen index (OI)

a.
$$\text{OI} = 100 \times \frac{(\bar{P}_{\text{aw}}) \times (\text{FiO}_2)}{\text{PaO}_2}$$

\bar{P}_{aw} = mean airway pressure

b. OI greater than 40 for 3 blood gases 30 min apart predictive of high mortality

3. Unresponsive to treatment ($\text{PaO}_2 < 55$ Torr and $\text{pH} < 7.3 \times 3$ h)

4. Barotrauma (multiple or persistent air leaks)

5. Uncontrollable hemodynamic instability

J. Denouement

1. Patient switched to HFOV and given iNO, 20 ppm

2. OI greater than 50 for 3 h

3. Started on continuous IV flolan

4. OI greater than 40 for 3 more hours

5. Placed on venovenous ECMO for 140 h

6. Decannulated and extubated without difficulty

7. Discharged with normal physical examination at 17 days of age.

Chapter 65

Congenital Diaphragmatic Hernia

Deepak Kalbigiri Vasudev and David Field
(Case Study by Brooke D. Vergales and Jay P. Goldsmith)

I. Background

Congenital diaphragmatic hernia (CDH) has a reported incidence of between 1 in 2,500 to 1 in 4,000 live births with an estimated 30% spontaneous abortion rate.

A. Embryology—failure of normal development of the diaphragm during first trimester. Types:

1. Posterolateral defect or Bochdalek CDH: the most common, is most often observed on the left side (85%) but can also occur on the right side (13%) or bilaterally (2%). Classical picture, a hernia of Bochdalek consists of a posterolateral defect of approximately 3 cm in diameter.
2. Anterior or central portion defects account for less than 5% of cases.
3. Complete absence of diaphragm; rare, the most severe, worst prognosis.
4. Eventration. Not a true hernia, results from a failure of muscle development in the primitive diaphragm.

B. In approximately 60% of cases, CDH is isolated (nonsyndromic). The remainder are complex, nonisolated, or syndromic CDH and can be part of a syndrome (e.g., Fryns) or associated with a chromosomal anomaly (e.g., Trisomy 13 or 18). Prognosis is worse in syndromic CDH.

C. Pathophysiology.

1. Compression of both lungs during pregnancy results in hypoplasia, especially in the ipsilateral lung.
2. In most severe cases, cardiac function can also be compromised in utero.
3. After delivery, gaseous distension of gut within the chest can result in further cardiorespiratory compromise.

D.K. Vasudev, MBBS, DCH, MRCPCH • D. Field, MBBS, FRCPCH, FRCP(Ed), DM (✉)
Leicester Royal Infirmary, Neonatal Unit, Infirmary Square, Leicester LE1 5WW, UK
e-mail: Deepak.Vasudev@uhl-tr.nhs.uk; df63@le.ac.uk

4. Pulmonary hypoplasia (including abnormalities of the pulmonary vasculature) and poor oxygenation following delivery commonly result in severe persistent pulmonary hypertension of the newborn (PPHN).
5. In mild cases, cardiopulmonary development and function may be sufficient to enable normal extrauterine adaptation with presentation at a later age.

II. Presentation and diagnosis

A. Antenatal

1. Can normally be detected on routine maternal sonographic scan during second or third trimester; herniated abdominal viscera and mediastinal shift should be identifiable. However, a scan reported as “normal” does not conclusively exclude the diagnosis. Cases not detected on antenatal scan tend to have a better prognosis.
2. Right-sided lesions are more difficult to detect because of the similar echogenicity of lung and liver.
3. Polyhydramnios is commonly seen.
4. Various other anomalies have been noted in association with diaphragmatic hernia; hence, all aspects of fetal anatomy should be reviewed once CDH has been detected.

B. Postnatal (where not suspected antenatally) presentations

1. At delivery, with failure to respond to normal resuscitative measures. In such cases, a barrel chest and scaphoid abdomen may be noted.
2. Within the first 48 h of life with respiratory distress.
3. In later childhood (up to 10%), where signs can be variable and may be respiratory and/or gastrointestinal in nature, with a mean age at diagnosis of 1 year (32 days–15 years).

C. Differential diagnosis

Cystic lesions of the lung (most commonly cystic adenomatoid malformation) and growths or effusions, which render one hemithorax opaque, can cause confusion.

D. Investigations

Antenatal ultrasound findings or clinical presentation alone may strongly suggest the diagnosis. Useful additional investigations are the following:

1. Chest radiograph is essential.
2. Contrast studies—used to confirm presence of stomach/gut in the chest—rarely necessary.
3. Ultrasound or (rarely) isotope study to document position of the liver.
4. Echocardiography can be helpful in assessing the degree of pulmonary hypertension.
5. CT scan is rarely necessary.

III. Predicting outcome

Rationale—diaphragmatic hernia produces a spectrum of pathology from very mild pulmonary hypoplasia (causing minimal compromise) to severe (incompatible with life). Significant numbers fall into the latter category. Can they be identified in order that pointless exposure to surgery and intensive care can be avoided?

A. Antenatal period

Features including early diagnosis (<25 weeks), polyhydramnios, and presence of the stomach or liver in the chest have all been suggested to equate with poor prognosis. None has been found to be consistently reliable. The ratio of lung diameter to head circumference (LHR) provides an estimation of fetal lung growth, with an LHR of <0.6 being correlated with high mortality, whereas an LHR > 1.4 is associated with virtually no mortality. For the CDH fetus with an LHR in the midrange, it has proved less useful. Fetal magnetic resonance imaging (MRI) has been suggested as a tool to give a three-dimensional estimation of lung growth. Currently, a combination of LHR and presence or absence of liver in the thoracic cavity is used by fetal surgical centers considering antenatal intervention.

B. Postnatal chest radiograph (intrathoracic stomach, estimated degree of pulmonary hypoplasia—limited help in predicting outcome).

C. Postnatal lung function (lung volumes, pulmonary compliance—limited help in predicting outcome).

D. Echocardiography (ventricular thickness—limited help in predicting outcome).

E. Defect size noted at surgery is related to survival in infants with CDH. The CDH study group, which collected data on 3,062 live born infants between 1995 and 2004 with CDH, reported overall survival of 69%; 18% of patients did not undergo an operation and died. Infants with a near absence of the diaphragm had a survival rate of 57%; infants suitable for a primary repair had a survival rate of 95%. Infants without agenesis but who required a patch for repair had a survival rate of 79%.

IV. Management

A. Antenatal. Once a diagnosis is made, families should be counseled by the obstetrician, neonatologist, and pediatric surgeon regarding available options:

1. Termination (criteria and regulations vary markedly between countries).
2. Continuing the pregnancy and performing postnatal repair.
3. Prenatal fetal surgery—practiced in only a few centers around the world. In utero anatomical repair using hysterotomy and direct fetal surgery is no longer performed in view of poor results and also because it could not be performed in fetuses with liver herniation. Fetal endoscopic tracheal occlusion (FETO) is the current preferred mode of treatment for the fetus

with moderate to severe CDH to promote lung growth and restrict severity of pulmonary hypoplasia. Using fetal tracheoscopy, a balloon is inserted (ideally at 26–28 weeks) and the occlusion is reversed in utero at 34 weeks. This is much less invasive than earlier techniques using tracheal clips and/or larger access cannulas. Harrison et al. concluded that fetal tracheal occlusion did not improve survival and morbidity. Recently, there have been published case reports of increased survival rates in those who underwent FETO, paving the way for larger randomized trials.

B. At delivery in cases diagnosed antenatally:

1. Avoid distending the gastrointestinal tract with face mask ventilation.
 - a. Intubate and ventilate as soon as possible (i.e., in the delivery room). Consider elective paralysis.
 - b. Pass a nasogastric tube in the delivery room and ensure that it is left to free drainage, and aspirate it every 30 min. Alternatively, insert a Replogle tube and use continuous suction.
2. Minimize factors that could precipitate PPHN and also lung injury.
 - a. Use adequate sedation.
 - b. Try to ensure adequate ventilation. The main goal of ventilation is adequate gas exchange. Gentle ventilation techniques, which tolerate a PaCO₂ of 60–65 mmHg with adequate oxygenation (defined as preductal oxygen saturation >85% and ideally >90%) allowing minimal peak inspiratory pressure represents the most significant advance in CDH management with marked improvement in survival in selected centers.

C. In the NICU, pre-operatively:

1. Infants who are not diagnosed antenatally but present soon after delivery with respiratory distress should have efforts made to minimize PPHN and avoid gaseous distension of the bowel.
2. In all affected babies, establish continuous monitoring. Invasive blood pressure/arterial access is essential (remember that samples obtained from sites other than the right arm will be affected by right-to-left shunting). Central venous pressure monitoring, if available via the umbilical vein, is of great help in fluid management.
3. Ensure adequate systemic blood pressure (maintains tissue perfusion and minimizes right-to-left shunting). May require infusion of both volume and inotropes. Take care not to induce fluid overload. A postductal pH > 7.25 is acceptable as long there is evidence of good tissue perfusion, such as good capillary refill, adequate urine output, and normal serum lactic acid levels.

4. Provide adequate ventilatory support. Local policy usually governs the first choice. Both conventional and high frequency ventilation can be used with success. Aim to provide stability as a minimum (i.e., sufficient oxygenation to prevent metabolic acidosis, sufficient control of carbon dioxide elimination to prevent respiratory acidosis). If this cannot be achieved despite maximum support [including extracorporeal membrane oxygenation (ECMO)], the child should be considered nonviable. In those babies who stabilize, their clinical condition should be optimized prior to surgery. Again, local practice often governs the timing of operation; however, evidence to support specific criteria is weak.
 5. Introduce pulmonary vasodilators as indicated. PPHN is a common and major complication of diaphragmatic hernia. Nitric oxide empirically would appear to be the agent of choice, but data in relation to CDH suggest its use is unhelpful and potentially harmful.
 6. Surfactant. There is no evidence to support the recommendation of surfactant use in CDH. Its use may be indicated in premature babies with chest radiographic findings of alveolar atelectasis suggestive of surfactant deficiency.
- D. Surgical repair is clearly essential, but should occur only when the baby is stable. Open repair may be performed through the abdomen (allows correction of associated malrotation at the same time) or chest (a large defect may require use of a patch). Minimally invasive CDH repair using endoscopy has greater recurrence rates and operative times but similar survival and patch usage compared to open repair.
- E. Postoperative care.
1. Essentially the same pattern of management is recommended.
 2. Failure to be able to wean respiratory support in the days following operation may indicate lethal pulmonary hypoplasia.
- F. ECMO is clearly able to provide stability and control PPHN; however, no evidence of benefit over other forms of care in terms of long-term outcome has been demonstrated. The most recent Cochrane review concluded that the benefit of ECMO for babies with CDH is unclear. Survivors of severe CDH who have been supported on ECMO have significant late mortality and morbidity.
- G. Postnatal management of infants with CDH varies markedly between centers. The CDH EURO Consortium has published consensus document/guidelines providing neonatologists and intensivists with a protocolized European treatment strategy (the document sets out the findings of a consensus meeting between high volume centers with expertise in the treatment of CDH in Europe).

V. Outcomes

- A. Short term. Approximately two-thirds of live born infants with CDH will survive to hospital discharge. Almost all published results are difficult to interpret, since they are hospital-based and as a result may:
 - 1. Contain referral bias
 - 2. Not make clear the effect of antenatal counseling and selective termination
 - 3. Exclude high risk groups, such as those with associated anomalies
- B. Medium term. A proportion of infants who survive the neonatal period will die in the first 2 years of life as a result of pulmonary hypertension/hypoplasia.
- C. Long-term morbidity
Infants with CDH often require intensive treatment after birth, have prolonged hospitalizations, and have other congenital anomalies. After discharge from the hospital, they may have long-term sequelae such as respiratory insufficiency, gastroesophageal reflux (up to 50%), poor growth, neurodevelopmental delay, behavior problems, hearing loss, hernia recurrence, and orthopedic deformities.
 - 1. Pulmonary morbidity—Survivors with CDH may require treatment for chronic lung disease (incidence varies from 25 to 32%), bronchospasm, aspiration, pneumonia, pulmonary hypertension, and pulmonary hypoplasia. Respiratory syncytial virus prophylaxis is also suggested for infants with CDH who have chronic lung disease in addition to routine childhood vaccinations.
 - 2. Gastroesophageal reflux is common and the need for fundoplication for severe reflux has been reported in as many as 19–31% of CDH survivors.
 - 3. The American Academy of Pediatrics has published postdischarge follow-up guidelines for health-care providers involved in the care of infants with CDH.

VI. New approaches under development

- A. Further attempts at in utero intervention. It is hoped that with the advancement of imaging techniques it will become possible to define more precisely the degree of pulmonary hypoplasia present in utero, and that through well-conducted randomized controlled trials clear indications and guidelines for prenatal intervention will emerge.
- B. Liquid ventilation (Chap. 57) may be able to maintain gas exchange while encouraging increased lung volume. It has been used in association with ECMO. There has been little or no expansion of its clinical use in recent years.
- C. Minimally invasive repair techniques have been developed but are not of proven benefit over more conventional approaches.

Suggested Reading

- American Academy of Pediatrics Committee on Fetus and Newborn, Lally KP, Engle W. Post discharge follow-up of infants with congenital diaphragmatic hernia. *Pediatrics*. 2008; 121(3):627–32.
- Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. *Prenat Diagn*. 2008;28:592–603.
- Harrison MR, Keller RL, Hawgood SB, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med*. 2003;349(20): 1916–24.
- Hedrick HL. Management of prenatally diagnosed congenital diaphragmatic hernia. *Semin Fetal Neonatal Med*. 2010;15(1):21–7.
- Jani J, Gratacos E, Greenough A, et al. Percutaneous fetal endoscopic tracheal occlusion (FETO) for severe left-sided congenital diaphragmatic hernia. *Clin Obstet Gynecol*. 2005;48(4):910–22.
- Keijzer R, Puri P. Congenital diaphragmatic hernia. *Semin Pediatr Surg*. 2010a;19:180–5.
- Keijzer R, Puri P. Congenital diaphragmatic hernia. *Semin Pediatr Surg*. 2010b;19(3):180–5.
- Lally KP, Lally PA, Lasky RE, et al., CDH Study Group. Defect size determines survival in infants with congenital diaphragmatic hernia. *Pediatrics*. 2007;120(3):e651–7.
- Lansdale N, Alam S, Losty PD, Jesudason EC. Neonatal endoscopic congenital diaphragmatic hernia repair: a systematic review and meta-analysis. *Ann Surg*. 2010;252(1):20–6.
- Logan JW, Rice HE, Goldberg RN, Cotton CM. Congenital diaphragmatic hernia; a systematic review and summary of best-evidence practice strategies. *J Perinatol*. 2007;27(9):535–49.
- Migliazza L, Colombo A, et al. Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and pre-surgical stabilization. *J Pediatr Surg*. 2007;42(9):1526–32.
- Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory distress in newborn infants. *Cochrane Database Syst Rev*. 2008;(3):CD001340.
- Pober BR. Genetic aspects of human congenital diaphragmatic hernia. *Clin Genet*. 2008;74(1): 1–15.
- Reiss I, Schaible T, Van den Hout L, et al. Standardised postnatal management of infants with congenital diaphragmatic hernia in Europe: The CDH EURO Consortium Consensus. *Neonatology*. 2010;98:354–64.
- Robinson PD, Fitzgerald DA. Congenital diaphragmatic hernia. *Paediatr Respir Rev*. 2007; 8:323–35.
- Rossi AC. Indications and outcomes of intrauterine surgery for fetal malformations. *Curr Opin Obstet Gynecol*. 2010;22(2):159–65.
- Smith NP, Jesudason EC, Losty PD. Congenital diaphragmatic hernia. *Paediatr Respir Rev*. 2002;3(4):339–48.

Ventilatory Case Study

Brooke D. Vergales, MD

Jay P. Goldsmith, MD

A. Prenatal data

1. Mother: 27-year-old G1P0 → 1 with good prenatal care
2. 19-week ultrasound: interpreted as normal
3. Prenatal labs: O+, hepatitis B negative, HIV negative, GBS negative
4. Spontaneous labor at level I hospital at 39 weeks' gestation

B. Patient data

1. 2,758 g female delivered by spontaneous vaginal delivery
2. Apgar scores: 5 (1 min), 7 (5 min), 7 (10 min)
3. Respiratory distress at birth. Heart rate >100

C. Physical findings

1. Severe respiratory distress, deep retractions, decreased breath sounds on the left
2. Barrel shaped chest and scaphoid abdomen
3. No murmur appreciated but heart sounds heard best on the right side of the chest

D. Clinical course

1. Placed on CPAP in delivery room secondary to respiratory distress; transferred to special care nursery
2. CBC, blood culture obtained, and antibiotics started
3. CXR obtained in newborn nursery (Fig. 65.1)—bowel in left hemithorax consistent with CDH
4. Intubated at 1 h of life after diagnosis
5. Orogastric tube placed for decompression
6. Transferred to Level III NICU
7. Placed on HFOV on admission to level III NICU
8. Required 1.0 FiO₂, iNO started at 20 ppm—FiO₂ to 0.5
9. Surgery consulted

E. Diagnosis: left congenital diaphragmatic hernia

F. Differential diagnoses:

1. Cystic lesions of the lung
2. Prior to one hemithorax showing bowel gas, a unilateral opaque lung may be confused with atelectasis or effusion

(continued)

(continued)

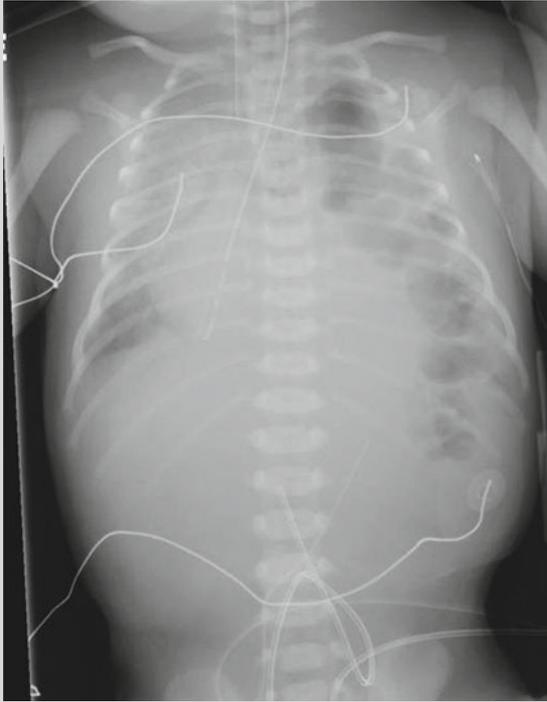


Fig. 65.1 Chest radiograph at 1 h of age demonstrating bowel in left chest and shift of mediastinum to right

G. Management:

1. Gentle ventilation:
 - a. HFOV with P_{aw} to maintain adequate chest expansion (8–9 ribs on CXR)
 - b. Maintain pH (7.30–7.35) and allow permissive hypercapnea as long as pH > 7.30
2. ECMO—if HFOV in conjunction with iNO unable to achieve adequate gas exchange
3. Elective surgery once patient stabilized on ventilator and preferably off ECMO

H. Denouement

1. Maintained with gentle ventilation on HFOV and iNO. No need for ECMO
2. CDH repaired at 1 week of life
3. Extubated to nasal CPAP at 2 weeks of life and room air at 3 weeks of life
4. Discharged on full feeds at 1 month of age

Chapter 66

Pulmonary Hypoplasia/Agenesis

Deepak Kalbigiri Vasudev and David Field

I. Classification

A. Pulmonary

1. Agenesis. Can be isolated or part of a syndrome. Failure of one or both lung buds to develop at the very beginning of lung development (Chaps. 1 and 2). Bilateral agenesis is always fatal. Unilateral defect may be asymptomatic.
2. Hypoplasia (structural)
 - a. Primary. Rare defect may be associated with other congenital anomalies.
 - b. Secondary. Consequence of any lesion which impairs normal development (Table 66.1).
3. Hypoplasia (biochemical), primary. A small number of cases have been identified which present with features of pulmonary hypoplasia but structurally normal lungs. Abnormalities of surfactant have been identified, in particular absence of surfactant protein B.

B. Vascular

1. Macroscopic. Atresia of the main pulmonary trunk can disrupt normal pulmonary vascular development; however, pulmonary function is normally satisfactory. Presentation is with severe cyanosis, which can be remedied by improving pulmonary blood flow.
2. Microscopic. Pulmonary vasculature can be disrupted at the alveolar level and result in severely reduced gas exchange. Dysplasia is rare, but

D.K. Vasudev, MBBS, DCH, MRCPCH • D. Field, MBBS, FRCPCH, FRCP(Ed), DM(✉)
Leicester Royal Infirmary, Neonatal Unit, Infirmary Square, Leicester LE1 5WW, UK
e-mail: Deepak.Vasudev@uhl-tr.nhs.uk; df63@le.ac.uk

Table 66.1 Factors which can impair lung growth in utero

1. Compression of chest (e.g., oligohydramnios—all causes)
2. Compression of lung (e.g., effusion, diaphragmatic hernia)
3. Reduction in fetal breathing (e.g., neuromuscular disorder)

a small number of patterns have been recognized (e.g., alveolar capillary dysplasia), and these are now being linked to specific genetic abnormalities.

II. Pathophysiology

The exact pathophysiology varies with the underlying mechanism.

- A. Reduced lung size (e.g., secondary to thoracic dystrophy).
- B. Structural immaturity (e.g., secondary to oligohydramnios).
- C. Diffusion deficit (e.g., secondary to alveolar capillary dysplasia). The main functional problem that results in all the above is pulmonary insufficiency. The main clinical problem tends to be oxygen transfer (lack of adequate pulmonary surface area).

III. Diagnosis

- A. Antenatal. Diagnosis may be anticipated on the basis of maternal antenatal ultrasound scan (e.g., severe oligohydramnios, small fetal chest cavity). Magnetic resonance imaging is also being used.
- B. Postnatal. Diagnosis may be apparent immediately after birth if hypoplasia is severe (i.e., cannot be resuscitated, or severe respiratory distress from birth), or is part of recognizable syndrome (e.g., oligohydramnios sequence). When the infant presents later with apparently isolated mild to moderate respiratory distress, the diagnosis may be delayed. Syndromes either primarily or secondarily associated with pulmonary hypoplasia should be considered. Similarly, conditions that can mimic these signs (e.g., infection) should be excluded. In all cases where hypoplasia is the possible diagnosis, the following should be considered:
 1. Genetics consult
 2. Measurement of lung volumes
 3. Measurement of pulmonary compliance
 4. Examination of surfactant genotype
 5. Lung biopsy
- C. The choice of investigation will vary with the severity of the child's problem. In severe respiratory failure, lung biopsy may be performed as a terminal event to permit diagnosis and counselling for future pregnancies (see below). If more minor respiratory problems (e.g., unexplained persistent tachypnea), assessment of pulmonary mechanics is appropriate.

IV. Management

- A. Antenatal. If a diagnosis of pulmonary hypoplasia is made in utero, families should be counselled by the obstetrician, neonatologist, clinical geneticist, and surgeon (if appropriate). Potential options will vary according to the following:
 1. Primary diagnosis and its prognosis
 2. Degree of diagnostic certainty resulting from the evaluation. Essentially parents must decide between
 - a. Termination of pregnancy (criteria and regulations vary markedly among and within countries).
 - b. Continuing the pregnancy with postnatal intervention and “treatment.”
 - c. Antenatal intervention, practiced only in relation to certain conditions (e.g., bilateral pleural effusions). Results vary with both the nature and severity of underlying problem. Evidence of benefit for such interventions is not established.
- B. At delivery, standard resuscitation should take place. Where antenatal scans indicate, special measures (e.g., draining pleural effusions) should be performed. Vigorous resuscitation of infants with small volume lungs often results in pneumothorax. If dysmorphic features in the child indicate a lethal syndrome, or if oxygenation proves impossible, intensive care may be withdrawn.
- C. In the NICU
 1. Establish routine monitoring. Invasive blood pressure/arterial access is essential in the severest cases; central venous pressure monitoring, if available via the umbilical vein, is of great help in fluid management.
 2. Ensure adequate systemic blood pressure (maintain tissue perfusion and minimize right-to-left shunting). This may require both infusion of fluids and inotropes. Take care not to induce fluid overload.
 3. Provide adequate respiratory support. Infants with mild hypoplasia may not require ventilation. For those requiring invasive support, local practice usually governs the first choice; both conventional and high-frequency devices can be used with success. Aim to provide stability of blood gases (i.e., sufficient oxygenation to prevent metabolic acidosis). More aggressive ventilation may induce pulmonary damage and further impair lung function. If blood gas control proves impossible despite maximum support, the child should be considered nonviable.
 4. Attempts to “treat” pulmonary hypoplasia using a combination of continuous positive airway pressure (CPAP) with inhaled nitric oxide (iNO) over a prolonged period has shown some promise but requires fuller evaluation.

5. Introduce pulmonary vasodilators as indicated; pulmonary hypertension is often a complication. Echocardiography may help confirm the diagnosis. Inhaled nitric oxide appears to be the agent of choice.
6. Surfactant. There is no clear role for surfactant use in this situation (other than treatment of RDS if the baby has it), but it is frequently tried in an attempt to rescue a deteriorating baby.
7. Extracorporeal Membrane Oxygenation (ECMO) is clearly able to provide stability, but there is no evidence of benefit over other forms of care in pulmonary hypoplasia.
8. A role for the use of partial liquid ventilation is not established.
9. Investigate to establish the diagnosis. Where there are no clear features to support a diagnosis of pulmonary hypoplasia, routine tests should exclude all other causes of respiratory distress.

V. Prognosis

Pulmonary hypoplasia results from a large number of different conditions. The prognosis is governed mainly by the etiology and any associated anomalies.

- A. Mild cases often become asymptomatic with growth. Abnormalities of function can still be measured in later childhood.
- B. Infants with moderate hypoplasia can survive with intensive care but often need long-term respiratory support. The effect of growth is uncertain and death in later childhood can occur.
- C. Severely affected babies die despite full support. No current intervention is known to help in such cases.

VI. Counselling about future pregnancies

- A. Some infants will be affected by conditions that can recur in future pregnancies.
- B. A proportion of severely affected cases cannot be diagnosed without examination of lung tissue. Lung biopsy may be impossible to perform safely while the child is alive.
- C. Postmortem study should be obtained whenever possible. If permission for postmortem examination is not obtained, an open or needle biopsy of the lung obtained soon after death may still allow a tissue diagnosis (in many areas, consent to do so is required).

Suggested Reading

- Aiton NR, Fox GF, Hannam S, et al. Pulmonary hypoplasia presenting as persistent tachypnea in the first few months of life. *Br Med J*. 1996;312:1149–50.
- Bishop NB, Stankiewicz P, Steinhorn RH. *Am J Respir Crit Care Med*: Alveolar Capillary Dysplasia; 2011. Epub ahead of print.

- Correia-Pinto J, Gonzaga S, Huang Y, Rottier R. Congenital lung lesions—underlying molecular mechanisms. *Semin Pediatr Surg.* 2010 Aug;19(3):171–179. Review.
- DeMello D. Pulmonary pathology. *Sem Neonatol.* 2004;9:311–29.
- Kallapur SG, Ikegami M. Physiological consequences of intrauterine insults. *Paediatr Respir Rev.* 2006;7(2):110–116. Epub 2006 May 30.
- Kilbride HW, Yeast J, Thibeault DW. Defining limits of survival: lethal pulmonary hypoplasia after midtrimester premature rupture of membranes. *Am J Obstet Gynecol.* 1996;175:675–81.
- Major D, Cadenas M, Cloutier R, et al. Morphometrics of normal and hypoplastic lungs in preterm lambs with gas and partial liquid ventilation. *Pediatr Surg Int.* 1997;12:121–5.
- Nogee LM, deMello DE, Dehner LP, Colten HR. Deficiency of pulmonary surfactant protein B in congenital pulmonary alveolar proteinosis. *N Engl J Med.* 1993;328:404–10.
- Swenson AW, Becker MA, Donn SM, Attar MA. The use of high frequency jet ventilation to treat suspected pulmonary hypoplasia. *J Neonatal Perinatal Med.* 2011;4:33–7.
- Swenson AW, Donn SM. Alveolar capillary dysplasia: a lethal developmental lung malformation. *Curr Respir Med Rev.* 2009;5:110–4.
- Welzing L, Bagci S, Abramian A, Bartmann P, Berg C, Mueller A. CPAP combined with inhaled nitric oxide for treatment of lung hypoplasia and persistent foetal circulation due to prolonged PPROM. *Early Hum Dev.* 2011;87(1):17–20.

Chapter 67

Apnea Syndromes

Alan R. Spitzer

I. Terminology

- A. Apnea is the absence of respiratory air flow.
- B. There is no universally accepted definition of pathologic apnea. When discussed in this chapter, however, pathologic apnea commonly refers to the cessation of respiratory air flow for >20 s, or a briefer pause associated with abrupt onset of pallor, cyanosis, bradycardia, or hypotonia. It has been demonstrated that many completely well infants occasionally have events that could be described as pathologic apnea, and these events seem to have no serious long-term consequences for the infant.
- C. Apnea of Infancy (AOI) is pathologic apnea that presents in an infant who is >37 weeks' gestational age for which no specific cause can be readily identified.
- D. Apnea of Prematurity (AOP) is pathologic apnea or excessive periodic breathing in preterm infants (<37 weeks' gestational age).
- E. Periodic Breathing (PB) is a respiratory pattern in which there are three or more consecutive central pauses of greater than three seconds duration, separated by <20 s of breathing between each pause. The relationship of periodic breathing to pathologic apnea is not well understood, but it appears to reflect immaturity of respiratory control.
- F. Apparent Life-Threatening Episode (ALTE) refers to an event that is frightening to the observer and is characterized by some combination of apnea, color change (often notable pallor or cyanosis), marked change in muscle tone, choking, gagging, or a physical appearance that suggests the potential for the demise of the infant to an observer.

A.R. Spitzer, MD (✉)
Department of Research, Education, and Quality, MEDNAX, Inc.,
1301 Concord Terrace, Sunrise, FL 33323, USA
e-mail: alan_spitzer@pediatrix.com

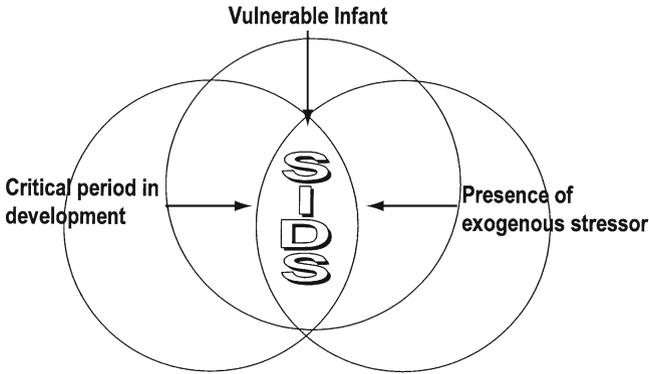


Fig. 67.1 This figure is a Venn diagram of the three events that must occur simultaneously for a death from SIDS to result. The infant must be vulnerable, due to genetic factors or past medical history, reach a critical period during development, and be subjected to a stressor that triggers a SIDS death. Adapted from Filiano JJ, Kinney HC. A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model. *Biol Neonat.* 1994;65:194–7

- G. Sudden Infant Death Syndrome (SIDS) is the unexpected death of an infant between 1 month and 1 year of age that remains unexplained after a review of the past medical records of the child, a postmortem examination, and a death scene investigation. To date, no specific etiology of SIDS has been defined, and it appears likely that SIDS represents a final common pathway for a number of unrelated clinical phenomena. For children to die of SIDS, it is also probable that the triple risk theory of SIDS must be satisfied (Fig. 67.1).
- II. Etiology of apnea (Table 67.1)
- A. All children and adults occasionally demonstrate apnea. Apnea can be normal if it is brief, infrequent, and not associated with any underlying problems.
 - B. If abnormal, apnea represents a sign rather than a specific pathologic process. Many diverse conditions can be associated with pathologic apnea.
- III. Risk groups for apnea
- A. Premature infants
 1. An interplay of an immature ventilatory center, impaired central and peripheral nervous system chemoreceptors, and functional obstruction of the upper airway results in AOP.
 2. Approximately 25–70% of premature infants have AOP during their hospitalization in the NICU. The more immature an infant is, the greater the likelihood of clinical apnea.
 3. Apnea in premature infants is predominantly central apnea, though transient loss of muscle tone in the upper airway with relative degrees of obstruction may also play a role.

Table 67.1 Medical conditions associated with pathologic apnea

Acute conditions	Chronic conditions
Thermal instability	Apnea of prematurity, apnea of infancy
Infection (meningitis, bacteremia, respiratory syncytial virus infection, pertussis, infantile botulism)	Gastroesophageal reflux disease
Central nervous system pathology (seizure, intracranial hemorrhage including child abuse)	Airway obstruction (congenital anomaly, sleep apnea)
Metabolic disturbance (inborn errors of metabolism, hypernatremia, hyponatremia, hypoglycemia, hypocalcemia)	Cardiac disease (dysrhythmia, marked shunt including PDA)
Airway obstruction (neck flexion, laryngospasm, glossoptosis)	CNS pathology (seizure, hemorrhage, malformation including arnold–chiari)
Necrotizing enterocolitis	Marked anemia
Postsurgical apnea	Chronic lung disease
Drug-induced	Hypoventilation syndrome (Ondine’s curse) Idiopathic

B. Term infants

1. Approximately 2–3% of term infants will have apnea in the weeks shortly after birth.
2. Term infants rarely need to be treated for their apnea.

C. Infantile pathologic gastroesophageal reflux (GER)

1. The peak period of onset is 1–4 months of age.
2. Manifestations include esophagitis, failure to thrive, recurrent pneumonia, intractable wheezing, or obstructive apnea.
3. Groups with the greatest risk for pathologic GER include premature infants, neurologically impaired children, infants with underlying lung disease (cystic fibrosis or bronchopulmonary dysplasia [BPD]), and children who require gastrostomy feedings.
4. Although about 50% of infants will “spit up” in the first months of life, very few children have pathologic GER disease that requires therapy.
5. *The diagnosis of GER-related apnea is made far too often in the NICU, unnecessarily exposing many infants to antireflux medications that have little effect in this patient population and have the potential for serious adverse neurological consequences, such as dystonia.*

D. Apparent life-threatening event (ALTE)

1. Occurs in 0.5–6% of all infants at some time in the first 6 months of life.
2. Represents a clinical presentation rather than a specific disease process.

3. Children present with in a variety of ways in which it appears that their life is in jeopardy.
 4. Causes include systemic infections, upper airway obstruction, seizures, GER, cardiac disease, or idiopathic apnea and bradycardia.
 5. There is an increased incidence of SIDS in these children, especially if vigorous resuscitation during sleep has previously been needed.
- E. Siblings of SIDS victims
1. Two- to fourfold increase in SIDS rate has been demonstrated in numerous studies.
 2. Infanticide and hereditary disorders must be explored if more than one child has died of SIDS in a family.
- F. Chronic conditions, such as BPD and tracheostomy dependency
- G. Neurologic birth injury
1. Children with perinatal hypoxic–ischemic injury following difficult deliveries often have apnea for a period of time.
 2. The frequency and duration of apnea in these children may reflect the severity of injury.
- H. Central alveolar hypoventilation syndrome (Ondine’s curse)
1. Inability to regulate ventilation during sleep secondary to inadequate output from brainstem centers.
 2. Should be considered with persistent pathologic central apnea or ventilator dependency exists in the presence of minimal pulmonary disease.
 3. Infrequently associated with Hirschsprung’s disease.
- IV. Sudden infant death syndrome (SIDS)
- A. In spite of a marked decrease in incidence since 1992, SIDS remains a leading cause of postneonatal infant mortality (approximately 0.5–0.6 infant deaths per 1,000 live births).
 - B. Peak age is 2–4 months with the majority (95%) by age 6 months.
 - C. A statistically rare event, with poor predictability.
 - D. Multiple risk factors (Table 67.2).
 - E. Etiology unknown, probably a final common pathway of several entities.
- V. Approach to the infant with apnea (Table 67.3)
- A. Cardiopulmonary stabilization.
 - B. Detailed history and physical examination.
 - C. The diagnostic evaluation is directed by the clinical presentation and the infant’s associated findings.
 - D. Indication for hospitalization of infants with apnea (Table 67.4).

Table 67.2 Risk factors for sudden infant death syndrome (SIDS)

Modifiable	Less modifiable
Prone sleep position ^a	Prematurity
Tobacco exposure	Young mother
Inadequate health care	Less educated mother
Lack of breast-feeding	Poverty
Day care situations in which a child is placed prone when used to supine sleep	Low birth weight/intrauterine growth retardation
	Colder climate
	Previous apparent life-threatening event

^aRisk of SIDS for infants in the prone sleep position is greater if there has been a recent illness, the child sleeps on soft bedding surfaces, gas-trapping objects (e.g., pillows, stuffed animals) are present in the crib, or swaddling is used

Table 67.3 Diagnostic clues for infants with apnea or apparent life-threatening episodes

Clinical features	Underlying pathology
Choking during a feed	Pharyngeal dyscoordination, laryngospasm, gastroesophageal reflux disease (GERD)
Postfeed spitting, color change, posturing (back arching)	GERD
Abnormal eye movement, muscle tone change and postictal activity; abnormal neurologic findings, developmental delay	Seizures
Fever, activity change, or recalcitrant apnea	Serious bacterial or Viral infection
Family history of SIDS or ALTE; presence of bruising	Familial disorder (inborn error of metabolism) or child abuse

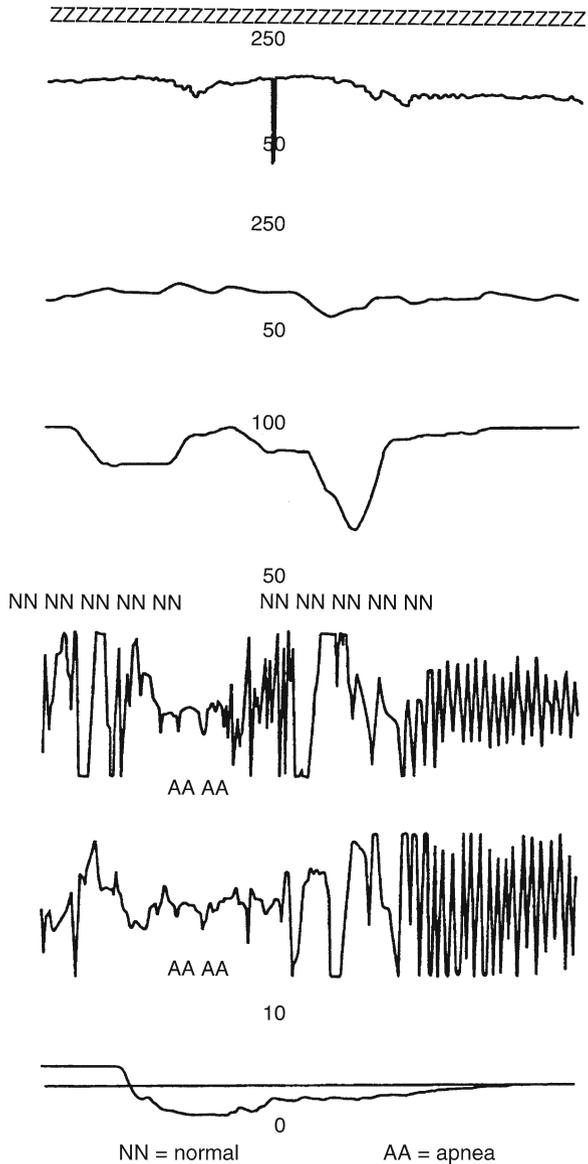
Table 67.4 When to hospitalize an infant with suspected apnea

Ill appearance
Frequent clinical episodes or monitor alarms
Initiation of resuscitation
Color change (i.e., cyanosis or duskienss)
Change in muscle tone
Discrepancy in medical history
Extreme parental anxiety

VI. Diagnostic considerations

- A. Complete blood count and cultures of blood, urine, and spinal fluid are necessary if a serious bacterial infection is suspected.
- B. Continuous multichannel recording should be performed (Fig. 67.2).
 1. Measures chest wall movement, nasal/oral air flow (or change in air temperature), oxygen saturation, and heart rate trend.

Fig. 67.3 This figure is a multichannel recording of an episode of gastroesophageal reflux triggering an episode of apnea. The *top channel* is the averaged heart rate from the ECG monitor, the *next channel* is heart rate from the pulse oximeter, the *third channel* indicates the oxygen saturation, the *fourth channel* is the thermistor probe indicated nasal air flow, while the *fifth channel* demonstrates thoracic impedance. The *bottom channel* is the esophageal pH probe, with a line indicating a pH of 4.0, below which significant esophageal acidity is denoted. Figure courtesy of Joseph DeCristofaro, MD



- C. Intraesophageal pH recording with a multichannel recording should be used if gastroesophageal reflux is suspected as a precipitating event (Fig. 67.3).
- D. A radiographic contrast swallow study is useful if the infant has signs of swallowing dysfunction or anatomic anomalies such as esophageal web or tracheoesophageal fistula.

- E. A gastric emptying study and an abdominal sonogram are useful if there is a clinical picture of a generalized gastrointestinal motility disorder or pyloric stenosis.
- F. A chest radiograph and a radionuclide milk scan are helpful if the child has persistent, yet unexplained, lower airway signs.
- G. Upper airway evaluation (lateral neck radiograph and otolaryngology evaluation with possible laryngoscopy or bronchoscopy) may be of value if there is fixed or recurrent stridor, as well as unexplained pathologic obstructive apnea.
- H. An EEG should be considered in infants suspected of apneic seizures or having persistent pathologic central apnea without an identifiable cause.
- I. Imaging studies of the brain are necessary in the presence of developmental delay, suspicion of an intracranial hemorrhage (including nonaccidental trauma), dysmorphic features, an abnormal neurologic examination, or mental status changes. In general, magnetic resonance imaging (MRI) is the study of choice.
- J. Serum ammonia, as well as urine and serum amino acids and organic acids, are indicated if a metabolic disorder is suspected. Filter paper supplemental newborn metabolic screening may also be useful in some cases.
- K. Serum electrolytes and glucose can help diagnose a recent stressful condition, a metabolic process, or chronic hypoventilation.
- L. An echocardiogram and a cardiology referral are necessary if the history or physical examination suggests cardiac disease (e.g., feeding difficulties, tachypnea, heart murmur, and cyanosis).
- M. An echocardiogram (ECG) is useful when severe unexplained tachycardia or bradycardia exists. Cardiac conduction abnormalities (e.g., prolonged QT Syndrome) are rare, but important, causes of infant apnea.
- N. A stool specimen for botulism is helpful if the apneic infant has associated constipation and hypotonia.
- O. The polysomnogram is useful in older children with sleep apnea associated with features such as bizarre behaviors, abnormal body movements, or nocturnal enuresis. This multichannel recording includes an EEG, a chin muscle EMG, and an electrooculogram.

VII. Treatment

- A. The therapy of an apneic infant, as with the evaluation, must be directed at identifying and managing the underlying cause. As with many medical conditions, if the cause is not removed, the signs will usually continue or reappear.
- B. Apnea of prematurity
 - 1. Xanthine derivatives (i.e., caffeine or theophylline)
 - a. Proposed mechanisms include stimulation of skeletal and diaphragmatic muscle contraction, increase in the respiratory center's

sensitivity to carbon dioxide, and stimulation of the central respiratory drive. Caffeine appears to be a safer drug, can be given less frequently than theophylline, and is more effective in treating apnea.

- b. Dosage.
 - (1) Active caffeine alkaloid: 2.5 mg/kg daily (5 mg/kg/day of caffeine citrate) 24 h after a loading dose of 10 mg/kg of active caffeine.
 - (2) Theophylline: 1–2 mg/kg every 8 h after a loading dose of 5–6 mg/kg.
 - c. Therapeutic serum concentrations.
 - (1) Caffeine: 5–25 mg/L.
 - (2) Theophylline: 5–10 mg/L. Higher concentrations may be necessary in some cases.
 - d. Side effects include nausea, vomiting, CNS excitability, seizures, tachycardia, and cardiac arrhythmia. Serious toxic effects are rare at serum levels below 20 mg/L.
 - e. Caution is necessary if an intercurrent viral illness, certain drugs (primarily metabolized by the liver), coexisting seizures (lowers the seizure threshold), or coexisting GER (lowers the esophageal sphincter tone) are present.
 - f. The wider therapeutic range and longer half-life of caffeine over theophylline results in less frequent monitoring of drug concentrations and in less serious toxicity.
 - g. Recent Cochrane reviews indicate the effectiveness of methylxanthines for apnea. Caffeine appears to be the preferred drug of choice. It has also been shown to decrease the incidence of BPD in preterm infants.
 - h. The prophylactic use of methylxanthines to prevent the development of AOP is not currently substantiated in the literature.
2. High flow nasal cannula
 - a. Appears to reduce the incidence of AOP, though not well-studied to date in large series; most reports are anecdotal
 - b. Possible mechanisms
 - (1) Support of upper airway tone
 - (2) Stimulation of nasal mucosa and face
 3. Continuous positive airway pressure (CPAP)
 - a. Proposed mechanism
 - (1) Improvement in oxygenation
 - (2) Maintenance of upper airway patency

- (3) Reduction in intercostal-phrenic inhibitory reflex
 - (4) Alteration of Hering–Breuer deflation reflex
 - b. Indications
 - (1) Poor response to xanthine derivatives
 - (2) Inability to maintain airway patency and obstructive apnea
 - c. Low positive pressure (2–5 cm H₂O) by nasal prongs is suggested as a starting point, some infants may need 7–10 cm H₂O
4. Mechanical ventilation
- a. Failure to breathe remains an absolute indication for ventilator support.
 - b. If this level of therapy needs to be introduced or restarted, one must actively look for possible causes of sudden deterioration as previously described (sepsis, CNS bleeding, etc.).
5. Discharge margin of safety
- a. A common NICU problem involves deciding when a premature infant with a history of apnea can be safely discharged from the hospital.
 - b. The concept of “discharge margin of safety” was first introduced in 1997, indicating that neonates with apnea may go as long as 8 days between documented events. This study suggested an observation period of at least this duration of time to insure safe home discharge.
 - c. The problem with an 8-day observation (or observation of any period of time) is that it establishes an “apnea clock,” which continues to reset whenever there is a new episode of apnea, potentially delaying discharge for many days or weeks until the child is deemed apnea free.
 - d. Because of the practical difficulty in the modern era for observing babies for this duration, many clinicians have arbitrarily shortened the observation window to 3–5 days, or elected to protect infants with the use of home monitoring if events continue.
 - e. No studies have been performed recently to establish the optimal time for discharge in a premature infant with a history of apnea in the NICU. As a result, discharge practices vary widely.
- C. Pathologic gastroesophageal reflux
1. Nonpharmacologic therapy
- a. Small, frequent thickened feeds (e.g., rice cereal in formula).
 - b. Postprandial prone-elevated position.
 - c. Avoid the use of an infant car seat immediately following a feeding if the infant’s posture is poor. Placement of rolled towels to support the back may be of value in keeping the baby upright.

2. Pharmacologic therapy

- a. Consider in a child who does not respond to traditional therapy or who has documented GERD
- b. Metoclopramide
 - (1) Should only be used when clear evidence of reflux-associated apnea has been documented.
 - (2) Stimulates gastroesophageal motility and increases lower esophageal sphincter tone.
 - (3) Side effects include restlessness, drowsiness, and extrapyramidal signs.
 - (4) Avoid in the presence of bowel obstruction.
 - (5) Dosage: 0.1 mg/kg/dose up to four times daily (30 min prior to meals and at bedtime).
- c. Histamine H₂ receptor antagonists are useful with symptomatic esophagitis (e.g., back arching, irritability) or if the patient has had a protracted medical course
- d. Omeprazole
 - (1) Proton pump inhibitor.
 - (2) Useful if there has been a poor response to traditional pharmacologic agents.
 - (3) Long-term safety is unknown. May result in increased infection rates in preterm infants. Recently associated with decreased bone mineralization with chronic use.
- e. Both of the above agents will alter gastric pH and have been associated with an increased risk of necrotizing enterocolitis

D. Protective strategies for sudden infant death syndrome (Table 67.5)

1. Good health care
2. Supine sleep position for healthy infants
 - a. Reduces SIDS rates by 40–50%.
 - b. Proposed harmful mechanisms that may enhance SIDS risk in the prone position:
 - (1) Airway obstruction
 - (2) Inadequate oxygenation and hypercarbia from rebreathing
 - (3) Thermal stress
 - (4) Decreased cerebral blood flow
 - (5) Efficient or deeper sleep
 - c. No proven increased risk of aspiration, GER, ALTE in supine sleep.

Table 67.5 Protective strategies for sudden infant death syndrome

Good health care
Supine sleep position for healthy infants (term and premature)
Avoid prone sleep position in a child who has been sleeping supine (especially in day care setting)
Avoid soft bedding (e.g., sheep skin)
Avoid gas-trapping objects (e.g., pillows, stuffed animals, bumpers around crib)
Smoke-free environment
Documented home monitors
Avoid alcohol and drug use if cosleeping

- d. Consider prone position if any of the following are present:
 - (1) Severe GER
 - (2) Certain upper airway anomalies (e.g., Pierre-Robin Syndrome)
 - (3) Premature infants with serious ongoing respiratory disease
- e. Factors that exacerbate SIDS in the prone position.
 - (1) Recent illness
 - (2) Soft bedding (e.g., sheep skin) or crib “bumpers”
 - (3) Thermal insulation (e.g., swaddling, no central heating)
3. Avoid soft bedding (e.g., sheep skin).
4. Avoid gas-trapping objects near the baby’s head (e.g., pillows, stuffed animals, crib bumpers).
5. A smoke-free environment is very beneficial.
6. Note: In children kept on their back to sleep who enter day care, caution should be used in allowing children to nap on their abdomen. Children with no exposure to prone sleep may be at even higher risk for SIDS when initially placed prone.
7. Documented home monitors.
 - a. Measured parameters
 - (1) Chest wall movement (central apnea) and heart rate trends
 - (2) Monitor compliance
 - b. Benefits/uses
 - (1) Alert caregivers to potentially serious central apnea or bradycardia
 - (2) Transition of a technology-dependent child
 - (3) Shortening the hospital stay for a symptomatic premature apneic infant
 - (4) Guidance of pharmacologic therapy
 - (5) Alleviation of family anxiety
 - (6) Reduction of SIDS (controversial)

- c. Indications for continued monitoring
 - (1) Premature infant with pathologic apnea or very young gestational age
 - (2) Infant with GERD and associated apnea or bradycardia
 - (3) Infant with ALTE
 - (4) Sibling of infant who died of SIDS
 - (5) Infant with certain underlying neurologic, cardiac, or pulmonary conditions (e.g., tracheostomy, central alveolar hypoventilation syndrome)
 - d. Indications: Special consideration cases
 - (1) Infant with oxygen dependency
 - (2) Infant with apneic seizures
 - (3) Technology-dependent child
 - (4) Infant with a difficult medical course
 - e. Limitations
 - (1) False alarms (especially with advancing age)
 - (2) Misguided faith and overdependence on monitor technology
 - (3) Additional family stress in some cases
 - (4) Poor compliance
 - (5) Limitation as a diagnostic tool (e.g., obstructive apnea)
 - (6) Dermatologic problems (skin irritation) from the monitor leads
 - (7) Vulnerable child syndrome
 - (8) Sibling jealousy
 - f. Criteria for discontinuation of monitoring
 - (1) Four to six weeks after last significant clinical or documented event
 - (2) Four weeks free of events if the infant has a self-limited or treated condition (e.g., GER, respiratory syncytial virus)
 - (3) Age 6 months or until 1 month after the age of previous sibling's death if the child is an asymptomatic sibling of a SIDS victim
 - g. Key to safe, yet less stressful, use of a home monitor: a comprehensive program of evaluation, treatment, and follow-up
 - (1) Cardiopulmonary resuscitation (CPR) and monitor training for primary caregivers
 - (2) 24 h availability of vendor repair team and qualified support staff
 - (3) Regular review of recordings by an experienced professional
 - (4) Frequent communication among the experienced monitor professions, the family, and the primary medical provider
8. Parents should avoid alcohol and drug use if co-sleeping

Suggested Reading

- Abu-Shaweesh JM, Martin RJ. Neonatal apnea: what's new? *Pediatr Pulmonol.* 2008; 43(10):937–44.
- Al-Saif S, Alvaro R, Manfreda J, Kwiatkowski, Cates D, Qurashi M, Rigatto H. A randomized controlled trial of theophylline versus CO₂ inhalation for treating apnea of prematurity. *J Pediatr.* 2008;153:513–8.
- Altman RL, Li KL, Brand DA. Infections and apparent life-threatening events. *Clin Pediatr (Phila).* 2008;47:372–8.
- American Academy of Pediatrics Task Force on Prolonged Infantile Apnea. Prolonged Infantile Apnea. *Pediatrics.* 1985;76:129–31.
- American Academy of Pediatrics Task Force on Infant Positioning and SIDS. Positioning and SIDS. *Pediatrics.* 1992;89:1120–6.
- American Academy of Pediatrics Task Force on Infant Positioning and SIDS Update: *Pediatrics.* 1996; 98:1216–18.
- Aranda JV, Beharry K, Valencia GB, et al. Caffeine impact on neonatal morbidities. *J Matern Fetal Neonatal Med.* 2010;Suppl 3:20–3.
- Bhat RY, Rafferty GF, Hannam S, Greenough A. Acid gastroesophageal reflux in convalescent preterm infants: effect of posture and relationship to apnea. *Pediatr Res.* 2007;62:620–3.
- Bloch-Salisbury E, Hall MH, et al. Heritability of apnea of prematurity: a retrospective twin study. *Pediatrics.* 2010;126:e779–87.
- Buchanan GF, Richerson GB. Central serotonin neurons are required for arousal to CO₂. *Proc Natl Acad Sci U S A.* 2010;107:16354–9.
- Charles BG, Townsend SR, Steer PA, et al. Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. *Ther Drug Monit.* 2008;30(6):709–16.
- Claudius I, Keens T. Do all infants with apparent life-threatening events need to be admitted? *Pediatrics.* 2007;119(4):679–83.
- Committee on Fetus and Newborn. Apnea, sudden infant death syndrome, home monitoring. *Pediatrics.* 2003;111:914–7.
- Cooper PA, Madhi SA, Huebner RE, et al. Apnea and its possible relationship to immunization in ex-premature infants. *Vaccine.* 2008;26:3410–3.
- Dani C, Pratesi S, Migliori C, Bertini G. High flow nasal cannula therapy as respiratory support in the preterm infant. *Pediatr Pulmonol.* 2009;44:629–34.
- Darnall RA, Kattwinkel J, Nattie C, Robinson M. Margin of safety for discharge after apnea in preterm infants. *Pediatrics.* 1997;100:795–801.
- Davis PG, Schmidt B, Roberts RS, et al. Caffeine for Apnea of Prematurity Trial Group. Caffeine for Apnea of Prematurity trial: benefits may vary in subgroups. *J Pediatr.* 2010;156:382–7.
- Di Fiore J, Arko M, Herynk B, et al. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. *J Perinatol.* 2010;30:683–7.
- Dukhovny D, Lorch SA, Schmidt B, et al. Economic evaluation of caffeine for apnea of prematurity. *Pediatrics.* 2011;127:e146–55.
- Edner A, Wennborg M, Alm B, Lagercrantz H. Why do ALTE infants not die in SIDS? *Acta Paediatr.* 2007;96:191–4.
- Eichenwald EC, Blackwell M, Lloyd JS, et al. Inter-neonatal intensive care unit variation in discharge timing: influence of apnea and feeding management. *Pediatrics.* 2001;108:928–33.
- Eichenwald EC, Zupancic JA, Mao WY, et al. Variation in diagnosis of apnea in moderately preterm infants predicts length of stay. *Pediatrics.* 2011;127:e53–8.
- Esani N, Hodgman JE, Ehsani N, Hoppenbrouwers T. Apparent life-threatening events and sudden infant death syndrome: comparison of risk factors. *J Pediatr.* 2008;152:365–70.
- Fu LY, Colson ER, Corwin MJ, Moon RY. Infant sleep location associated maternal and infant characteristics with sudden infant death syndrome prevention recommendations. *J Pediatr.* 2008;153:503–8.

- Gelinas JF, Davis GM, Arlegui C, Cote A. Prolonged, documented home-monitoring of oxygenation in infants and children. *Pediatr Pulmonol.* 2008;43:288–96.
- Genizi J, Pillar G, Ravid S, Shahar E. Apparent life-threatening events: neurological correlates and the mandatory work-up. *J Child Neurol.* 2008;23:1305–7.
- Gibson E, Spinner S, Cullen JA, et al. Documented home apnea monitoring: effect on compliance, duration of monitoring, and validation of alarm reporting. *Clin Pediatr.* 1996;35:505–13.
- Hayes MJ, Akilesh MR, Fukumizu M, et al. Apneic preterms and methylxanthines: arousal deficits, sleep fragmentation and suppressed spontaneous movements. *J Perinatol.* 2007;27:782–9.
- Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. *Cochrane Database Syst Rev.* 2010;12:CD000139.
- Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev.* 2010a;12:CD000140.
- Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. *Cochrane Database Syst Rev.* 2010b;12:CD000432.
- Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev.* 2010;12:CD000273.
- Hofstetter AO, Legnevall L, Herlenius E, Katz-Salamon M. Cardiorespiratory development in extremely preterm infants: vulnerability to infection and persistence of events beyond term-equivalent age. *Acta Paediatr.* 2008;97:285–92.
- Hoppenbrouwers T, Hodgman JE, Ramanathan A, Dorey F. Extreme and conventional cardiorespiratory events and epidemiologic risk factors for SIDS. *J Pediatr.* 2008;152:636–41.
- Hunt CE, Corwin MJ, Weese-Mayer DE, et al. Assessment of hemoglobin oxygen saturation in preterm and term infants in the first six months of life. *J Pediatr.* 2011;159(3):377.e1–83.e1.
- Julien CA, Joseph V, Bairam A. Caffeine reduces apnea frequency and enhances ventilatory long-term facilitation in rat pups in chronic intermittent hypoxia. *Pediatr Res.* 2010;68:105–11.
- Klein NP, Massolo ML, Greene J, et al. Vaccine Safety Datalink. Risk factors for developing apnea after immunization in the neonatal intensive care unit. *Pediatrics.* 2008;121:463–9.
- Krous HF, Haas EA, Chadwick AE, et al. Intrathoracic petechiae in SIDS: a retrospective population-based 15-year study. *Forensic Sci Med Pathol.* 2008;4:234–9.
- Litman RS, Sooin K, Salam A. Chloral hydrate sedation in term and preterm infants: an analysis of efficacy and complications. *Anesth Analg.* 2010;110:739–46.
- Malloy MH. Sudden Infant Death Syndrome among extremely premature infants: United States 1997–1999. *J Perinatol.* 2004;24:181–7.
- Moon RY, Oden RP, Joyner BL, Ajao TI. Qualitative analysis of beliefs and perceptions about sudden infant death syndrome in African-American mothers: implications for safe sleep recommendations. *J Pediatr.* 2010;157:92–7.
- Murphy JJ, Swanson T, Ansermino M, Milner R. The frequency of apneas in premature infants after inguinal hernia repair: do they need overnight monitoring in the intensive care unit? *J Pediatr Surg.* 2008;43:865–8.
- Natarajan G, Botica ML, Thomas R, Aranda JV. Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics.* 2007;119:936–40.
- Naulaers G, Daniels H, Allegaert K, et al. Cardiorespiratory events recorded on home monitors: the effect of prematurity on later serious events. *Acta Paediatr.* 2007;96:195–8.
- Omari TI. Apnea-associated reduction in lower esophageal sphincter in premature infants. *J Pediatr.* 2009;154:374–8.
- Pantalitschka T, Sievers J, Urschitz MS, et al. Randomised crossover trial of four nasal respiratory support systems for apnoea of prematurity in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed.* 2009;94:F245–8.
- Paul K, Melichar J, Miletin J, Dittrichova J. Differential diagnosis of apneas in preterm infants. *Eur J Pediatr.* 2009;168:195–201.
- Peter CF, Sprodowski N, Bohnhorst B, et al. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. *Pediatrics.* 2002;109:8–11.

- Pillekamp F, Hermann C, Keller T, et al. Factors influencing apnea and bradycardia of prematurity – implications for neurodevelopment. *Neonatology*. 2007;91:155–61.
- Poets CF. Apnea of prematurity: what can observational studies tell us about pathophysiology? *Sleep Med*. 2010;11:701–7.
- Ralston S, Hill V. Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: a systematic review. *J Pediatr*. 2009;155:728–33.
- Ramanathan R, Corwin MJ, Hunt CE, et al. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. *JAMA*. 2001;285:2199–207.
- Richardson HL, Walker AM, Horne RSC. Influence of swaddling experience on spontaneous arousal patterns and autonomic control in sleeping infants. *J Pediatr*. 2010;157:85–91.
- Richardson HL, Walker AM, Horne R. S.C. Minimizing the risks of sudden infant death syndrome: to swaddle or not to swaddle? *J Pediatr*. 2009;155:475–81.
- Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357:1893–902.
- Semeniuk J, Kaczmarek M, Wasilewska J, Nowowiejska B. Is acid gastroesophageal reflux in children with ALTE etiopathogenetic factor of life threatening symptoms? *Adv Med Sci*. 2007;52:213–21.
- Sharma BR. Sudden infant death syndrome: a subject of medicolegal research. *Am J Forensic Med Pathol*. 2007;28:69–72.
- Skouroliakou M, Bacopoulou F, Markantonis SL. Caffeine versus theophylline for apnea of prematurity: a randomized controlled trial. *J Paediatr Child Health*. 2009;45:587–92.
- Soloveychik V, Bin-Nun A, Ionchev A, Sriram S, Meadow W. Acute hemodynamic effects of caffeine administration in premature infants. *J Perinatol*. 2009;29:205–8.
- Slocum C, Arko M, Di Fiore J, et al. Apnea, bradycardia and desaturation in preterm infants before and after feeding. *J Perinatol*. 2009;29:209–12.
- Spitzer AR. Apnea and Home Cardiorespiratory Monitoring. In: McConnel MS, editor. *Guidelines for Pediatric Home Health Care* American Academy of Pediatrics Publications. American Academy of Pediatrics Publications: Elk Grove Village; 2002. p. 357–87.
- Sridhar R, Thach BT, Kelly DH, Henslee JA. Characterization of successful and failed autoresuscitation of human infants, including those dying of SIDS. *Pediatr Pulmonol*. 2003;36:113–22.
- Thach BT. Some aspects of clinical relevance in the maturation of respiratory control in infants. *J Appl Physiol*. 2008;104:1828–34.
- Tieder JS, Cowan CA, Garrison MM, Christakis DA. Variation in inpatient resource utilization and management of apparent life-threatening events. *J Pediatr*. 2008;152(629–35):635.e1–e2.
- Weese-Mayer DE, Corwin MJ, Peucker MR, et al. Comparison of apnea identified by respiratory inductance plethysmography with that detected by end-tidal CO₂ of thermistor. *Am J Resp Crit Care Med*. 2000;162:471–80.
- Weese-Mayer DE, Berry-Kravis EM, Zhou L, et al. Sudden infant death syndrome: case-control frequency differences at genes pertinent to early autonomic nervous system embryological development. *Pediatr Res*. 2004;56:391–5.
- Willing M, Hoffman HJ, Hartford RB. Infant sleep position and risk for sudden infant death syndrome: report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, Maryland. *Pediatrics*. 1994;93:814–9.

Chapter 68

Weaning and Extubation

Steven M. Donn and Sunil K. Sinha
(Case Study by Brooke D. Vergales and Jay P. Goldsmith)

I. General concepts

A. Weaning

1. Process of shifting work of breathing from ventilator to patient by decreasing level of support
2. Generally heralded by the following:
 - a. Improvement in gas exchange
 - b. Improving spontaneous drive
 - c. Greater assumption of work of breathing by patient

B. Imposed work of breathing

1. Endotracheal tube resistance
2. Ventilator circuit
3. Demand valve
4. Estimated to require V_T of 4 mL/kg to overcome imposed work of breathing

C. Physiologic essentials for weaning

1. Respiratory drive
 - a. Must be adequate to sustain alveolar ventilation
 - b. Pre-extubation assessments

S.M. Donn, MD, FAAP (✉)
Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

S.K. Sinha, MD, PhD, FRCP, FRCPC
Department of Neonatal Medicine, The James Cook University Hospital,
University of Durham, Marton Road, Marton-in-Cleveland, Middlesbrough TS4 3BW, UK
e-mail: sunil.sinha@tees.nhs.uk

- (1) Observation
- (2) Measurement of V_T
- (3) Trial
 - (a) Low IMV rate
 - (b) ETC PAP
 - (c) Minute ventilation test (see below)

2. Reduced respiratory system load

- a. Respiratory system load—forces required to overcome the elastic and resistive properties of lung and airways
- b. Part of total pressure generated by respiratory muscles must overcome elasticity to change lung volume, while the remainder must overcome resistive properties to generate gas flow.
- c. Time constant
 - (1) Product of compliance and resistance
 - (2) Describes how quickly gas moves in and out of lung
 - (3) Determines whether there is adequate time to empty lung and avoid gas trapping and inadvertent PEEP

3. Maintenance of Minute Ventilation

- a. Product of V_T and rate
- b. Normal range 240–360 mL/kg/min
- c. Inadequate alveolar ventilation can result from inadequate V_T , rate, or both.

D. Elements of Weaning

1. Tidal volume (V_T) determinants
 - a. Amplitude (ΔP)—the difference between PIP and PEEP
 - b. Inspiratory time (T_I)
 - c. Gas flow rate
 - d. Compliance
2. Frequency (rate)
 - a. Impacts carbon dioxide removal
 - b. If too rapid, may lead to hypocapnia and decreased spontaneous drive
3. Minute ventilation
 - a. Measure V_T and rate
 - b. Assess spontaneous vs. mechanical components
4. Work of breathing
 - a. Force or pressure necessary to overcome forces which oppose volume expansion and gas flow during respiration
 - b. Product of pressure and volume, or the integral of the pressure-volume loop

- c. Proportional to compliance
 - d. Additional components
 - (1) Imposed work
 - (2) Elevated resistance
 - e. Indirect measure is energy expenditure (oxygen consumption)
5. Nutritional aspects
- a. Inadequate calories may preclude successful weaning by not providing sufficient energy.
 - b. Prevent catabolism.
 - c. Avoid excess nonnitrogen calories, which increase CO_2 production.

II. Weaning strategies

A. General principles

- 1. Decrease the most potentially harmful parameter first.
- 2. Limit changes to one parameter at a time.
- 3. Avoid changes of a large magnitude.
- 4. Document the patient's response to all changes.
- 5. *The most common reason for failing to wean is failing to wean.*

B. Gas exchange

- 1. A normal blood gas is an invitation to decrease support, not stand pat.
- 2. Always interpret blood gases in light of the pulmonary status. For example, normocapnia in a baby with severe BPD represents overventilation.
- 3. Capillary blood gases become less reliable as a baby gets older.

C. Oxygenation

1. Primary determinants

- a. FiO_2
- b. Mean airway pressure
 - (1) Peak inspiratory pressure (PIP)
 - (2) PEEP
 - (3) Inspiratory time

2. Sequence

- a. Try to decrease $\text{FiO}_2 \leq 0.4$
- b. If PaO_2 is high, PaCO_2 normal, decrease PIP, PIP, and PEEP, or T_1
- c. If PaO_2 is high, PaCO_2 low, decrease PIP, rate (if IMV)
- d. If PaO_2 is high, PaCO_2 high, decrease PEEP or T_1 , and/or increase rate

3. Practical hints

- a. If $\text{FiO}_2 > 0.4$, consider maintaining $\text{Hgb} > 15 \text{ g/dL}$.
- b. Weaning is facilitated by continuous pulse oximetry.
- c. Avoid “flip-flop” by making small FiO_2 changes early in disease course.
- d. Avoid a mean airway pressure which is too low to maintain adequate alveolar volume.

D. Ventilation

1. Primary determinants

- a. Amplitude (ΔP) = $\text{PIP} - \text{PEEP}$
- b. Rate (frequency, f)
- c. Minute ventilation = $V_T \times f$
- d. T_E (or I:E ratio)

2. Sequence

- a. If PaCO_2 is low, PaO_2 high, decrease PIP or rate (if IMV)
- b. If PaCO_2 is low, PaO_2 normal, decrease rate (if IMV), or T_E
- c. If PaCO_2 is low, PaO_2 low, increase PEEP or decrease T_E (longer I:E ratio), or decrease rate (if IMV)

3. Practical hints

- a. Try to maintain normal minute ventilation.
- b. Keep V_T in 4–8 mL/kg range.
- c. Avoid overdistention but maintain adequate lung volumes.
- d. Low PaCO_2 diminishes spontaneous respiratory drive.
- e. Avoid pre-extubation fatigue. Weaning below an adequate level of support to overcome the imposed work or breathing may doom the baby to fail extubation.

E. Weaning specific modes of ventilation

1. Assist/control

- a. Decrease PIP (decreases in rate have no effect if spontaneous rate is above control rate).
- b. Maintain sufficient ΔP to achieve adequate ventilation.
- c. Provide adequate V_T to avoid tachypnea.
- d. Alternative strategy: slowly increase assist sensitivity to increase patient effort and condition respiratory musculature.
- e. Extubate from assist/control or consider switching to SIMV/PSV.

2. SIMV

- a. Decrease SIMV rate.
- b. Decrease PIP.

- c. Maintain minute ventilation.
 - d. Alternative: increase assist sensitivity.
 - e. Add PSV.
3. IMV
- a. Decrease PIP (lower Paw) for O₂.
 - b. Decrease rate for CO₂.
 - c. Maintain minute ventilation and adequate V_T.
4. SIMV/pressure support
- a. Decrease SIMV rate.
 - b. Decrease pressure support level.
 - c. Extubate when V_T ≤ 4 mL/kg.
5. High-frequency ventilation (Chaps. 36–38)

III. Adjunctive treatments for weaning

A. Methylxanthines (Theophylline, Aminophylline, Caffeine)

1. Mechanisms of action
- a. Increase diaphragmatic contractility and decrease fatigability
 - b. Direct stimulant of respiratory center
 - c. Reset CO₂ responsiveness
 - d. Diuretic effect
2. Indications
- a. Ventilatory support. A secondary outcome of the CAP trial was a reduction in BPD with caffeine use.
 - b. Peri-extubation support.
 - c. Apnea or periodic breathing.
3. Complications
- a. Gastric irritation, vomiting
 - b. Tachycardia
 - c. CNS irritation, seizures
4. Comments
- a. Follow serum concentrations (aminophylline, theophylline).
 - b. Peri-extubation support usually discontinued 48–72 h postextubation.

B. Diuretics

1. Mechanism of action—treat pulmonary edema
2. Indications
- a. Pulmonary edema
 - b. PDA
 - c. Chronic lung disease

3. Complications

- a. Electrolyte disturbances
- b. Contraction alkalosis
- c. Nephrolithiasis/nephrocalcinosis (furosemide)

4. Comments

- a. Follow serum electrolytes.
- b. May need supplemental Na, K, Cl.
- c. Long-term furosemide therapy not advised; spironolactone and chlorothiazide preferred.
- d. *There is no evidence to support the routine use of diuretics to facilitate weaning.* They may create fluid and electrolyte disturbances, which actually impede weaning.

C. Bronchodilators

1. Mechanism of action—relaxation of bronchial smooth muscle
2. Indication—bronchospasm or reactive airways leading to increased airway resistance
3. Complications
 - a. Tachyphylaxis
 - b. Tachycardia
 - c. Hypertension
4. Comments
 - a. Document efficacy before continuing.
 - b. May be given systemically or by inhalation.
 - c. If inhalational route, use spacer.
 - d. *There is no evidence to support the routine use of bronchodilators to facilitate weaning.*

D. Corticosteroids

1. Mechanisms of action
 - a. Anti-inflammatory
 - b. Decrease edema
2. Indications
 - a. Upper airway edema
 - b. Pulmonary edema
 - c. BPD
3. Complications
 - a. Hypertension
 - b. Hyperglycemia
 - c. Increased risk of infection

- d. Gastric bleeding
- e. Myocardial hypertrophy (long-term use)
- f. Decreased growth velocity (long-term use)

4. Comments

- a. Highly controversial. Several dosing regimens have been suggested (Chap. 52).
- b. Use for short duration.
- c. Be aware of need for stress doses for infection, surgery, etc.
- d. Inhalational route *may* be effective.
- e. Some administer concomitant histamine-2 blocker such as ranitidine. These have been associated with NEC.

IV. Impediments to weaning

- A. Infection (especially pulmonary)
- B. Neurologic dysfunction or neuromuscular disease
 - 1. Decreased respiratory drive
 - 2. Neuromuscular incompetence
 - 3. Alveolar hypoventilation
- C. Electrolyte disturbances
 - 1. Chronic diuretic therapy
 - 2. Renal tubular dysfunction
 - 3. Excess free water intake
 - 4. TPN
- D. Metabolic acidosis
 - 1. Infant may hyperventilate
 - 2. Correct underlying abnormality
- E. Congestive heart failure
 - 1. Pulmonary edema
 - 2. Impaired gas exchange
 - 3. Organ hypoperfusion
 - 4. May require high PEEP
- F. Anemia
 - 1. Decreased oxygen carrying capacity
 - 2. High circulatory demands and excessive energy expenditure
 - 3. Apnea
- G. Pharmacologic agents
 - 1. Sedatives may depress respiratory drive.
 - 2. Prolonged use of paralytics may lead to atrophy of respiratory musculature.

H. Nutritional

1. Inadequate caloric intake
2. Too many nonnitrogen calories, resulting in excess carbon dioxide production

V. Extubation and post-extubation care

A. Extubation

1. Assessment
 - a. Reliable respiratory drive and ability to maintain adequate alveolar ventilation
 - b. Low ventilatory support
 - c. No contraindications
2. Extubation
 - a. The stomach should be empty. If infant recently fed, aspirate stomach contents, in the event reintubation becomes necessary.
 - b. Suction endotracheal tube and nasopharynx.
 - c. When heart rate and SaO_2 are normal, quickly remove endotracheal tube.
 - d. Provide FiO_2 as needed.

B. Post-extubation care

1. Nasal CPAP (Chap. 26)
 - a. Clinical trials show mixed results. Some clinicians prefer to extubate directly to NCPAP to maintain continuous distending pressure and decrease work of breathing.
 - b. Use 4–6 cm H_2O .
 - c. May also be useful to maintain upper airway patency in infants with stridor.
2. Nasal cannula (Chap. 25)
 - a. Can provide necessary FiO_2
 - b. Can provide gas flow to help overcome nasal resistance
 - c. Allows most patient freedom
3. Oxygen hood
 - a. Can provide necessary FiO_2
 - b. More confining than nasal cannula but easier to regulate specific FiO_2
4. Prone positioning
 - a. Stabilizes chest wall.
 - b. Improves diaphragmatic excursion by allowing abdominal viscera to fall away from diaphragm and thus decreases work of breathing.
 - c. Umbilical catheters should be removed.

5. Stridor

- a. May result from subglottic edema or laryngotracheomalacia.
- b. Treatment options
 - (1) FiO₂/humidity
 - (2) CPAP
 - (3) Inhalational sympathomimetics (e.g., racemic epinephrine)
 - (4) Corticosteroids
- c. If persistent, consider reintubation or airway evaluation (Chap. 24).
- d. Subglottic stenosis may require tracheostomy.

6. Methylxanthines

- a. Some studies have suggested efficacy in the peri-extubation setting.
- b. Duration of treatment 24–96 h (longer if respiratory control irregularities occur).

7. Ongoing assessments

- a. Blood gas assessment. Assure adequate gas exchange.
- b. Chest radiograph. Not routinely necessary unless clinical evidence of respiratory distress.
- c. Weight gain. If inadequate, may indicate excessive caloric expenditure for respiratory work.

Suggested Reading

- Balsan MJ, Jones JG, Watchko JF, Guthrie RD. Measurements of pulmonary mechanics prior to the elective extubation of neonates. *Pediatr Pulmonol.* 1990;9:238–43.
- Barrington KJ, Finer NN. A randomized, controlled trial of aminophylline in ventilatory weaning of premature infants. *Crit Care Med.* 1993;21:846–50.
- Baumeister BL, El-Khatib M, Smith PG, Blumer JL. Evaluation of predictors of weaning from mechanical ventilation in pediatric patients. *Pediatr Pulmonol.* 1997;24:344–52.
- Bernstein G, Mannino FL, Heldt GP, et al. Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. *J Pediatr.* 1996;128:453–63.
- Browne LP. What is the optimal imaging for vascular rings and slings? *Pediatr Radiol.* 2009;39:S191–5.
- Chan V, Greenough A. Comparison of weaning by patient triggered ventilation or synchronous intermittent mandatory ventilation in preterm infants. *Acta Paediatr.* 1994;83:335–7.
- Davis P, Jankow R, Doyle L, Henschke P. Randomised, controlled trial of nasal continuous positive pressure in the extubation of infants weighing 600 to 1250 g. *Arch Dis Child.* 1998;79:F54–7.
- Dimitriou G, Greenough A, Laubscher B. Lung volume measurements immediately after extubation by prediction of “extubation failure” in premature infants. *Pediatr Pulmonol.* 1996;21:250–4.
- Donn SM, Sinha SK. Controversies in patient-triggered ventilation. *Clin Perinatol.* 1998;25:49–61.
- El-Khatib MF, Baumeister B, Smith PG, et al. Inspiratory pressure/maximal inspiratory pressure: does it predict successful extubation in critically ill infants and children? *Intensive Care Med.* 1996;22:264–8.
- Fiastro JF, Habib MP, Quan SF. Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. *Chest.* 1988;93:499–505.

- Gillespie LM, White SD, Sinha SK, Donn SM. Usefulness of the minute ventilation test in predicting successful extubation in newborn infants: a randomized clinical trial. *J Perinatol.* 2003; 23:205–7.
- Gupta S, Sinha S, Tin W, Donn SM. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus infant flow driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. *J Pediatr.* 2009;154:645–50.
- Halliday HL. Towards earlier neonatal extubation. *Lancet.* 2000;355:2091.
- McIntyre NR, Leatherman NE. Mechanical loads on the ventilatory muscles. *Am Rev Respir Dis.* 1989;139:968–72.
- Robertson NJ, Hamilton PA. Randomised trial of elective continuous positive airway pressure (CPAP) compared with rescue CPAP after extubation. *Arch Dis Child.* 1998;79:F58–60.
- Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Caffeine for apnea of prematurity trial group. *N Engl J Med.* 2006;354(20):2112–21.
- Sheth RD, Pryse-Phillips WEM, Riggs JE, Bodensteiner JB. Critical illness neuromuscular disease in children manifested as ventilator dependence. *J Pediatr.* 1995;126:259–61.
- Sillos EM, Veber M, Schulman M, et al. Characteristics associated with successful weaning in ventilator-dependent preterm infants. *Am J Perinatol.* 1992;9:374–7.
- Sinha SK, Donn SM. Weaning newborns from mechanical ventilation. *Semin Neonatol.* 2002a;7:421–8.
- Sinha SK, Donn SM. Difficult extubation in babies receiving assisted mechanical ventilation. *Arch Dis Child Educ Pract Ed.* 2006;91:ep42–6.
- Sinha SK, Donn SM, Gavey J, McCarty M. A randomised trial of volume-controlled versus time-cycled, pressure-limited ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child.* 1997;77:F202–5.
- Sinha SK, Donn SM. Weaning newborns from mechanical ventilation. *Semin Neonatol.* 2002b; 7:421–8.
- Tapia JL, Cancalari A, Gonzales A, Mercado ME. Does continuous positive airway pressure (CPAP) during weaning from intermittent mandatory ventilation in very low birth weight infants have risks or benefits? A controlled trial. *Pediatr Pulmonol.* 1995;19:269–74.
- Veness-Meehan KA, Richter S, Davis JM. Pulmonary function testing prior to extubation in infants with respiratory distress syndrome. *Pediatr Pulmonol.* 1990;9:2–6.
- Walsh MC, Fanaroff JM. Meconium stained fluid: approach to the mother and the baby. *Clin Perinatol.* 2007;34:653–65.
- Wilson Jr BJ, Becker MA, Linton ME, Donn SM. Spontaneous minute ventilation predict readiness for extubation in mechanically ventilated preterm infants? *J Perinatol.* 1998;18:436–9.

Ventilatory Case Study

Brooke D. Vergales, MD

Jay P. Goldsmith, MD

A. Prenatal data

1. 18 year-old G2 P1→2 mother
2. Nonreassuring fetal status (meconium-stained amniotic fluid) at 41 weeks gestation

B. Patient data

1. 4,670 g male infant born by urgent Cesarean section at level II hospital
2. Apgar scores 1 (1 min), 3 (5 min), and 7 (10 min)
3. Intubated and suctioned for meconium, ventilated in delivery room; no medications or chest compressions required.
4. Extubated→oxyhood; pH at 1 h of age = 7.16 →reintubated.
5. Transported to level III NICU

C. Physical examination on admission

1. Large for gestational age; depressed
2. Moderate respiratory distress: tachypnea, retractions, rales at lung bases
3. Duplication of right thumb
4. Liver 4 cm below right costal margin

D. Chest radiograph on admission (Fig. 68.1)

1. Mild hyperinflation
2. Patchy infiltrates consistent with aspiration syndrome or retained lung fluid

E. Laboratory values

1. Normal CBC, normal renal and liver function panels
2. Excellent arterial blood gases despite minimal ventilatory support ($P_{aw} = 7$ cm H₂O)

F. Clinical course

1. Numerous technical problems with endotracheal tube thought to result from plugging, displacement
2. Heart murmur heard on day 3→2-dimensional echocardiogram→Endocardial cushion defect
3. Comparative Genomic Hybridization (CGH) sent to evaluate for trisomy 21 (reported later as negative)
4. Attempts to extubate from day 4 through 7 unsuccessful despite appropriate low PIP and rate on conventional ventilator.

(continued)

(continued)

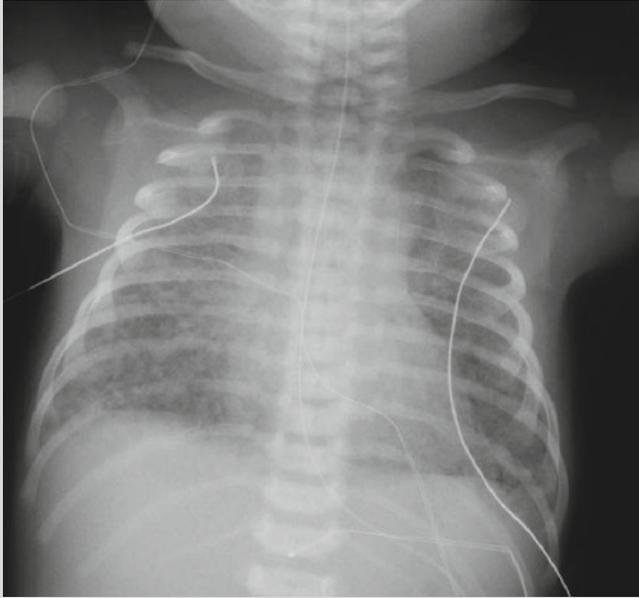


Fig. 68.1 Chest radiograph on admission showing mild hyperinflation and patchy infiltrates

G. Extubation failure: Differential diagnosis (see Table 68.1)

H. Repeat CXR at 7 days of age (Fig. 68.2)

1. Severe hyperinflation
2. Volume loss in both upper lobes

I. Adjuncts to successful weaning and extubation

1. Transition to pressure support ventilation or nasal CPAP
2. Diuretics and bronchodilators
3. Methylxanthines, racemic epinephrine, or systemic peri-extubation steroids

J. Denouement

1. Barium esophagoscopy, cardiac catheterization → true vascular ring with double aortic arch
2. Surgical division of vascular ring and ductus arteriosus ligation accomplished without complication
3. Patient successfully extubated postoperative day 2

(continued)

(continued)

Table 68.1 Modified from Goldsmith JP, Karotkin, EH, *Assisted Ventilation of the Neonate*, 5th Edition, p 123, 2010. Elsevier, Philadelphia with permission

Major causes of extubation failure

-
- I. Pulmonary
 - A. Primary lung disease not resolved
 - B. Post-extubation atelectasis
 - C. Pulmonary insufficiency of prematurity
 - D. Chronic lung disease
 - E. Eventration, paralysis, or dysfunction of diaphragm
 - F. Pneumonia
 - II. Upper Airway
 - A. Edema and/or excess tracheal secretions
 - B. Subglottic stenosis
 - C. Laryngotracheomalacia
 - D. Congenital vascular ring
 - E. Necrotizing tracheobronchitis
 - III. Cardiovascular
 - A. Left to Right Shunt—Patent ductus arteriosus
 - B. Fluid overload
 - C. Congenital heart disease with increased pulmonary flow
 - IV. Central Nervous System (CNS)
 - A. Apnea, hypopnea, (extreme immaturity)
 - B. Intraventricular hemorrhage/periventricular leukomalacia
 - C. Hypoxic ischemic brain damage/seizures
 - D. Sedation, depressant, or narcotic drugs
 - E. CNS Infection
 - F. Prolonged neuromuscular blockade
 - V. Miscellaneous
 - A. Unrecognized diagnosis (nerve palsy, myasthenia gravis, etc.)
 - B. Sepsis/hyperthermia
 - C. Metabolic abnormality/severe electrolyte disturbances/alkalosis
 - D. Malnutrition/weakness
 - E. Severe abdominal distention, elevated diaphragms
-

(continued)

(continued)

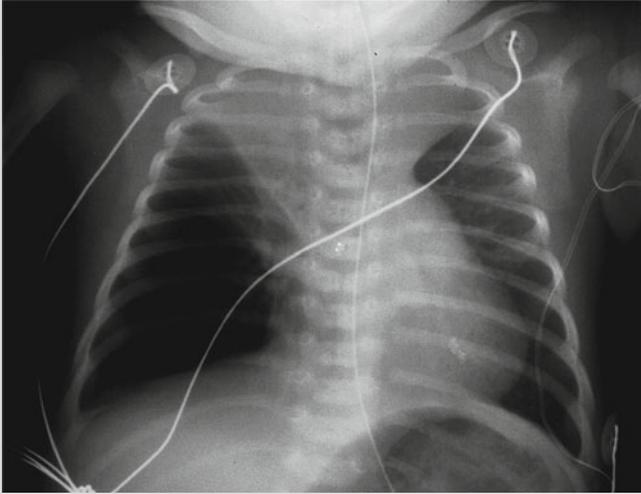


Fig. 68.2 Chest radiograph at 7 days of age showing severe hyperinflation and bilateral upper lobe volume loss

Part XI
Bronchopulmonary Dysplasia

Chapter 69

Etiology and Pathogenesis

Natasha Henner and Jonathan M. Davis

I. Introduction

- A. Bronchopulmonary Dysplasia (BPD) is the chronic lung disease (CLD) that develops in newborns treated with oxygen and mechanical ventilation for a primary lung disorder. BPD remains the most prevalent and one of the most serious long-term sequelae of prematurity, affecting approximately 14,000 preterm infants born in the USA each year.
- B. There are many health consequences of BPD, including asthma, pulmonary hypertension, failure to thrive, cognitive impairment, and neurodevelopmental deficits. There is a high incidence of postnatal mortality and frequent rehospitalizations in those infants diagnosed with BPD.

II. Definition

- A. BPD has generally been defined using characteristics such as the presence of chronic respiratory signs, a persistent oxygen requirement, and an abnormal chest radiograph at 36 weeks' postmenstrual age (PMA). Unfortunately, this definition lacks specificity and fails to account for important clinical distinctions related to extremes of prematurity and wide variability in criteria for the use of prolonged oxygen therapy.
- B. A consensus conference of the National Institutes of Health suggested a new definition of BPD that incorporates many elements of previous definitions and attempts to categorize the severity of the disease process (Table 69.1).
- C. To further standardize the definition of BPD, a physiologic assessment of the need for oxygen at 36 weeks' PMA has been proposed, using an oxygen reduction test. Despite these approaches, there is increasing evidence that a

N. Henner, MD • J.M. Davis, MD (✉)
Department of Pediatrics, The Floating Hospital for Children at Tufts Medical Center,
800 Washington Street, TMC #44, Boston, MA 02111, USA
e-mail: JDavis@tufts-nemc.org

Table 69.1 NIH consensus conference: diagnostic criteria for establishing BPD

Gestational age	<32 weeks	>32 weeks
Time point of assessment	36 weeks' PMA or discharge to home, whichever comes first	>28 day but <56 day postnatal age or discharge to home, whichever comes first
Mild BPD	Treatment with oxygen >21% for at least 28 days Breathing room air at 36 week PMA or discharge, whichever comes first	Breathing room air by 56 day postnatal age, or discharge, whichever comes first
Moderate BPD	Need for <30% O ₂ at 36 weeks PMA or discharge, whichever comes first	Need for <30% O ₂ to 56 day postnatal or discharge, whichever comes first
Severe BPD	Need for >30% O ₂ ± PPV or CPAP at 36 weeks PMA or discharge, whichever comes first	Need for >30% O ₂ ± PPV or CPAP at 56 day postnatal age or discharge, whichever comes first

PMA postmenstrual age, *PPV* positive pressure ventilation, *NCPAP* nasal continuous positive pressure

diagnosis of BPD may not accurately predict which infants will develop chronic respiratory morbidity later in life.

III. Incidence

- A. Incidence depends on the definition used and the gestational age of the population studied. While surfactant treatment has improved overall survival for premature infants, the incidence of BPD remains approximately 30–40% (inversely proportional to gestational age at birth). With the use of standardized oxygen saturation monitoring involved in the physiologic definition, the incidence might be further decreased by as much as 10%.
- B. Using the NICHD definition of BPD, the incidence is 52% in infants with birth weights 501–750 g, 34% among those with birth weights 751–1,000 g, 15% in those with birth weights 1,001–1,200 g, and 7% in infants born between 1,201 and 1,500 g.
- C. Demographic factors linked to BPD include: gestational age, lower birth weight, male sex, white race, a family history of asthma, impaired growth for gestational age, and possibly several genetic factors.

IV. Pathogenesis (Fig. 69.1)

- A. Ventilator induced lung injury (VILI)
 1. Use of mechanical ventilation to establish functional residual capacity (FRC) in a surfactant deficient lung can alter fluid balance and increase endothelial and epithelial cell permeability, causing lung injury.
 2. “Low-volume injury zone” predisposes an atelectatic lung to shear stress, while the use of high tidal volumes (>6 mL/kg) may cause volutrauma in the “high-volume injury zone.” Preterm infants are more prone to volutrauma because their compliant chest wall allows uncontrolled expansion.

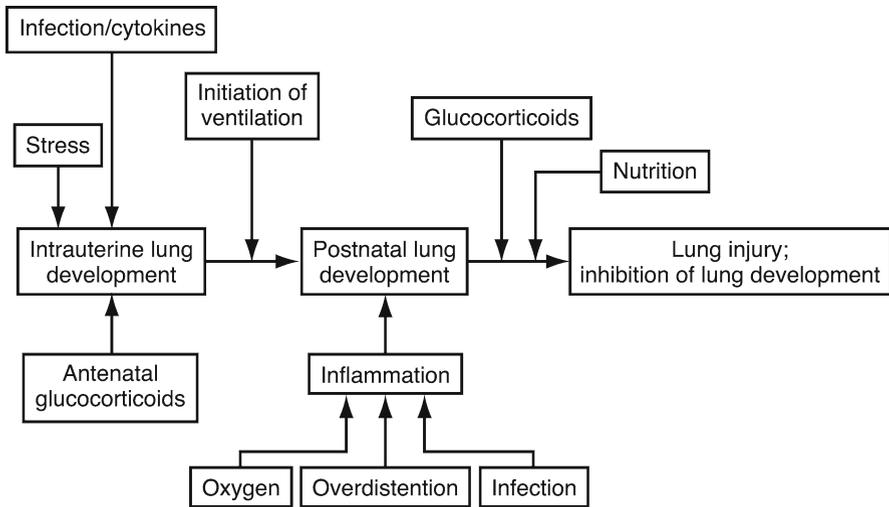


Fig. 69.1 Pathogenesis of BPD

3. VILI contributes to a cascade of inflammation and cytokine release, further amplifying the lung injury process.

B. Oxygen/antioxidants

1. Oxidative lung injury has been increasingly recognized as a very important causative factor in the development of BPD. Many animal studies have suggested that hyperoxia may be the most important trigger for the pathologic changes seen in BPD.
2. Under normal conditions, a delicate balance exists between the production of reactive oxygen species (ROS) and the antioxidant defenses that protect cells *in vivo*. Increased generation of ROS can occur secondary to hyperoxia, reperfusion, or inflammation. In addition, ROS can increase injury because of inadequate antioxidant defenses.
3. The premature newborn may be more susceptible to ROS-induced injury since antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase (which develop at a rate similar to pulmonary surfactant) may be relatively deficient at birth and are not induced secondary to an ROS challenge.
4. ROS also have potent proinflammatory effects in the lung, such as increasing IL-8, IL-6, and TNF- α expression, and facilitating bacterial adherence to epithelial cells while impairing mononuclear cell function.

C. Inflammation

1. There is controversy whether antenatal infection and inflammation (chorioamnionitis) is a risk factor for BPD. The majority of studies suggest that the presence of inflammation in the chorionic plate or the

umbilical cord is not associated with the development of BPD. However, there is some evidence that levels of IL-6, IL-1 β , and IL-8 in amniotic fluid are greater in those who develop BPD than in those who do not.

2. Mechanism: Early elevations of cytokines (IL-6, IL-8), followed by neutrophil/mononuclear cell influx leading to increased elastase activity and protease/anti-protease imbalance, which leads to decreased endothelial cell integrity, pulmonary edema, and exudate.
 - a. The consequence of exaggerated neutrophil recruitment to the neonatal lung can be severe. Proteases and ROS generated by these cells can indiscriminately damage healthy local tissue, leading to simplification and enlargement of alveolar structures, which is a notable feature of the “new BPD.” Altered vascular endothelial growth factor (VEGF) expression is also thought to contribute to the process of alveolar simplification through vascular remodeling.
 - b. The process of programmed apoptotic cell death, which acts to restrict neutrophil activity during inflammation, is also diminished in infants with BPD.

D. Infection

1. A large body of evidence suggests that intrauterine infection and the resulting fetal inflammatory response primes the lung for further injury upon exposure to postnatal infection, mechanical ventilation, oxygen (even room air is supraphysiologic), and abnormal blood flow through a patent ductus arteriosus (PDA).
2. *Ureaplasma urealyticum* has been associated with higher cord levels of IL-6, IL-1 α , and IL-1 β . These proinflammatory mediators cause lung microvascular injury, decreased VEGF production, reduce nitric oxide synthase activity, smooth muscle proliferation, and an arrest in alveolar septation.

Interestingly, aggressive use of macrolide antibiotics to treat *Ureaplasma* infections failed to reveal any reduction in the incidence of BPD in a recent meta-analysis.

E. Nutrition

1. Poor caloric intake during a respiratory illness may result in respiratory muscle fatigue and a longer duration of mechanical ventilation. In one case-controlled study, infants who developed BPD had lower mean energy intakes than matched controls.
2. Vitamin A derivatives are critical in regulation of growth and differentiation of lung epithelial cells. In animals, deficiency of vitamin A results in abnormal lung growth following prolonged exposure to hyperoxia. Preterm infants have lower levels of vitamin A, which has been associated with the development of BPD. Although trials of vitamin A supplementation appear to reduce BPD to a small degree, longer term studies show no benefit on respiratory morbidity at 1 year corrected gestational age.

F. Fluids/patent ductus arteriosus (PDA)

1. Pulmonary edema, both alveolar and interstitial, has been associated with the development of BPD. A large retrospective study showed that the incidence of BPD and/or death was significantly lower in extremely preterm infants if they lost weight in the first 10 days of life. In contrast, the longer a hemodynamically significant PDA remains (especially after 4 weeks of age), the higher the incidence of BPD.
2. Meta-analysis of trials using diuretics have demonstrated improvements in short-term pulmonary mechanics, but failed to demonstrate decreased overall incidence of BPD.
3. Adverse effects of PDA on respiratory status have been reported, including the need for prolonged respiratory support. The mechanism is thought to be similar to that of fluid overload, as well as histopathologic changes in the vascular network, resulting in hypertrophy of the medial smooth muscle layer leading to increased pulmonary arterial pressure.
 - a. Infection in the presence of a PDA can significantly increase the incidence and severity of BPD.
 - b. It is important to note that despite the evidence of a PDA playing an important role in development of BPD, early and aggressive closure has not been associated with a decreased incidence of BPD overall.

V. Pathophysiologic changes

- A. Radiographic aspects: the radiograph appearance of BPD has changed with time, and cystic changes in particular are less common. A new computerized tomography (CT) scoring system exists, with three key elements being hyperexpansion, emphysema (but only as bullae and blebs), and fibrous interstitial changes (including subpleural triangular densities). A significant relationship has been found between the CT score and duration of oxygen therapy and mechanical ventilation.
- B. Pulmonary mechanics
 1. Tachypnea and shallow breathing increase dead space ventilation. Non-uniform damage to the lungs results in worsening ventilation-perfusion (V/Q) mismatch.
 2. Lung compliance is markedly decreased, even in those infants who no longer need oxygen therapy. The reduction in compliance results from a variety of factors, including interstitial fibrosis, airway narrowing, edema, and atelectasis.
 3. Increased airway resistance, with significant flow limitations especially at low lung volumes is common.
 4. FRC is often reduced in the early stages of BPD because of atelectasis. However, during later stages of BPD, gas trapping and hyperinflation can result in increased FRC.
 5. Pulmonary circulation changes include smooth muscle cell proliferation of the pulmonary arteries and incorporation of fibroblasts into the

vessel walls, both contributing to high pulmonary vascular resistance. Abnormal vasoreactivity and early injury to pulmonary circulation leads to pulmonary hypertension, which contributes significantly to the mortality and morbidity of BPD.

6. Airway pathologic changes include patchy loss of cilia from columnar epithelial cells, mucosal edema and/or necrosis (focal or diffuse), infiltration of inflammatory cells, and granulation tissue at the area of the endotracheal tube.
7. Alveolar pathologic changes include early interstitial and alveolar edema, followed by atelectasis, inflammation, exudates, and fibroblast proliferation. Alveolar simplification and failure of secondary alveolar crests to form alveoli reduces surface area for gas exchange.

Suggested Reading

- Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. *Semin Neonatol.* 2002;7:353–60.
- Bancalari E. Bronchopulmonary dysplasia. *Semin Perinatol.* 2003;8:1–92.
- Bry K, Hogmalm A, Backstrom E. Mechanisms of inflammatory lung injury in the neonate: lessons from a transgenic mouse model of bronchopulmonary dysplasia. *Semin Perinatol.* 2010;34:211–21.
- Chakrabarty M, McGreal EP, Kotecha S. Acute lung injury in preterm newborn infants: mechanism and management. *Pediatr Respir Rev.* 2010;11:162–70.
- Davis JM, Rosenfeld WN, Sanders RJ, Gonenne A. The prophylactic effects of human recombinant superoxide dismutase in neonatal lung injury. *J Appl Physiol.* 1993;74:22–34.
- Davis JM, Parad RB, Michele T, et al. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant CuZn superoxide dismutase. *Pediatrics.* 2003;111:469–76.
- Davis JM, Rosenfeld W. Bronchopulmonary dysplasia. In: Avery GB, Fletcher MA, MacDonald MG, editors. *Textbook of neonatology.* 6th ed. Philadelphia: JB Lippincott Company; 2005. p. 578–99.
- Davis JM, Auten RL. Maturation of the antioxidant system and the effects on preterm birth. *Semin Fetal Neonatal Med.* 2010;15:191–5.
- De Paoli AG, Davis PG, Lemyre B. Nasal continuous positive airway pressure versus nasal intermittent positive pressure ventilation for preterm neonates: a systematic review and meta-analysis. *Acta Paediatr.* 2003;92:70–5.
- Ehrenkranz RA, Walsch MC, Vohr BR, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics.* 2005;116:1353–60.
- Frank L, Groseclose EE. Preparation of birth into an O₂ rich environment: the antioxidant enzymes in the developing rabbit lung. *Pediatr Res.* 1984;18:240–4.
- Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Resp Crit Care Med.* 2001;163:1723–9.
- Jobe AH. The new BPD: an arrest of lung development. *Pediatr Res.* 1999;46:641–3.
- Kinsella JP, Greenough A, Abman SA. Bronchopulmonary dysplasia. *Lancet.* 2006;367:1421–31.
- Laughon MM, Smith PB, Bose C. Prevention of BPD. *Sem Fetal Neonatal Med.* 2009;14:374–82.
- Munshi UK, Niu JO, Siddiq MM, Parton LA. Elevation of interleukin-8 and interleukin-6 precedes the influx of neutrophils in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. *Pediatr Pulmonol.* 1997;24:331–6.
- Merritt TA, Demming DD, Boyton BR. The ‘new’ bronchopulmonary dysplasia: challenges and commentary. *Sem Fetal Neonatal Med.* 2009;14:345–57.

- Van Marter LJ. Epidemiology of bronchopulmonary dysplasia. *Sem Fetal Neonatal Med.* 2009;14:358–66.
- Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. *J Perinatol.* 2003;23:451–6.
- Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics.* 2004;114:1305–11.
- Wilson AC. What does imaging the chest tell us about bronchopulmonary dysplasia? *Pediatric Resp Rev.* 2010;11:158–61.
- Yoon BH, Romero R, Jun JK, et al. Interleukin-8 and the risk for the development of bronchopulmonary dysplasia. *Am J Obstet Gyn.* 1997;177:825–30.

Chapter 70

Management

Eduardo Bancalari

- I. The management of the infant with BPD is aimed at maintaining adequate gas exchange while limiting the progression of the lung damage. The big challenge is that the supplemental oxygen and mechanical ventilation needed to maintain gas exchange are the same factors implicated in the pathogenesis of the lung damage.
- II. Oxygen therapy
 - A. Reduce the FiO_2 as quickly as possible to avoid oxygen toxicity, while maintaining the PaO_2 at a level sufficient to ensure adequate tissue oxygenation and avoid pulmonary hypertension and cor pulmonale.
 - B. There is no sufficient information to recommend a specific range of oxygen saturation, but there is sufficient evidence that oxygen saturation values above 95% and PaO_2 above 70 Torr are associated with a higher incidence of ROP and worse respiratory outcome. Because of this, it is advisable to maintain saturation between 90 and 95% or the PaO_2 between 50 and 70 Torr to minimize the detrimental effects of hypo- and hyperoxemia. Lower saturation targets have been associated with increased mortality.
 - C. After extubation, oxygen can be administered through a hood, or a nasal cannula. In some cases, patients with severe BPD are discharged home with oxygen therapy.
 - D. Adequacy of gas exchange is monitored by blood gas levels.
 1. Blood gas determinations obtained by arterial puncture may not be reliable because the infant responds to pain with crying or apnea.
 2. Transcutaneous PO_2 electrodes may also be inaccurate in these infants and they frequently underestimate the true PaO_2 .

E. Bancalari, MD (✉)
Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, 1611 NW 12th Avenue, Central building, Room 740, Miami, FL 33136, USA
e-mail: ebancalari@med.miami.edu

- E. Pulse oximeters offer the most reliable estimate of arterial oxygenation and are simple to use and provide continuous information during different behavioral states.
- F. It is important to maintain a relatively normal blood hemoglobin concentration. This can be accomplished with blood transfusions or by the administration of recombinant erythropoietin. However, limiting the amount of blood taken for laboratory tests is the most effective and safest measure to prevent anemia.

III. Mechanical ventilation

- A. Use the lowest settings necessary to maintain satisfactory gas exchange, and limit the duration of mechanical respiratory support to a minimum.
- B. Use the lowest peak airway pressure to deliver adequate tidal volumes (4–7 mL/kg).
- C. Use inspiratory times between 0.3 and 0.5 s.
 - 1. Avoid shorter inspiratory times and high flow rates that may exaggerate maldistribution of the inspired gas.
 - 2. Longer inspiratory times may increase the risk of alveolar rupture and of negative cardiovascular side effects.
- D. Adjust end-expiratory pressure between 4 and 8 cm H₂O so that the lowest oxygen concentration necessary to keep oxygen saturation above 90% (PaO₂ above 50 Torr) is used. Higher PEEP levels (6–8 cm H₂O) may help reduce expiratory airway resistance and can improve alveolar ventilation in infants with severe airway obstruction.
- E. Limit the duration of mechanical ventilation as much as possible to reduce the progression of ventilator-induced lung injury and infection.
- F. Weaning from mechanical ventilation must be accomplished gradually, by reducing peak inspiratory pressures below 15–18 cm H₂O and FiO₂ to less than 0.3–0.4.
- G. Reduce ventilator rate gradually to 10–15 breaths per minute to allow the infant to perform an increasing proportion of the respiratory work.
- H. The use of patient triggered ventilation, volume targeted ventilation, and pressure support of the spontaneous breaths can accelerate weaning and reduce the total duration of mechanical ventilation.
 - I. During weaning from CMV it may be necessary to increase the FiO₂ to maintain adequate oxygen saturation levels.
 - J. Concurrently, the PaCO₂ may rise to values in the 50–60 Torr or higher. As long as the pH is within acceptable range, hypercapnia should be tolerated to wean these patients from the ventilator.
- K. Aminophylline or caffeine can be used as respiratory stimulants during the weaning phase. Earlier use may actually help to ameliorate BPD.
- L. When the patient is able to maintain acceptable blood gas levels for several hours on low ventilator settings (RR 10–15 breaths/minute, PIP 12–15 cm H₂O, FiO₂ < 0.3–0.4), extubation should be attempted.

- M. After extubation, it may be necessary to provide chest physiotherapy to prevent airway obstruction and lung collapse caused by retained secretions.
- N. In smaller infants, nasal CPAP 4–6 cm H₂O or nasal IPPV can stabilize respiratory function and reduce the need for reintubation and mechanical ventilation.

IV. Fluid management

- A. Infants with BPD tolerate excessive fluid intake poorly and tend to accumulate water in their lungs and this excess fluid contributes to their poor lung function.
- B. Water and salt intake must be limited to the minimum required to provide the necessary fluid intake and calories to cover for their metabolic needs and growth.
- C. If pulmonary edema persists despite fluid restriction, diuretic therapy can be used successfully. The use of diuretics can produce a rapid improvement in lung compliance and decrease in resistance, but blood gases do not always show improvement. There is, however, no evidence at present to support the chronic use of diuretics in these patients.
- D. Chronic use of loop diuretics can be associated with hypokalemia, hyponatremia, metabolic alkalosis, hypercalciuria with nephrocalcinosis and nephrolithiasis, hypochloremia, and hearing loss. Some of these side effects may be reduced by using furosemide on alternate days.
- E. Because of the side effects and the lack of evidence that prolonged use of diuretics changes the incidence or severity of BPD, this therapy is not recommended for routine use and is only indicated for acute episodes of deterioration associated with pulmonary edema.
- F. Distal tubular diuretics such as thiazides and spironolactone are also used in infants with BPD, but the improvement in lung function with these diuretics is less consistent than with proximal loop diuretics. Side effects such as nephrocalcinosis and hearing loss may be less frequent than with furosemide and for this reason these diuretics can be used in infants with established BPD who require prolonged diuretic therapy.

V. Bronchodilators

- A. Infants with severe BPD frequently have airway smooth muscle hypertrophy and airway hyperreactivity.
- B. Because hypoxia can increase airway resistance in these patients, maintenance of adequate oxygenation is important to avoid bronchoconstriction.
- C. Inhaled bronchodilators including β -agonists such as isoproterenol, salbutamol, metaproterenol and isoetharine, and anticholinergic agents such as atropine and ipratropium bromide can reduce airway resistance in some infants with BPD. Their effect is short lived, and their use can be associated with cardiovascular side effects such as tachycardia, hypertension, and arrhythmias. Chronic use is not supported by evidence.

- D. Methylxanthines also have been shown to reduce airway resistance in these infants.
1. These drugs have other potential beneficial effects, such as respiratory stimulation and mild diuretic effect, and aminophylline may also improve respiratory muscle contractility.
 2. These drugs must also be used with caution because of their multiple side effects.
- E. There is no evidence that prolonged use of bronchodilators changes the course of infants with BPD and for this reason their use should be limited to episodes of acute exacerbation of airway obstruction. When indicated, β agonists are given by inhalation using a nebulizer or a space inhaler connected to a mask or head chamber or inserted in the inspiratory side of the ventilator circuit.

VI. Corticosteroids

- A. Many studies have shown rapid improvement in lung function after systemic administration of steroids, facilitating weaning from the ventilator, and a reduction in BPD. Steroids can enhance production of surfactant and antioxidant enzymes, decrease bronchospasm, decrease pulmonary and bronchial edema and fibrosis, improve vitamin A status, and decrease the response of inflammatory cells and mediators in the injured lung.
- B. Potential complications of prolonged steroid therapy include masking the signs of infection, arterial hypertension, hyperglycemia, increased proteolysis, adrenocortical suppression, somatic and lung growth suppression, and hypertrophic cardiomyopathy. Of more concern is the fact that long-term follow-up studies showed that infants who received prolonged steroid therapy have worse neurologic outcome, including an increased incidence of cerebral palsy.
- C. Because of the seriousness of the neurologic side effects, specifically when systemic steroids are used early after birth, the use of systemic steroids should only be considered after the first 2 weeks of life in infants who show clear evidence of severe and progressive pulmonary damage and who remain oxygen and ventilator dependent.
- D. The duration of steroid therapy must be limited to the minimum necessary to achieve the desired effects, usually 5–7 days, and following the recommendation of the American Academy of Pediatrics, the benefits and potential side effects should be discussed with the family before initiating this therapy.
- E. Steroids can also be administered by nebulization to ventilator-dependent infants. Inhaled steroids may reduce the need for systemic steroids, reducing the side effects associated with prolonged systemic therapy, but data on effectiveness of topical steroids are not conclusive enough to recommend their routine use.

VII. Nutrition (Chapter 50)

VIII. Pulmonary vasodilators

- A. Because pulmonary vascular resistance is extremely sensitive to changes in alveolar PO₂ in infants with BPD, it is important to assure normal oxygenation at all times (Chap. 50).
- B. In infants with severe pulmonary hypertension and cor pulmonale, the calcium channel blocker nifedipine has been shown to decrease pulmonary vascular resistance.
 - 1. This drug is also a systemic vasodilator and can produce a depression of myocardial contractility.
 - 2. Its safety and long-term efficacy in these infants has not been established.
- C. Inhaled nitric oxide has been administered to infants with BPD in an attempt to improve outcome.
 - 1. Nitric oxide can improve ventilation–perfusion matching, reduce pulmonary vascular resistance, and reduce inflammation.
 - 2. Although iNO has been shown to improve oxygenation in some infants with BPD, there is no clear evidence that this therapy improves long term outcome and should still be considered experimental.
- D. Phosphodiesterase inhibitors (Sildenafil), Prostacyclin (Epoprostenol), and ET-1 antagonists are also potent pulmonary vasodilators that have been used successfully to treat pulmonary hypertension, but there is not enough information to recommend their routine use in infants with BPD.

Suggested Reading

- AAP. Postnatal Corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics*. 2002;109:330–8.
- Ambalavanan N, Schelonka RL, Carlo WA. Ventilation strategies (chapter 15). In: Goldsmith JP, Karotkin EH, editors. *Assisted ventilation of the neonate*. 5th ed. Philadelphia, PA: Elsevier; 2010. p. 265–76.
- Aschner JL. New therapies for pulmonary hypertension in neonates and children. *Pediatr Pulmonol*. 2004;26(Suppl):132–5.
- Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med*. 2003;349:959–67.
- Atkinson SA. Special nutritional needs of infants for prevention of and recovery from bronchopulmonary dysplasia. *J Nutr*. 2001;131:942S–6.
- Bancalari E. Bronchopulmonary dysplasia. *Semin Perinatol*. 2003;8:1–92.
- Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med*. 2007;357:1946–55.
- Brunton JA, Saigal S, Atkinson S. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. *J Pediatr*. 1998;133:340–5.

- Cole CH, Colton T, Shah BL, et al. Early inhaled glucocorticoid therapy to prevent bronchopulmonary dysplasia. *N Engl J Med*. 1999;340:1005–10.
- D'Angio CT, Maniscalco WM. Bronchopulmonary dysplasia in preterm infants: pathophysiology and management strategies. *Paediatr Drugs*. 2004;6:303–30.
- Committee on Fetus and Newborn; Postnatal corticosteroid to treat or prevent chronic lung disease in preterm infants. *Pediatrics*. 2002;109:330.
- Donn SM, Becker MA, Nicks JJ. Special ventilation techniques: I: patient triggered ventilation (chapter 12). In: Goldsmith JP, Karotkin EH, editors. *Assisted ventilation of the neonate*. 5th ed. Elsevier: Philadelphia, PA; 2010. p. 220–34.
- Doyle LW, Ehrenkranz RA, Halliday HL. Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. *Neonatology*. 2010;98:111–7.
- Greenough A. Update on patient-triggered ventilation. *Clin Perinatol*. 2001;28:533–46.
- Grier DG, Halliday HL. Corticosteroids in the prevention and management of BPD. *Sem Neonatol*. 2003;8:83–91.
- Kao LC, Durand DJ, McCrea RC, et al. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. *J Pediatr*. 1994;124:772–81.
- Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics*. 1999;104:1082.
- Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr*. 2009;154(3):379–84.
- O'Shea TM, Kothadia JM, Klinepeter KL, et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: Outcome of study participants at 1-year adjusted age. *Pediatrics*. 1999;104:15–21.
- Onland W, Offringa M, De Jaegere AP, van Kaam AH. Finding the optimal postnatal dexamethasone regimen for preterm infants at risk of bronchopulmonary dysplasia: a systematic review of placebo-controlled trials. *Pediatrics*. 2009;123:367–77.
- Reyes Z, Tauscher M, Claure N. Randomized, controlled trial comparing pressure support (PS) + synchronized intermittent mandatory ventilation (SIMV) with SIMV in preterm infants. *Pediatr Res*. 2004;55:466A.
- Schmidt B, Roberts R, Millar D, Kirpalani H. Evidence-based neonatal drug therapy for prevention of bronchopulmonary dysplasia in very-low-birth-weight infants. *Neonatology*. 2008;93:284–7.
- Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126:443–56.
- SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362(21):1970–9.
- Tin W. Optimal oxygen saturation for preterm babies. Do we really know? *Biol Neonate*. 2004;85:319–25.
- Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med*. 1999;340:1962–8.
- Watterberg KL. Committee on fetus and newborn: postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. *Pediatrics*. 2010;126:800–8.
- Yeh TF, Lin YJ, Huang CC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics*. 1998;101:1–8.
- Yeh TF, Lin YJ, Lin HC, et al. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. *N Engl J Med*. 2004;350:1304–13.

Chapter 71

Long-Term Outcome of Newborns with Bronchopulmonary Dysplasia

Sumesh Thomas, Prashanth Murthy, and Saroj Saigal

I. Introduction

- A. Bronchopulmonary dysplasia (BPD) is a complex disorder of the respiratory system affecting mostly preterm babies with an incidence of 30–40% in Extremely Low Birth Weight (ELBW, <1,000 g) and up to 50–70% in infants <750g. This complex disorder represents histological distortion of normal lung architecture by factors that causes lung injury and disruption to lung development. This is often a consequence of mechanical ventilation, infective and inflammatory processes, nutritional deficiencies and or underlying disease processes.
- B. “Old BPD” as described by Northway et al. in 1967 was characterized by extensive inflammatory and fibrotic changes in airways and lung parenchyma. With improved survival of more immature infants, in part from the use of antenatal steroids, gentler ventilatory strategies, and surfactant therapy, a different pattern of this disorder, “new BPD” has evolved. This condition represents mostly a developmental disorder of immature lungs in reaching full structural complexity. This is characterized by alveolar arrest and disordered pulmonary vasculature resulting in a smaller alveolar surface area for gas exchange.

II. Neonatal morbidity

- A. Very preterm infants are more prone to complications of prematurity such as nosocomial blood stream infections, ventilator-associated pneumonia, necrotizing enterocolitis (NEC), and growth failure. These comorbid factors trigger a systemic inflammatory response, adversely impacting the postnatal development of immature lungs contributing to the pathogenesis of BPD.

S. Thomas, MBBS, DCH, FRCP, FRCPC, FRCPC (✉)
• P. Murthy, MBBS, MD, MRCPC • S. Saigal, MD, FRCPC
Department of Pediatrics, McMaster Children’s Hospital,
1280 Main Street West, HSC 2V9, Hamilton, ON, Canada L8S 4K1
e-mail: spthomas@mcmaster.ca

- B. Survivors with BPD are also more prone to other comorbidities associated with prematurity such as IVH, PVL, and ROP; however, there is no direct causal association.

III. Long-term outcomes

A. Growth and development

1. Nutrition

- a. Sicker neonates are less likely to be fed. Recent studies suggest that VLBW infants with poor enteral nutrition within the first 2 weeks of life were more likely to develop BPD. Infants with BPD have greater protein and energy requirements from increased work of breathing as a result of poor lung compliance, hypoxic episodes, and infections. VLBW Infants with all forms of BPD have been shown to have lower weight, length, and head circumferences compared to VLBW infants without BPD. Several studies have shown a drop in weight-for-age z-scores following discharge of infants with BPD from the hospital. Long-term growth is also affected, with a significantly lower length and weight compared to non-BPD children. Infants with severe BPD appear to be more vulnerable to a negative growth outcome even when corrected for perinatal and demographic variables. Chronic and episodic hypoxia is well described in infants with BPD during feeding and sleep, which may be contributory to growth failure in infancy. Close monitoring of supplemental oxygen therapy and nutritional intake post discharge from is therefore recommended.
- b. Recurrent illnesses, hospitalization, and increased metabolic demands associated with BPD also result in poor growth. However, after controlling for confounding factors, studies during childhood have not demonstrated significant differences in the growth of VLBW children with and without BPD.
- c. In adult survivors with BPD, outcome is intricately linked to issues relating to low gestational age and weight with higher rates of many adverse health outcomes in early adulthood; however, the majority of survivors lead productive and healthy lives. Longer term studies are essential in evaluating fully the lifetime consequences of BPD and LBW.

2. Neurocognitive development

- a. Along with white matter abnormalities on cranial ultrasound scans in the neonatal period, BPD independently predicts adverse developmental outcome in early infancy.
 - (1) A volumetric magnetic resonance imaging study of preterm infants with BPD showed uniform reduction in cerebral volumes compared to regional reduction in brain volume as seen in preterm infants without BPD. The exact mechanism for this reduction in brain volume is unclear; however, it is likely that episodic

hypoxemia, inflammatory stress, nutritional deprivation and drugs, notably postnatal steroids may be contributory. This reduction in brain volume may correlate with functional deficits more frequently seen in survivors with BPD.

- (2) Studies have also shown that patients with severe BPD have an increased incidence of neurodevelopmental disability at 6 and 12 months, which is less notable in infants with mild to moderate BPD.

b. Motor development.

- (1) Abnormality of tone and movement affecting the limbs, neck, trunk, mouth, and tongue are seen in some infants with BPD. Significant improvement is expected by 2 years of age; however, some postural and balance differences persist into early childhood.
- (2) Recent studies have shown a greater incidence of quadriplegia and diplegia in infants who require mechanical ventilation at 36 weeks' corrected gestational age when assessed at 24 months.
- (3) Cognitive and motor delay is more prevalent in preschoolers with BPD compared to VLBW peers without BPD.
- (4) Cerebral palsy with impaired fine and gross motor function as well as poorer coordination is reported in up to 15% of VLBW children with BPD compared to non-BPD VLBW children.
- (5) Visual-spatial perceptual deficits are noted in about 30% of VLBW children with BPD on Visual Motor Integration testing. This deficit persists into adolescence and correlates to duration of oxygen therapy. A higher proportion of these children therefore require occupational and physiotherapy support.

c. Neurosensory impairments.

- (1) BPD independently predicts neurosensory impairment at 6 months of age. Beyond this age, PVL, severe ROP, and length of hospital stay are predictive of adverse neurosensory outcome.
- (2) Survivors with BPD who were treated with postnatal dexamethasone have shown a higher incidence of cerebral palsy and cognitive impairment compared to untreated BPD survivors.

d. Cognitive and academic consequences.

- (1) Studies have demonstrated one-quarter to two-thirds of a SD lower IQ scores in VLBW infants with BPD compared to non-BPD-VLBW children at school age. Memory and learning difficulties are also more prevalent in these infants.
- (2) Attention deficit hyperactivity disorders (ADHD) are reportedly as high as 15% in VLBW infants with BPD, twice as high compared to non-BPD VLBW children at school age. One study showed that 50% of school age VLBW infants with BPD enrolled for speech

and language therapy for difficulty with both expressive and receptive language skills, a similar percentage of preschool VLBW infants with BPD have needed special educational support with reading, spelling, and mathematics.

B. Other systems

1. Respiratory system

- a. Hospital readmission rates, mainly from reactive airway disease, pneumonia, and RSV infections are higher in BPD infants in the first few years of life in comparison to term controls. Respiratory abnormalities in infants with BPD improve over time, but there is a greater incidence of chronic coughing, wheezing, and other asthma-like symptoms in comparison to term controls.
- b. At school age, children with BPD had poorer lung function and reduced exercise tolerance in comparison to non-BPD survivors of similar weight. Recent studies of large cohorts of preterm infants have shown a significant decrease in exercise capacity despite normal mean lung function in comparison to term controls.

2. Cardiovascular system

- a. Pulmonary hypertension and potential resulting cor pulmonale in patients with BPD are produced by functional and structural changes in the lung. Pulmonary hypertension contributes to both increased morbidity and mortality.
- b. Infants with BPD can develop systemic hypertension by several mechanisms including stimulation of the renin–angiotensin system. Approximately 50% of infants with systemic hypertension require medical treatment.

3. Renal

- a. Nephrocalcinosis is reported in as many as 40% of VLBW infants, more prevalent in babies with severe respiratory disease, acidosis, treatment with drugs (loop diuretics, methylxanthines, and glucocorticoids) and parenteral nutrition in the neonatal period.
- b. The long-term consequence of this condition, previously thought to be benign, is unknown. While the majority resolves spontaneously, there is a risk of long-term renal damage and contribution to systemic hypertension. Long-term follow-up and predischarge renal ultrasound surveillance is advised.

IV. Summary

- A. BPD is a multisystem disorder with consequences beyond the neonatal period. Close attention to growth and development following discharge from neonatal units is essential in optimizing outcome by identifying needs for specialist intervention and avoiding potentially life threatening complications.

- B. Infants with BPD will require long term follow up well into adulthood to fully understand the health and lifestyle implications of this multisystem disorder.

Suggested Reading

- Baraldi E, Carraro S, Filippone M. Bronchopulmonary dysplasia: definitions and long-term respiratory outcome. *Early Hum Dev.* 2009;85(10 Suppl):S1–3.
- Doyle LW, the Victorian Infant Collaborative Study Group. Respiratory function at age 8–9 years in extremely low birthweight/very preterm children born in Victoria in 1991–92. *Pediatr Pulmonol.* 2006;41:570–6.
- Doyle LW, Anderson P. Long-term outcomes of bronchopulmonary dysplasia. *Sem Fetal Neonatal Med.* 2009;14:391–5.
- Doyle LW, Anderson PJ. Pulmonary and neurological follow-up of extremely preterm infants. *Neonatology.* 2010;97:388–94.
- Gray PH, O’Callaghan MJ, Poulsen L. Behaviour and quality of life at school age of children who had bronchopulmonary dysplasia. *Early Hum Dev.* 2008;84:1–8.
- Jeng SF, Hsu CH, Tsao PN, Chou HC, Lee WT, Kao HA, Hung HY, Chang JH, Chiu NC, Hsieh WS. Bronchopulmonary dysplasia predicts adverse developmental and clinical outcomes in very-low-birthweight infants. *Dev Med Child Neurol.* 2008;50:51–7.
- Kobaly K, Schluchter M, Minich N, Friedman H, Taylor HG, Wilson-Costello D, Hack M. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics.* 2008;121:73–81.
- Northway Jr WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med.* 1967;276:357–68.
- Short EJ, Kirchner HL, Asaad GR, Fulton SE, Lewis BA, Klein N, Eisengart S, Baley J, Kerckmar C, Min MO, Singer LT. Developmental sequelae in preterm infants having a diagnosis of bronchopulmonary dysplasia: analysis using a severity-based classification system. *Arch Pediatr Adolesc Med.* 2007;161:1082–7.

Part XII
Complications Associated
with Mechanical Ventilation

Chapter 72

Thoracic Air Leaks

Jennifer Dalton and Steven M. Donn

- I. Description: Thoracic air leak refers to a collection of gas outside the pulmonary space. A variety of disorders are included in this category including pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema, pneumoperitoneum, and subcutaneous emphysema.
- II. Incidence and risk factors: Estimates for the overall incidence of air leak in normal term infants range from 0.07% to 1%. The incidence increases to 6% in very low birth weight infants.
 - A. The incidence of air leak varies depending on:
 1. Degree of perinatal hypoxemia
 2. Technique of resuscitation
 3. Concomitant respiratory disease
 4. Type and style of assisted ventilation
 5. Quality of radiographs and their interpretation
 - B. The likelihood of pneumothorax being symptomatic without underlying lung disease is small and many go undetected.
 - C. Several disease states increase the risk of pulmonary air leaks:
 1. Respiratory distress syndrome, incidence 5–20%
 2. Meconium aspiration syndrome, incidence 20–50%
 3. Pulmonary hypoplasia
 4. Pneumonia

J. Dalton, MD

Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital, University of Michigan Health System, 1500 E. Medical Center Dr., Ann Arbor, MI 48109, USA

S.M. Donn, MD, FAAP (✉)

Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital, F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5254, USA

e-mail: smdonnmd@med.umich.edu

III. Pathophysiology: Air leak syndromes arise by a common pathway that involves damage of the respiratory epithelium, usually by high transpulmonary pressures. Damaged epithelium allows air to enter the interstitium, causing pulmonary interstitial emphysema. With continued high transpulmonary pressures, air dissects toward the visceral pleura and/or hilum via peribronchial or perivascular spaces.

- A. Pneumothorax results when the pleural surface is ruptured with air leaking into the pleural space.
- B. Pneumomediastinum results when air, following the path of least resistance, dissects toward the hilum and enters the mediastinum.
- C. Pneumopericardium results when air dissects into the pericardial space.
- D. Subcutaneous emphysema occurs when air from the mediastinum egresses into the fascial planes of the neck and skin.
- E. Pneumoperitoneum results from the dissection of retroperitoneal air, from pneumomediastinal decompression, into the peritoneum. (It can also occur from a ruptured abdominal viscus).

IV. Air leak syndromes

A. Pneumothorax often results from high inspiratory pressures, long inspiratory duration, and uneven ventilation.

1. Etiology

- a. Spontaneous pneumothoraces are seen in up to 1% of normal term infants around the time of birth, with only 10% of these being symptomatic.
- b. Lung diseases including meconium aspiration syndrome, congenital bullae, pneumonia, and pulmonary hypoplasia result in uneven lung compliance and alveolar overdistention.
- c. Direct injury by suctioning through the endotracheal tube is a rare cause.
- d. Ventilatory support.

- (1) Prolonged inspiratory time (I:E ratio greater than or equal to 1).
- (2) High mean airway pressure (>12 cm H₂O).
- (3) Low inspired gas temperature ($<36.5^{\circ}\text{C}$). This is especially true for infants weighing $<1,500$ g and is thought to result from decreased mucociliary clearance precipitating airway obstruction at lower temperatures and lower humidity.
- (4) Poor patient–ventilator interaction resulting in dyssynchrony (i.e., infants who actively expire during all or part of the positive pressure plateau).

2. Diagnosis is made using the combination of clinical signs, physical examination findings, arterial blood gases, transillumination (Chap. 22), and radiography (Chap. 21).

- a. Clinical signs of pneumothorax include those of respiratory distress, such as tachypnea, grunting, nasal flaring, and retractions. Cyanosis, decreased breath sounds over the affected side, chest asymmetry, episodes of apnea and bradycardia, shift in cardiac point of maximal impulse, and hypotension may also occur.
- b. Arterial blood gases may show respiratory or mixed acidosis and hypoxemia.
- c. Transillumination generally reveals increased transmission of light on the involved side.
- d. Chest radiography remains the gold standard for diagnosis of pneumothorax.

3. Prevention

- a. Fast rate ventilation (>60 bpm) may reduce active expiration, a precursor of pneumothorax. This is done in an attempt to provoke more synchronous respiration. High-frequency ventilation may also provide better ventilation and oxygenation while decreasing the incidence of pneumothorax.
- b. Patient triggered ventilation reduces the incidence of air leak by synchronizing respiration. Using this mode of ventilation, the infant's respiratory efforts trigger the delivery of the positive pressure inflation. Flow-cycling enables complete synchronization, even in expiration.
- c. Suppression of respiratory activity by patient sedation and/or paralysis may be an important means of preventing pneumothoraces in patients who are actively exhaling or "fighting" the ventilator.

4. Management

- a. Nitrogen washout is controversial, but can sometimes be an effective way of eliminating small pneumothoraces and alleviating respiratory distress.

(1) Technique

- (a) Infant is placed in a 1.0 FiO_2 oxygen hood for 12–24 h.
- (b) Vital signs including oxygen saturation, heart rate, and blood pressure are continuously monitored.

(2) Precautions

- (a) Should not be used in preterm infants.
- (b) Do not use if pneumothorax is under tension.
- (c) Exposure to high FiO_2 is not without risk.

- b. Needle aspiration can be used to treat a symptomatic pneumothorax. It is frequently curative in infants who are not mechanically ventilated and may be a temporizing treatment in infants who are mechanically ventilated.

(1) Technique

- (a) Attach a 23-gauge butterfly needle to a 50 cc sterile syringe by a three-way stopcock.
- (b) Locate the second or third intercostal space in the midclavicular line on the affected side.
- (c) Prepare the area with antiseptic solution.
- (d) Under sterile conditions, if possible, locate the intercostal space *above* the rib (to avoid lacerating intercostal vessels located on the inferior surface of the rib). Insert the needle through the skin and into the pleural space applying continuous suction with the syringe as the needle is inserted. A rush of air is usually experienced when the pleural space has been entered.
- (e) Once the pleural space has been entered, stop advancing needle to avoid the risk of puncturing the lung.
- (f) Apply slow, steady suction to the syringe until resistance is felt, indicating that no more air remains in the area surrounding the needle.
- (g) Air is evacuated from the syringe by turning the stopcock off to the infant and evacuating air from the side port.
- (h) Once all possible air is evacuated, the needle is removed and the site is dressed if necessary.

(2) Potential complications

- (a) Infection
 - (b) Laceration of intercostal vessels
 - (c) Incomplete evacuation of air leak
 - (d) Lung puncture
 - (e) Damage to other intrathoracic structures (e.g., phrenic nerve, thoracic duct)
 - (f) Recurrence of air leak
- c. Chest tube (thoracostomy) drainage is needed for continuous drainage of pneumothoraces that develop in infants receiving positive pressure ventilation as the air leak may be persistent under these conditions (Fig. 72.1).

(1) Straight chest tube technique

- (a) Select a chest tube of appropriate size for the infant. For very small infants, 10 French chest tubes are adequate while for larger infants, 12 French chest tubes function better. Be sure that the trocar is freely mobile inside the chest tube.
- (b) Locate the fifth intercostal space in the anterior axillary line on the affected side.
- (c) Prepare the site with antibacterial solution.

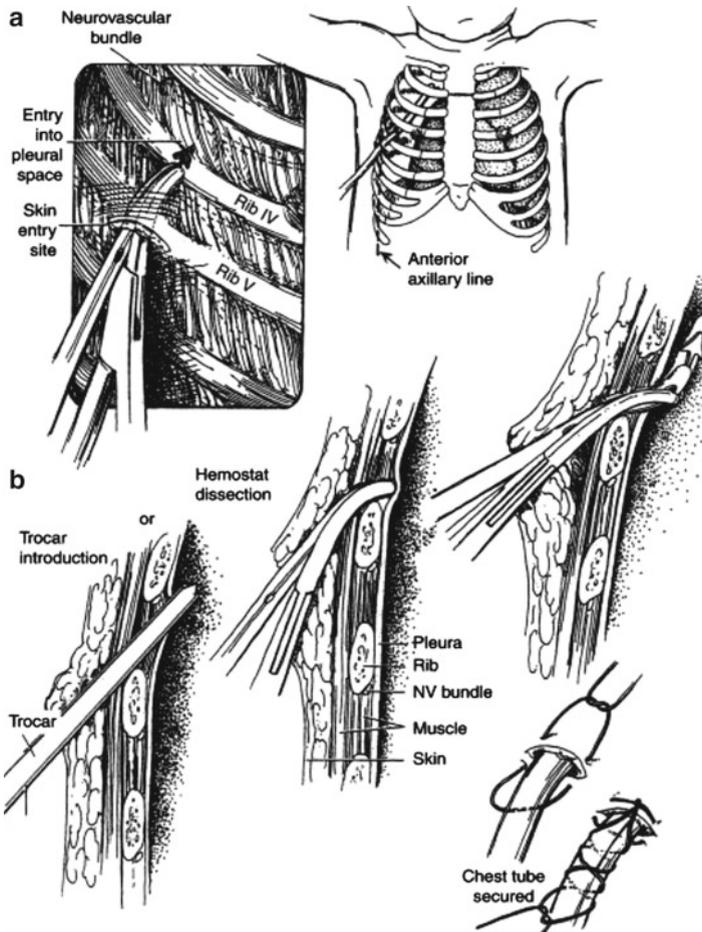


Fig. 72.1 Chest tube insertion in the newborn for pneumothorax. (a) Preferably a small hemostat is inserted through a small incision in the anterior or midaxillary line and is tunneled upward, entering the chest above the next rib. The chest tube is inserted and secured with a suture ligature. Several knots should be placed after each circumferential pass of the thread to avoid any slippage. (b) A trocar can be used as an alternative method of tube insertion, as long as the trocar is withdrawn by a few millimeters within the tube; this technique allows easier guidance of the tube, for example, if it has to be placed posteriorly and inferiorly to drain an effusion. Reproduced with permission from Grosfeld, S. (ed.). *Pediatric surgery*, 6th ed. 2006, Philadelphia, © Elsevier Publishing, p. 1022

- (d) Administer an analgesic to the patient.
- (e) Cover the site with sterile drapes.
- (f) Inject the area with a small amount of 1% Lidocaine solution. Do not exceed 4 mg/kg.
- (g) Make a small incision (approximately 1 cm) directly over the sixth rib. Avoid breast tissue and the nipple.

- (h) With a curved hemostat, dissect the subcutaneous tissue above the rib. Make a subcutaneous track to the third or fourth intercostals space.
 - (i) Applying continuous, firm pressure, enter the pleural space with the closed hemostat. Widen the opening by spreading the tips of the hemostat.
 - (j) Carefully insert the chest tube. If a trocar is used, insert it to only 1.0–1.5 cm to avoid puncturing the lung. Advance the chest tube a few centimeters to desired location while withdrawing the trocar. The anterior pleural space is usually most effective for infants in a supine position. Be certain the side ports of the chest tube are within the pleural space. Vapor is usually observed in the chest tube if it is in the pleural space.
 - (k) Attach the chest tube to an underwater drainage system under low (–10 to 20 cm H₂O) continuous suction.
 - (l) Suture the chest tube in place and close the skin incision using 3–0 or 4–0 silk. The chest tube is best held in place with a “purse string” stitch encircling it. Taping to secure the tube is also recommended.
 - (m) Cover the area with sterile petrolatum gauze and a sterile, clear plastic surgical dressing.
 - (n) Confirm proper chest tube placement radiographically. If residual air remains, the chest tube may need to be readjusted, or a second tube placed until air is evacuated or no longer causing hemodynamic compromise.
- (2) Pigtail Catheter Technique
- (a) Less dissection required compared to straight chest tube placement.
 - (b) 8.5 French pre-assembled kits are available.
 - (c) Prepare site with antibacterial solution.
 - (d) Administer analgesia to the patient.
 - (e) Drape the patient using sterile procedure.
 - (f) Identify the fifth intercostal space in the midaxillary line on the affected side.
 - (g) Inject this site with a small amount of 1% lidocaine. Do not exceed 4 mg/kg.
 - (h) Using the needle introducer attached to a syringe, enter the skin at a 30–45° angle distal to the fourth intercostal space avoiding breast tissue and nipple. Guide the needle superficially above the fifth rib, avoiding the inferior structures, and into the intercostal space.
 - (i) Gently apply negative pressure on the syringe while entering the pleural space. As air or fluid is aspirated, watch for

improvement in vital signs. Avoid evacuating the entire amount of air or fluid to avoid lung injury.

- (j) Remove the syringe and insert the guide wire into the needle introducer. In some kits, the guide wire is contained in a plastic bag to detect the presence of air. Advance the guide wire through the introducer until the guide wire marker enters the hub.
 - (k) Keeping the position of the guide wire, remove the needle introducer over the distal end of the guide wire.
 - (l) Advance the dilator over the guide wire and gently dilate the site.
 - (m) Remove the dilator, keeping the guide wire in place.
 - (n) Advance the pigtail catheter over the guide wire and into the pleural space. Advance until each of the side ports is intrathoracic in location. Leave 13 cm (measured from the chest wall to the hub of the catheter) of tubing extrathoracic.
 - (o) Attach the chest tube to an underwater drainage system as detailed above.
 - (p) Adequately secure the chest tube.
 - (q) Confirm placement radiographically.
 - (r) Complications are the same as those seen in needle aspiration.
- B. Pulmonary interstitial emphysema (PIE) occurs most often in ventilated, preterm infants with RDS. Interstitial air can be localized or widespread throughout one or both lungs. PIE alters pulmonary mechanics by decreasing compliance, increasing residual volume and dead space, and increasing V/Q mismatch. It also impedes pulmonary blood flow.
- 1. Diagnosis is made using a combination of clinical signs, transillumination, and chest radiography.
 - a. Clinical signs of PIE include profound respiratory acidosis, *hypercarbia*, and hypoxemia. Because air is interstitial instead of intra-alveolar, proper gas exchange does not occur and effective ventilation is decreased. The interstitial gas reduces pulmonary perfusion by compression of blood vessels, resulting in hypoxemia.
 - b. Transillumination of a chest with diffuse and widespread PIE will result in increased transmission of light, similar to that seen in a pneumothorax.
 - c. Chest radiography may reveal a characteristic cystic appearance or may be more subtle with rounded, nonconfluent linear microradiolucencies in earlier stages. In later stages of PIE, there may be large bullae formation with hyperinflation in the involved portions of lung.

2. Management

- a. Generalized PIE management is focused on reducing or preventing further barotrauma to the lung.
 - (1) Decreasing PIP to the minimum required to attain acceptable arterial blood gases (PaO_2 45–50 Torr or 6–6.7 kPa and $\text{PCO}_2 < 60$ Torr or 8 kPa).
 - (2) Adjust PEEP to maintain sufficient FRC and to stent airways.
 - (3) High-frequency jet ventilation (HFJV, Chap. 37) is a successful means of ventilation for infants with PIE. This mode results in improved ventilation at lower peak and mean airway pressures with more rapid resolution of PIE.
- b. Localized PIE may resolve spontaneously or persist for several weeks with a sudden enlargement and deterioration in the infant's condition. Progressive overdistension of the affected area can cause compression of the adjacent normal lung parenchyma.
 - (1) Supportive management includes positioning the infant with the affected side down to minimize aeration of the affected lung and promote aeration of the unaffected lung.
 - (2) Severe cases of unilateral PIE may respond to collapse of the affected lung by selective bronchial intubation of the unaffected lung.
- C. Pneumomediastinum is often of little clinical importance and usually does not need to be drained. Rarely, cardiovascular compromise occurs if the air accumulation is under tension and does not decompress *spontaneously*.

1. Diagnosis

- a. Clinical findings include tachypnea, cyanosis, and distant heart sounds on chest auscultation.
- b. Chest radiography is the gold standard for diagnosis.

2. Management

- a. Nitrogen washout, as described above.
 - b. Needle aspiration (using technique described above for pneumothorax). Insert the needle midline immediately subxiphoid and apply negative pressure as the needle is advanced in a cephalad direction.
 - c. A mediastinal tube is rarely needed, but if necessary, should be placed by a qualified surgeon.
- D. Pneumopericardium occurs when air from the pleural space or mediastinum enters the pericardial sac through a defect that is often located at the reflection near the ostia of the pulmonary veins. The majority of cases occur in infants ventilated with high PIP (>32 cm H_2O), high mean Paw (>17 cm H_2O), and/or long inspiratory time (>0.7 s).

1. The typical presentation is the abrupt onset of cardiovascular compromise from cardiac tamponade, which is a life-threatening complication that results from air entering the pericardial sac. A symptomatic pneumopericardium should be drained immediately.
2. Management
 - a. Needle aspiration via the subxiphoid route may be used as a temporizing measure or to treat symptomatic pneumopericardium.
 - (1) Prepare the subxiphoid area with an antiseptic solution.
 - (2) Attach a 20- or 22-gauge intravenous catheter to a short piece of IV tubing that is then attached via a stopcock to a syringe.
 - (3) Locate the subxiphoid space and insert the catheter with the needle at a 30°–45° angle pointed toward the infant's left shoulder.
 - (4) Aspirate with the syringe as the catheter is advanced.
 - (5) Stop advancing the catheter once air is aspirated. Remove the needle, sliding the plastic catheter into the pericardial space. Reattach the syringe and remove the remaining air. Once the air is removed, either remove the catheter, or place it to water seal if the leak is continuous.
 - (6) The procedure can be facilitated by transillumination guidance.
 - (7) Complications of pericardiocentesis include hemopericardium and laceration of the right ventricle or left anterior descending coronary artery.
 - b. Pericardial tube placement and drainage may be necessary if the pericardial air reaccumulates. The pericardial tube can be managed like a chest tube with less negative pressures are used for suction (–5 to –10 cm H₂O).
 - c. Prevention of further pericardial air leak by appropriate ventilator management is very important.
- E. Subcutaneous emphysema usually has no clinical significance, although large air collections in the neck can result in tracheal compromise.
 1. Typically presents as crepitus upon palpation of the affected area, although it can also be seen on radiography.
 2. Management
 - a. Supportive measures.
 - b. Surgical decompression may be necessary if tracheal compromise is present.
- F. Pneumoperitoneum often will not adversely affect the patient's clinical status, but treatment is warranted when respiratory compromise occurs. Upward pressure on the diaphragm may compromise ventilation from

decreased lung volumes and may reduce blood return to the heart by exerting pressure on the inferior vena cava.

1. Distinguishing the cause of a pneumoperitoneum is very important and will drastically change patient management. Pneumoperitoneum caused by a trans-thoracic air leak can be differentiated from pneumoperitoneum caused by bowel perforation by measuring the oxygen from a gas sample obtained from the peritoneum. A baseline gas concentration is obtained and compared to a gas concentration obtained from a peritoneal sample when ventilator FiO_2 is set at 1.0. If the PaO_2 from the latter sample is high, the source of the air leak is likely thoracic.
2. Management
 - a. Needle aspiration can be used as a temporizing measure or as treatment. Following the general procedure for needle aspiration of pneumothorax, the needle is inserted in the midline approximately one centimeter below the umbilicus. Negative pressure is applied while the needle is advanced through the peritoneum and air is evacuated.
 - b. Peritoneal drain placement may relieve a continuous peritoneal air leak.

Suggested Reading

- Abu-Shawesh JM. Part 5 Respiratory disorders in preterm and term infants. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 9th ed. St. Louis: Elsevier Mosby; 2010. p. 1164–6.
- Alpan G, Goder K, Glick F, et al. Pneumopericardium during continuous positive airway pressure in respiratory distress syndrome. *Crit Care Med*. 1984;37:511–5.
- Cabatu EE, Brown EG. Thoracic transillumination: Aid in the diagnosis and treatment of pneumopericardium. *Pediatrics*. 1979;64:958–60.
- Donn SM, Engmann C. Neonatal resuscitation: Special procedures. In: Donn SM, editor. *The Michigan Manual of Neonatal Intensive Care*. Philadelphia, PA: Hanley & Belfus; 2003. p. 33–41.
- Donn SM, Faix RG. Delivery room resuscitation. In: Spitzer AR, editor. *Intensive Care of the Fetus and Neonate*. St. Louis: Mosby-Year Book; 1996. p. 326–36.
- Donn SM, Kuhns LR. Pediatric Transillumination. Chicago: Year Book Medical; 1983.
- Donn SM, Sinha SK. Part 4 Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 9th ed. St. Louis: Elsevier Mosby; 2010. p. 1135–6.
- Douglas-Jones J, Bustamante S, Mirza M. Pneumopericardium in a newborn. *J Pediatr Surg*. 1981;16:75–8.
- Fuhrman BP, Landrum BG, Ferrara TB, et al. Pleural drainage using modified pigtail catheters. *Crit Care Med*. 1986;14:575–6.
- Goldsmith JP, Karotkin EH. Complications. In: Goldsmith JP, Karotkin EH, editors. *Assisted Ventilation of the Neonate*. 5th ed. St. Louis: Elsevier Saunders; 2010. p. 407–14.
- Keszler M, Donn SM, Bucciarelli RL, et al. Controlled multicenter trial of high frequency jet ventilation vs. conventional ventilation in newborns with pulmonary interstitial emphysema. *J Pediatr*. 1991;119:85–93.

- Lawless S, Orr R, Killian A, et al. New pigtail catheter for pleural drainage in pediatric patients. *Crit Care Med.* 1989;17:173–1–75.
- MacDonald MG. Thoracostomy in the neonate: a blunt discussion. *Neo Rev.* 2004;5:301–6.
- Madansky DL, Lawson EE, Chernick V, et al. Pneumothorax and other forms of pulmonary air leak in newborns. *Am Rev Respir Dis.* 1979;120:729–33.
- Smith J, Schumacher RE, Donn SM, Sarkar S. Clinical course of symptomatic spontaneous pneumothorax in term and late preterm Infants: report from a large cohort. *Am J Perinatol.* 2011;28:163–8.
- Zak LK, Donn SM. Thoracic air leaks. In: Donn SM, Faix RG, editors. *Neonatal Emergencies.* Mount Kisco: Futura Publishing Co.; 1991. p. 311–25.

Chapter 73

Patent Ductus Arteriosus

Jonathan Wyllie

I. Incidence

- A. The most common cardiologic problem in newborns
- B. Varies inversely with gestational age
 - 1. Up to 20% at GA >32 weeks
 - 2. 20–40% between 28 and 32 weeks
 - 3. 60% below 28 weeks

II. Ductus arteriosus in fetal circulation

- A. Derived from sixth aortic arch
- B. May be absent in association with congenital heart disease involving severe right outflow tract obstruction (rare)
- C. Carries most of RV output (50–60% of total cardiac output) from sixth to seventh week on; caliber equal to descending aorta
- D. Patency both passive (from high blood flow) and active (locally derived Prostaglandin E₂ [PGE₂])

III. Postnatal closure

- A. Mechanisms mature after 35 weeks.
- B. Initiated by spiral medial muscle layer starting at pulmonary end.
- C. Duct shortens and thickens with functional closure at 12–72 h.
- D. Factors promoting closure
 - 1. Low ductal flow (\uparrow systemic + \downarrow pulmonary resistance = \uparrow pulmonary flow)
 - 2. Reduced sensitivity to PGE₂

J. Wyllie, BSc(Hons), MB ChB, FRCPCH, FRCP, FERC (✉)
Department of Neonatology, The James Cook University Hospital,
Marton Road, Middlesbrough TS4 3BW, Cleveland, UK
e-mail: jonathan.wyllie@stees.nhs.uk

3. Decreased production of PGE₂
4. Increased arterial oxygen tension

IV. Persistent ductal patency

- A. Isolated PDA accounts for 3.5% of congenital heart disease presenting in infancy. It occurs despite ductal constriction and has a different pathogenesis from that in the preterm infant.
- B. Preterm PDA is related to the following:
 1. Immature closure mechanism
 2. Decreased sensitivity to constrictors such as oxygen tension
 3. Increased sensitivity to PGE₂
 4. Other associated factors
 - a. Acidosis
 - b. Severe lung disease
 - c. Exogenous surfactant use
 - d. Phototherapy
 - e. Furosemide use
 - f. Excessive fluid administration
 - g. Lack of antenatal steroid therapy

V. Physiologic effects of the PDA

- A. Left-to-right shunt
 1. Exacerbation of respiratory disease
 2. Altered pulmonary mechanics
 3. Increased cardiac work load
- B. Diastolic steal
 1. Altered perfusion of brain, systemic organs
 2. Risk of necrotizing enterocolitis

VI. Clinical effects of PDA from left-to-right shunt

- A. Increased oxygen requirement
- B. Increased ventilatory requirement
- C. Apnea
- D. Bronchopulmonary dysplasia
- E. Impaired weight gain
- F. Congestive heart failure

VII. Clinical features

- A. Occur after fall in pulmonary resistance
- B. Onset related to severity of lung disease and size of baby
- C. In VLBW infant most common manifestation is after four days of age, earlier in LBW

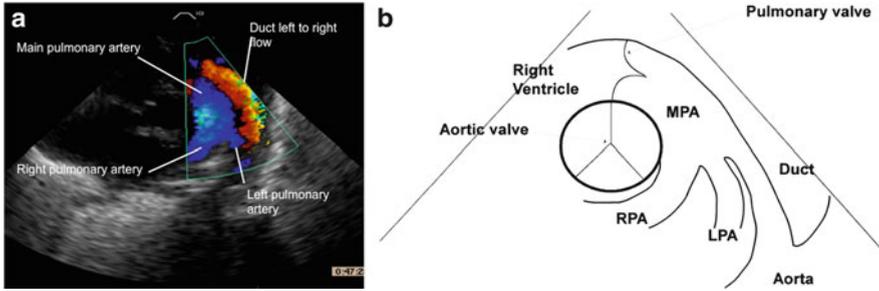


Fig. 73.1 (a) Color Doppler of the main pulmonary artery and patent ductus. *Blue* flow is away from the probe. *Red/yellow* flow is from the ductus toward the probe showing left to right flow. (b) Diagrammatic representation of (a)

D. Signs

1. Failure of RDS to improve (or deterioration) at 2–7 days
2. Increase FiO_2 /ventilator settings
3. Acidosis
4. Apnea
5. Hyperdynamic precordium (95%)
6. Bounding pulses (85%)
7. Murmur (80%)
 - a. Normally silent until day 4
 - b. Systolic murmur
 - c. Upper left sternal border
 - d. Variable
8. Refractory hypotension

VIII. Diagnosis

- A. Chest radiograph (poor specificity)
 1. Cardiac enlargement
 2. Pulmonary engorgement (hyperemia)
 3. Absence of pulmonary explanation for deterioration
- B. Electrocardiogram not usually helpful unless attempting to rule-out another condition
- C. Echocardiogram (Fig. 73.1a, b)
 1. Ductal patency
 2. Flow velocity/pattern
 3. Ductal diameter (>1.5 mm in first 30 h)
 4. LA volume load (LA:Ao ratio > 1.5)
 5. LVEDD:Aortic ratio > 2.0

6. LV output
7. LV function
8. Diastolic flow in descending aorta
9. Diastolic flow in celiac vessels

IX. Treatment

- A. Fluid restriction: little evidence except to keep <169 mL/kg/day at day 3
- B. Diuretics

1. Furosemide

- a. Little evidence except in congestive cardiac failure
- b. Improvement of pulmonary dynamics for 24 h

2. Chlorothiazide

- a. Little evidence except in congestive cardiac failure
- b. Temporizing measure

- C. Ventilation

1. Increase P_{aw} (PIP)
2. Increase PEEP

- D. Indomethacin

1. If baby $<2-3$ weeks old
2. Reasonable renal function (serum creatinine <1.3 mg/dL)
3. No thrombocytopenia (platelets $>50,000/\text{mm}^3$)
4. No significant hyperbilirubinemia
5. Closure in up to 79% but relapse in up to 33% of these
6. Prophylactic treatment treats up to 64% unnecessarily
7. Associated with spontaneous intestinal perforation
8. Dosage regimens:
 - a. 0.2 mg/kg $\times 2-3$ doses
 - b. 0.1 mg/kg/d $\times 6$ doses

- E. Ibuprofen

1. Fewer short term side effects than indomethacin
2. No longer term advantage over indomethacin
3. 5% incidence of severe pulmonary hypertension if used prophylactically
4. Dosage regimen: 10 mg/kg loading dose and 5 mg/kg at 24 and 48 h

- F. Surgical ligation

Suggested Reading

- Bose CL, Laughon M. Treatment to prevent patency of the ductus arteriosus: beneficial or harmful? *J Pediatr.* 2006;148:713–4.
- Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. *Pediatrics.* 2007;119:1165. doi:10.1542/peds.2006–3124.
- Negegme RA, O'Connor TZ, Lister G, Bracken MB. Patent ductus arteriosus. In: Sinclair JC, Bracken MB, editors. *Effective care of the newborn infant.* Oxford: Oxford University Press; 1992. p. 281–324.

Chapter 74

Neonatal Pulmonary Hemorrhage

Tonse N.K. Raju

- I. Description: A rare, but severe condition characterized by massive bleeding into the lungs and airways.
 - A. The clinical status deteriorates rapidly with the associated mortality ranging from 50% to 80%.
 - B. The incidence of long-term pulmonary morbidity, such as bronchopulmonary dysplasia (BPD) among the survivors exceeds 80%.
- II. Incidence: The reported incidence figures vary depending upon the definitions used, the diligence of monitoring for pulmonary hemorrhage, and the source of the data used in the study (e.g., autopsy versus clinical).
 - A. General NICU population. About 1.4% of all infants admitted to the NICU have been reported to develop pulmonary hemorrhage; more than 80% have RDS. Such infants are also likely to have been treated with exogenous surfactant, and were receiving mechanical ventilatory support at the time of bleeding.
 - B. Gestational age. The incidence is inversely proportional to gestational age, especially between 23 and 28 weeks' gestation.
 1. Exogenous surfactant. Ever since exogenous surfactant therapy became the standard of care for RDS, there has been a slight, but noticeable increase in the incidence of pulmonary hemorrhage. In a cohort of 14,464 VLBW infants, among the infants born at 25–26 weeks' gestation, pulmonary hemorrhage incidence was 10% in 1991, which increased to 16% in 2001. Among those born at 27–28 weeks' gestation, the incidence was 6.5% in 1991 and 8% in 2001.

T.N.K. Raju, MD, DCH (✉)
Eunice Kennedy Shriver National Institute of Child Health and Human Development,
6100 Executive Blvd, Room 4B03, Bethesda, MD 20892, USA
e-mail: rajut@mail.nih.gov

2. In a postmarketing surveillance study of an animal-derived natural surfactant, the incidence of pulmonary hemorrhage was 6.4% among the 903 infants treated with surfactant for RDS. This represents a slight increase from 3% to 4% reported in the presurfactant era.
 3. A meta-analysis concluded that exogenous surfactant increased the risk for pulmonary hemorrhage by 47%. The risk was slightly higher with animal-derived surfactants than with synthetic preparations.
 4. Exogenous surfactants. A 2010 Cochrane systematic review of pulmonary complications with the use of protein-free synthetic surfactants revealed that prophylactic administration of synthetic surfactant increases the risk of pulmonary hemorrhage (typical relative risk 3.28, 95% CI 1.50, 7.16). The role of newer surfactant preparations (discussed below) in pulmonary hemorrhage has not been well studied.
- C. Autopsy. In autopsy studies, about 80% of VLBW infants were found to have pulmonary hemorrhage.
- D. Other conditions. Among infants requiring ECMO therapy, about 6% (range 5–10%) of infants have been reported to develop pulmonary hemorrhage either during or after ECMO.

III. Other antecedent factors and infants at risk

- A. Prematurity, RDS, and exogenous surfactant therapy. In combination, these three are the most consistent risk factors for pulmonary hemorrhage, especially in infants <28 weeks' gestation (or birth weight <1,000 g). The rate of complication is not influenced by the type of surfactant used or its time of administration (prophylactic, early, or rescue).
- B. Lung complications. Pulmonary interstitial emphysema (PIE) and/or pneumothorax.
- C. Infections. Bacterial, viral, or fungal infections, such as *Listeria*, *Hemophilus influenzae*, and congenital cytomegalovirus, have been reported to be associated with pulmonary hemorrhage.
- D. General clinical status. Metabolic acidosis, especially in infants with RDS; hypothermia; hypoglycemia; shock; and disseminated intravascular coagulation (DIC).
- E. Meconium aspiration syndrome. Infants requiring ECMO.
- F. Inherited coagulation disorders. Although rare, one must consider familial bleeding disorders, such as von Willebrand disease. A report by the CDC found that von Willebrand disease was the underlying condition in two of five infants dying from idiopathic pulmonary hemorrhage.
- G. Trauma. Mechanical injury to the vocal cords, trachea, or other laryngeal and oropharyngeal structures, especially from endotracheal intubation.

IV. Pathophysiology. The pulmonary effluente has very high protein content, as well as a large number of cellular elements from the blood. Thus, the hemorrhage may be a consequence of increased trans-capillary pore size. A series of interrelated factors may lead to an eventual bleeding episode.

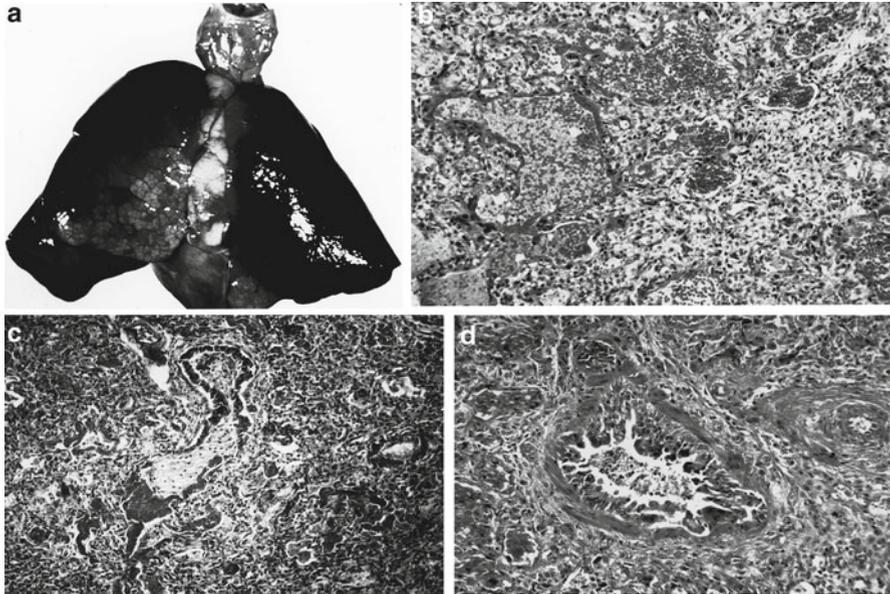


Fig. 74.1 (a) Gross appearance of the lungs in an infant who died of massive pulmonary hemorrhage. (b) Microscopic findings of lung section in the same infant shows large quantities of blood in the alveolar spaces and scattered bleeding sites in the interstitial spaces. Generalized features of hyaline membrane formation and widespread inflammatory reaction are seen. In (c) and (d), lung sections from two other cases are shown. (c) Massive pulmonary hemorrhage occurred 2 weeks prior to death. (d) Infant died at 4 weeks of age from respiratory failure secondary to bronchopulmonary dysplasia; there was no clinical evidence of pulmonary hemorrhage. Scattered areas of bleeding can be identified. Both infants show varying degrees of chronic changes in the lungs

- A. Hemodynamic factors. Some experts consider pulmonary hemorrhage as a manifestation of an exaggerated hemorrhagic pulmonary edema brought about by an acute increase in pulmonary blood flow. The latter can occur from multiple, interrelated causes, including the normal postnatal drop in the pulmonary vascular resistance, improved pulmonary compliance following surfactant therapy, and normal postnatal absorption of lung fluid. These changes may lead to an acute increase in pulmonary blood flow and hemorrhagic pulmonary edema.
 - B. Hematologic factors. DIC secondary to sepsis can lead to abnormal coagulation and hemorrhage. Bleeding may be found at other sites, such as the gastrointestinal and renal mucus membranes, and in the brain. Underlying sepsis or shock could further compromise local vascular integrity, leading to an acute episode of bleeding.
- V. Pathology. A wide range of pathologic appearances has been reported. In mild forms, scattered red blood cells in the intra-alveolar and intra-parenchymal spaces may be the only findings, with little or no blood in the airways. In infants who die from pulmonary hemorrhage, massive amounts of frank blood may be found in the parenchyma, small and large airways, trachea, and the oral cavity (Fig. 74.1).

- A. Macroscopic features. The lung weight is increased, its lobar borders are obliterated, and frank blood is seen in the airways, trachea, and the pleural space.
 - B. Microscopic features. Large islands of blood in the alveolar and parenchymal spaces may be seen. Blood may occupy the lumen of larger bronchi and the trachea. Pulmonary hemorrhage is reported to be predominantly alveolar in infants treated with exogenous surfactant, while it is predominantly interstitial in those not treated with surfactant. Thus, surfactant therapy may alter the distribution of bleeding sites rather than causing an increase the incidence of pulmonary hemorrhage.
 - C. Other changes. Reactive leukocytosis and changes of RDS and BPD may be found, along with that of pneumonia and bleeding in other organs, especially the intestine, kidneys, and the brain.
- VI. Clinical features. The severity and magnitude of clinical signs depend upon the magnitude of hemorrhage and the severity of the underlying condition leading to the episode. The clinical manifestations result from several interrelated pathophysiologic consequences of blood loss and hemorrhage into the lung parenchyma and the airways.
- A. A rapidly deteriorating pulmonary condition is the hallmark of massive pulmonary hemorrhage.
 - 1. Hypoxia, hypercarbia, and increasing requirements of ventilatory support are seen secondary to worsening of pulmonary compliance from blood in the lung tissue.
 - 2. Frank blood can be seen pouring out of the mouth, or in milder cases, blood-tinged tracheal and oropharyngeal effluent may be seen.
 - 3. The blood obstructs the airways, increasing resistance and causes worsening of the already deteriorating blood gas and acid–base status.
 - B. Extraneous blood in the lung parenchyma increases the consumption of the administered surfactant and inhibits its function. Plasma proteins and blood also inhibit endogenous surfactant production.
 - C. The pulmonary deterioration is almost invariably accompanied by an acute deterioration in the systemic status. A rapid drop in blood pressure and cardiac output leads to classic signs of shock, along with severe pallor and anemia.
 - D. In infants who survive the acute episode, widespread pulmonary inflammation from blood in the lung tissues can lead to later complications, such as pneumonia and a prolonged need for assisted ventilation and the development of BPD.
 - E. Because the clinical findings are interrelated and depend upon the severity of hemorrhage, in some cases, several hours may pass before the signs of shock and collapse evolve.

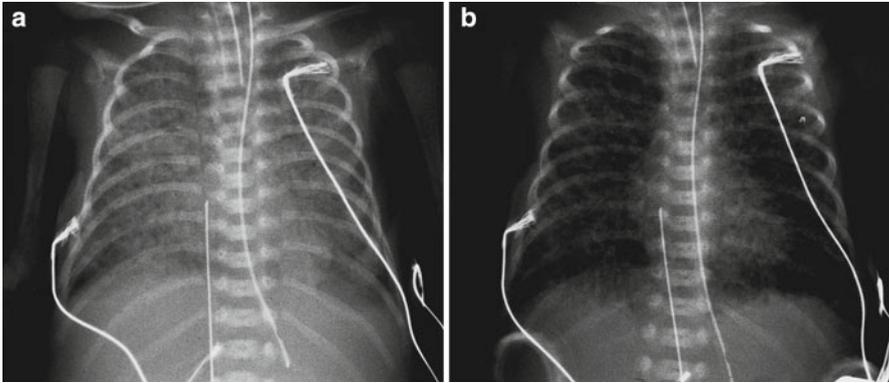


Fig. 74.2 Evolution of pulmonary hemorrhage in an infant with RDS. Chest radiographs show typical features of severe PIE on the fifth day (a) and severe pulmonary hemorrhage on the seventh day (b). Heart size is normal

1. Always suspect pulmonary hemorrhage in infants receiving assisted ventilation, who appear otherwise “stable,” but gradually manifest worsening hypoxemia, hypercapnia, and acidosis, requiring higher than the original ventilator settings.
 2. Localized, small, pulmonary hemorrhage may cause the signs to evolve over 6–8 h; in such cases, pulmonary hemorrhage should always be high on the list of differential diagnoses.
- F. In the presence of systemic shock and sudden deterioration, consider pulmonary hemorrhage even in the absence of blood or blood-tinged orotracheal effluent, since the bleeding may be interstitial.
1. A reduction in hematocrit and platelet counts may not occur initially.
 2. Cardiac murmur and/or other signs of PDA may be found.
- G. Other causes of left-to-right shunting and of pulmonary edema must be evaluated, such as congestive cardiac failure (VSD, ASD, or cerebral arteriovenous malformations).

VII. Investigations

- A. Chest radiograph. There are no specific diagnostic features on chest radiography.
1. Diffuse, scattered haziness, consolidation, fluffy radiodensities, and features of the underlying disease (RDS, BPD, or PIE) should suggest pulmonary hemorrhage.
 2. Cardiomegaly may or may not be present, depending upon the underlying cause of pulmonary hemorrhage (Figs. 74.2 and 74.3).

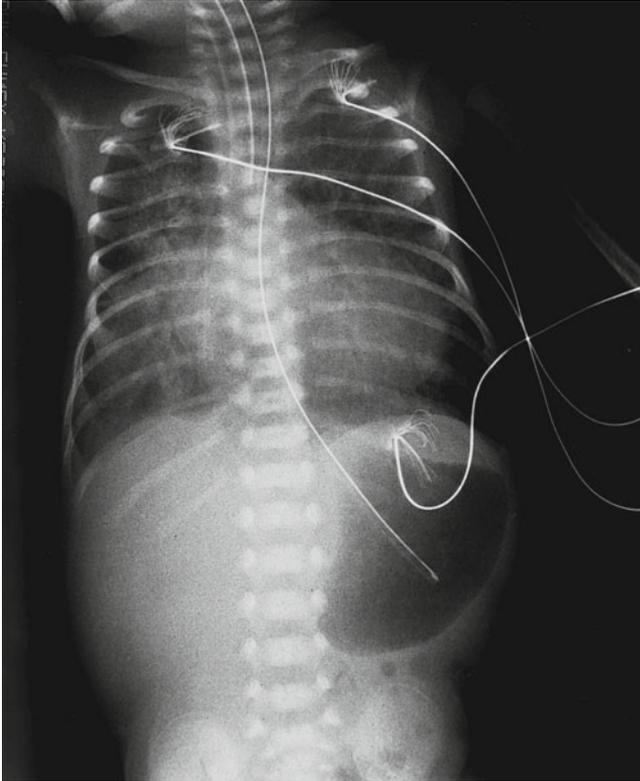


Fig. 74.3 Chest radiograph of a preterm infant developing severe pulmonary hemorrhage on the sixth day secondary to a large, florid patent ductus arteriosus and signs of congestive heart failure. Pulmonary hemorrhage was accompanied by respiratory deterioration. Scattered radiopaque densities, mostly in both lower lobes can be seen, and there is moderate cardiomegaly

B. Evaluating the PDA.

1. Suspect a significant PDA in infants with pulmonary hemorrhage, even in the absence of a typical “PDA murmur”; or a wide pulse pressure, or a hyperdynamic precordium.
2. An echocardiogram is indicated.

C. Blood tests and workup for sepsis

1. Blood gases and acid-base status.
2. Hemoglobin and hematocrit.
3. Platelet count.
4. Total and differential white blood cell count.
5. Bacterial culture from blood and urine should be considered.
6. Viral and fungal cultures may be indicated.
7. Tests for DIC (PT, PTT, fibrinogen, fibrin degradation products, etc.).

- D. Search for inherited disorders of coagulation (e.g., hemophilia, von Willebrand disease).
- E. For bleeding in other organs. urinalysis to rule out major bleeding in the kidney and a cranial ultrasound to rule out intracranial hemorrhage are recommended depending upon other findings.

VIII. Treatment

A. General supportive care

1. Intensive care and treatment of shock
 - a. Transfuse with blood, plasma, or platelets as indicated.
 - b. Correct metabolic acidosis.
 - c. Administer inotropic agents to improve systemic blood pressure.
2. Ventilatory support. with a few exceptions, most recommendations for ventilatory support have evolved based on empirical observations.
 - a. Conventional ventilatory support. increase ventilatory settings to provide a higher rate, higher positive end expiratory pressure (PEEP) and higher mean airway pressure (P_{aw}).
 - b. High-frequency oscillatory ventilation (HFOV) support. In a prospective observational study, it was found that 10/17 infants with massive pulmonary hemorrhage responded to early treatment with HFOV. All of them survived. By contrast, only a third offered conventional ventilatory support survived.
3. Treat the PDA. Unless there is severe thrombocytopenia, indomethacin or ibuprofen therapy can be used in proven or suspected pulmonary hemorrhage to treat the PDA, even if given earlier.
4. Treatment of infections. Antibiotics most likely to be effective against common bacterial pathogens are used: ampicillin (or vancomycin), along with a drug for gram-negative coverage may be given until a specific etiologic agent, if any, is identified.

B. Specific treatment strategies

1. Recombinant factor VIIa (rFVIIa). rFVIIa, a vitamin K-dependent glycoprotein, structurally similar to the plasma-derived natural factor VII, is considered a universal hemostatic agent. It acts by triggering the extrinsic coagulation cascade and forming a hemostatic seal at the site of capillary leak, providing a plug and stopping the bleeding. A dose of 80 mcg/kg (IV) rFVIIa can normalize prolonged prothrombin time. This drug has also been used with success in two isolated cases of neonatal pulmonary hemorrhage at a 50 mcg/kg/dose, repeated every 3 h for 2–3 days. In other studies, rFVIIa was used in infants developing pulmonary hemorrhage at much higher doses, also resulting in cessation of pulmonary hemorrhage. More work is needed to establish

the dosage and the frequency of its administration, as well as to assess the consistency of response in neonatal pulmonary hemorrhage.

2. Exogenous surfactant. Based on observational reports and limited retrospective studies, it appears that exogenous surfactant therapy improves the respiratory status in infants with pulmonary hemorrhage. The American Academy of Pediatrics Committee on Fetus and Newborn recommended that "...surfactant treatment for pulmonary hemorrhage is plausible, because blood inhibits surfactant function. However...the magnitude of benefit remains to be established. Such proof is unlikely to materialize soon, because pulmonary hemorrhage is an unpredictable complication, and randomized trials would be difficult to design and implement." The administered surfactant will also replenish the endogenous surfactant pool depleted from an inhibition or inactivation from blood and plasma in the alveoli.
3. Newer surfactants. Five new products have been introduced since the mid 1990s. Four of these are animal-derived: Calfactant (*Infasurf*[®] from calf lung lavage); Poractant alfa (*Curosurf*[®] from porcine minced lung); Bovactant (*Alveofact*[®] from bovine lung lavage), and Bovine lipid extract surfactant (BLES[®] from bovine lung lavage). The fifth and the latest among the newer surfactant is a synthetic surfactant with an added bioengineered surfactant protein-B mimic, Lucinactant KL-4 (*Surfaxin*[®]). Many of these have not yet been approved by the US FDA or the EMEA, and are not available for routine clinical use. Moreover, the relative merits and limitations with regard to their efficacy in treating pulmonary hemorrhage have not been studied.
4. Other measures to stop pulmonary hemorrhage. Nebulized epinephrine with or without 4% cocaine has been found to temporize massive bleeding. Experience using these drugs in newborns is limited.

IX. Outcome

- A. Mortality: Average 50%; range 30–90%.
- B. Morbidity: 50–75% of survivors develop BPD of varying severity.

X. Prevention

- A. Antenatal corticosteroids. Enhancing lung maturity may reduce pulmonary hemorrhage through its indirect effect on the lungs, and pulmonary vascular bed.
- B. Preventing PDA. Although early indomethacin or ibuprofen therapy has shown a strong effect in reducing the incidence of significant PDA, whether such a strategy will affect pulmonary hemorrhage incidence is unclear.
- C. Monitoring for PDA and its prompt therapy. Vigilant monitoring for the signs of PDA in preterm infants treated with exogenous surfactants for RDS should be the mainstay for preventing pulmonary hemorrhage. In infants with rapid improvement in pulmonary compliance, even a minimally patent

ductus arteriosus can cause a sudden worsening of pulmonary compliance, and lead to pulmonary hemorrhage.

- D. High-frequency oscillatory ventilation (HFOV). In a large trial the incidence of pulmonary hemorrhage was 5/244 (2%) in a group of small preterm infants treated with HFOV compared to 17/254 (7%) in the CMV group ($p < 0.02$).

Suggested Reading

- Alkharfy TM. High-frequency ventilation in the management of very-low-birth-weight infants with pulmonary hemorrhage. *Am J Perinatol.* 2004;1:19–26.
- Amizuka T, Shimizu H, Niida Y, Ogawa Y. Surfactant therapy in neonates with respiratory failure due to hemorrhagic pulmonary oedema. *Eur J Pediatr.* 2003;162:69.
- Baroutis G, Kaleyias J, Liarou T, et al. Comparison of three treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. *Eur J Pediatr.* 2003;62:476–80.
- Centers for Disease Control and Prevention: Investigation of acute idiopathic pulmonary hemorrhage among infants—Massachusetts, December 2002–June 2003. *MMRW Morb Mortl Wkly Rep.* 2004;3:817.
- Courtney SE, Durand DJ, Asselin M, et al. High-frequency oscillatory ventilation versus conventional ventilation for very-low-birth-weight infants. *N Engl J Med.* 2002;347:643–52.
- Dufourq N, Thomson M, Adhikari M, Moodley J. Massive pulmonary hemorrhage as a cause of death in the neonate—a retrospective review. *S Afr Med J.* 2004;94:299–302.
- Engle WA, American Academy of Pediatrics Committee on Fetus and Newborn. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. *Pediatrics.* 2008;121:419–32.
- Findlay RD, Tausch HW, David WR, Walther FJ. Lysis of blood cells and alveolar epithelial toxicity by therapeutic pulmonary surfactants. *Pediatr Res.* 1995;37:26–30.
- Fuji AM, Carillo M. Animal-derived surfactant treatment of respiratory distress syndrome in premature neonates: a review. *Drugs Today.* 2009;45:697–709.
- Gharehbaghi MM, Sakha SH, Ghajzadeh M, Firoozi F. Complications among premature neonates treated with Beractant and Poractant Alfa. *Indian J Pediatr.* 2010;77:751–4.
- Goretzky MJ, Martinasek D, Warner BW. Pulmonary hemorrhage: a novel complication after extracorporeal life support. *J Pediatr Surg.* 1996;1:1276–81.
- Greisen G, Andreasen RB. Recombinant factor VIIa in preterm neonates with prolonged prothrombin time. *Blood Coagul Fibrinol.* 2003;14:117–20.
- Gluckow M, Evans N. Ductal shunting, high pulmonary flow, and pulmonary hemorrhage. *J Pediatr.* 2000;137:68–72.
- Lambole-Gilmer G, Lacaze-Masmonteil T, Neonatologists of the Curosurf® Study Group. The short-term outcome of a large cohort of very preterm infants treated with Poractant Alfa (Curosurf®) for respiratory distress syndrome. A postmarketing phase IV study. *Pediatr Drugs.* 2003;5:639.
- Leibovitch L, Kenet G, Mazor K. Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. *Pediatr Crit Care Med.* 2003;4:444–6.
- Lin TW, Su BH, Lin HC, et al. Risk factors of pulmonary hemorrhage in very-low-birthweight infants: a two-year retrospective study. *Acta Pediatr Taiwan.* 2004;45:255–8.
- Olomu N, Kulkarni R, Manco-Johnson M. Treatment of severe pulmonary hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight infants. *J Perinatol.* 2002;22:672–4.
- Pandit PB, Dunn MS, Colucci EA. Surfactant therapy in neonates with respiratory deterioration due to pulmonary hemorrhage. *Pediatrics.* 1995;95:32–6.

- Pappin A, Shenker N, Jack M, Redline RW. Extensive intraalveolar pulmonary hemorrhage in infants dying after surfactant therapy. *J Pediatr.* 1994;124:621–6.
- Poralla C, Hertfelder H-J, Oldenburg J, Müller A, Bartmann P, Heep A. Treatment of acute pulmonary haemorrhage in extremely preterm infants with recombinant activated factor VII. *Acta Paediatr.* 2010;99:298–300.
- Raju TNK, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a meta-analysis. *J Pediatr.* 1993;123:603–10.
- Rao KVS, Michalski L. Intrauterine pulmonary hemorrhage secondary to antenatal Coxsackie B-2 infection. *Pediatr Res.* 1997;1:265A.
- Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. *Cochrane Database Syst Rev* 2009, Issue 2.
- Soll R, Özek E. Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2010, Issue 1.
- St. John EB, Carlo WA. Respiratory distress syndrome in VLBW infants: changes in management and outcomes observed by the NICHD neonatal research network. *Semin Perinatol.* 2003;27:288–92.
- Suresh GK, Soll RF. Exogenous surfactant therapy in newborn infants. *Ann Acad Med Singapore.* 2003;32:335–45.
- Tobias J, Berkenbosch JW, Russo P. Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. *Pediatr Crit Care Med.* 2003;41:49–51.
- van Houten J, Long W, Mullett M, et al. Pulmonary hemorrhage in premature infants after treatment with synthetic surfactant: an autopsy evaluation. *J Pediatr.* 1992;120:540–4.

Chapter 75

Retinopathy of Prematurity

Alistair R. Fielder

I. Introduction

- A. Retinopathy of prematurity (ROP) is a major cause of childhood blindness but is particularly important because visual disability can largely be prevented by timely treatment.
- B. The therapeutic window is very short and treatment needs to be performed, depending on its severity, within a maximum of 72 h.
- C. Such a short period of opportunity for successful ROP treatment requires precise guidelines for screening and treatment, which is possible in countries with a high standard of neonatal care, where the population at risk has been defined by audit and research (e.g., the USA and the UK). However, this presents a major challenge in countries which neonatal care can be more variable and larger babies can be at risk of sight-threatening ROP.
- D. Acute phase ROP has five stages (Table 75.1).
 - 1. Mild disease is defined as ROP less than prethreshold ROP either Types I and II and resolves fully without visually disabling sequelae.
 - 2. Severe disease is the consequence of prethreshold Types I or II ROP which does not resolve and includes stages 4 and 5 (both associated with retinal detachment).

II. Prophylaxis

- A. Standard of care remains critical in keeping severe disease to a minimum, although it is recognized that despite meticulous neonatal care, ROP is not entirely preventable.

A.R. Fielder, FRCP, FRCS, FRCOphth (✉)
Optometry & Visual Science, City University, Northampton Square,
London, UK EC1 0HB, UK
e-mail: a.fielder@city.ac.uk

Table 75.1 International classification of retinopathy of prematurity revisited

A.	Severity by stage
1.	Demarcation line Thin white line, lying within the plane of the retina and separating avascular from vascular retinal regions.
2.	Ridge The line of stage 1 has increased in volume to extend out of the plane of the retina. Isolated vascular tufts may be seen posterior to the ridge at this stage.
3.	Ridge with extraretinal fibrovascular proliferation This may: (a) be continuous with the posterior edge of the ridge (b) be posterior, but disconnected, from the ridge (c) extend into the vitreous
4.	Retinal detachment—subtotal Extrafoveal (4 A), or involving the fovea (4 B)
5.	Retinal detachment—total The detached retina is funnel-shaped which may be open or closed along all or part of its extent. <i>Aggressive Posterior ROP (AP-ROP)</i> Commences with posterior pole vessel dilatation and tortuosity in all four quadrants. Deceptively featureless (which is why it has only recently been defined) it does not progress from stage 1 to 3, but appears as a flat network of vessels at the junction between vascularized and nonvascularized retina. Typically, AP-ROP is circumferential and may be located in zone I or posterior zone II.
B.	Location by zone Retinal blood vessels grow out from the optic disc in zone I toward the periphery (zone III), thus the retinal zone vascularized reflects maturity. ROP in zone I affects the most immature baby and is very likely to become severe with a poor outcome, whereas ROP located in zone III carries a very low risk to become severe and for an adverse outcome.
C.	Extent ROP extent around the retinal circumference is recorded in “clock hours” 1–12.
D.	Plus disease Plus disease is an indicator of ROP activity—in order of increasing severity: venous dilatation and arteriolar tortuosity of the posterior pole retinal vessels, iris vessel engorgement, pupil rigidity and vitreous haze. <i>Plus involves vessels in 2 or more quadrants. Preplus describes abnormalities that are insufficient for the diagnosis of plus. Plus and preplus are critical indicators that ROP is, or will become, severe.</i>

B.	The major ROP risk factor is the degree of prematurity, but many associations and complications of preterm birth have also been implicated including:
1.	Oxygen.
a.	Hyperoxia, hypoxia, and fluctuations of arterial oxygen even within the normal range.
b.	It is important therefore to keep arterial oxygen levels within the recommended range. Avoid fluctuations of arterial oxygen levels when possible.

2. Steroids.

- a. Steroids administered antenatally have been shown to reduce the incidence of severe ROP.
- b. Steroids administered postnatally may be associated with more severe ROP, but it is not established whether this is a causal relation.

3. Surfactant treatment does not affect the ROP incidence.

4. Light reduction by lowering the ambient illumination of the NICU does not reduce the incidence or severity of ROP.

5. Many other risk factors have been suggested including vitamin E deficiency, exchange transfusions, necrotizing enterocolitis, treatment for patent ductus arteriosus, and other complications of prematurity.

III. Screening

A. Purpose: to identify severe ROP which might require treatment, and which even if it does not, is associated with a high incidence of visually severe sequelae.

B. Which babies should be examined?

1. UK guideline:

- a. All babies <1251 g BW or < 31 weeks' GA *must* be screened.
- b. All babies 1,251–15,01 g BW or 31–32 weeks' GA *should* be screened, regardless of clinical condition.
- c. UK guideline has no sickness criteria.

2. US guideline:

Infants with a birth weight <1,500 g or GA \leq 30 weeks should be screened. In addition, selected infants with a birth weight 1,501–2,000 g or GA >30 weeks with an unstable clinical course, and who are believed to be at high risk may also be screened.

3. Countries with more variable standards of neonatal care:

- a. The UK and US guidelines are applicable for babies less than 32 weeks.
- b. The UK and US guidelines are not applicable to babies \geq 32 weeks who occasionally develop blinding ROP very rapidly.
- c. This emphasizes the need for locally derived protocols.

IV. Examination protocol

A. Principles

1. ROP develops to a defined temporal trajectory, which ends when the retina is fully vascularized at about 40 weeks' GA.
2. Age at ROP onset and its rate of progression are both governed mainly by postmenstrual age (PMA). Thus, its onset is later in the very immature compared to the more mature baby.

Table 75.2 Schedule of screening

Age at first screening examination (in weeks)		
GA	PMA	PNA
22 ^a	30	8
23 ^a	30	7
24	30	6
25	30	5
26	30	4
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4
33 ^a	36	3
34 ^a	36	2

Data for babies 24–32 weeks GA provided by clinical studies (Reynolds et al. 2002)

^aEstimates based on limited clinical data

3. Neonatal events influence the risk of developing ROP but not its timing. Sight-threatening ROP is most unlikely to be present before 31 weeks' PMA.
 - a. The screening program needs to be designed so that ROP requiring treatment is identified in a timely manner.
 - b. The mean age for treatment at prethreshold is 35 weeks' PMA.
 - c. The time available for treatment is short, but the degree of urgency is not identical for all cases.
 - (1) Aggressive posterior ROP should be treated as soon as possible and within 48 h.
 - (2) Other eyes, considered less urgent but requiring treatment, should normally be treated within 48–72 h.
4. The initial examination should be scheduled as in Table 75.2 (after Reynolds et al. 2002). In those countries in which babies more than 32 weeks' GA are at risk, screening will need to commence postnatally earlier than in smaller babies.
5. Subsequent examinations
 - a. Every 1–2 weeks. This frequency minimizes loss to follow-up, and ensures that almost all screening is completed while the baby is in hospital.
 - b. Eyes with progressing ROP and certainly those eyes with Type 2 prethreshold ROP should be examined at least once a week to ensure that treatment, if necessary, is optimally timed.

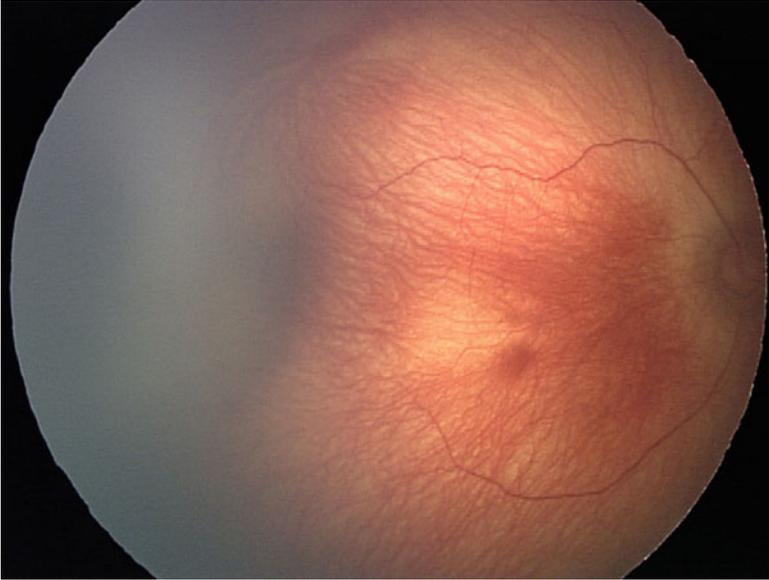


Fig. 75.1 Normal retina of preterm baby. The retinal vessels extend up to the *gray* area, to the *left* of the image, but do not reach the retinal periphery. The *gray* region is the normal, yet to be vascularized, retina. ROP develops at the junction of the vascularized and yet to be vascularized retina

- c. For babies who are transferred to another hospital prior to completion of the screening program, ensure that the receiving hospital is alerted to screening requirements of the baby and when the next examination needs to be scheduled.
 - d. For babies discharged home, ensure follow-up until screening is completed.
6. Completion of screening
- a. Premature cessation of screening is a major cause for litigation.
 - b. For the eye without ROP it is critical to continue screening until the risk for sight-threatening ROP has passed—vascularization has entered zone III (peripheral most portion of the temporal retina). Because assessing whether the retinal vessels are in zone III is prone to misinterpretation, it is recommended that screening continues at least of 37 weeks' PMA.
 - c. For the eye with ROP, the need for examinations is dictated by clinical criteria (Figs. 75.1–75.3).
7. Screening examination
- a. To be carried out by an experienced ophthalmologist following pupillary dilation.



Fig. 75.2 Stage 2 and 3 ROP in the peripheral retina. The *gray* line toward to top and bottom of the image are stage 2 while in the middle section are fronds of neovascularization, stage 3. The *gray* appearance is because the image comes from a black baby

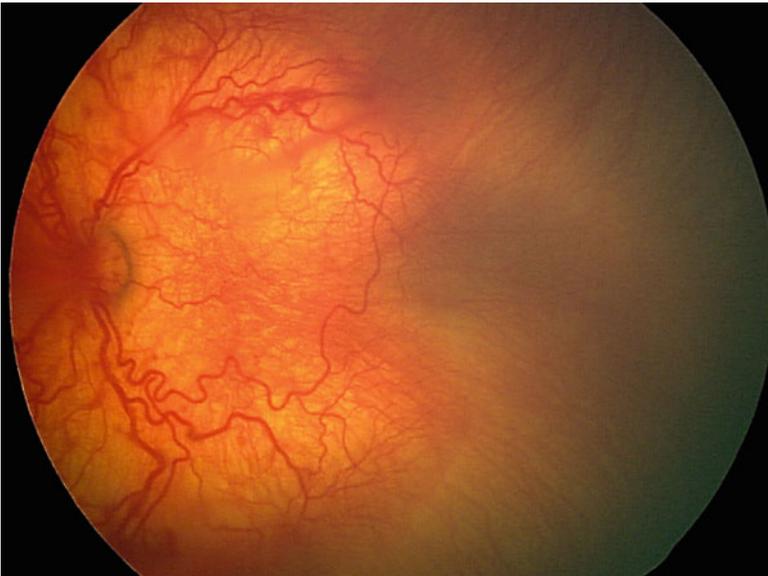


Fig. 75.3 Aggressive posterior ROP. Note extreme vascular congestion and tortuosity but subtle if any peripheral ROP lesion. This eye needs treatment within 48 h. Because of the absence of an obvious ROP lesion—compare with stage 3 above—in the last the severity of the situation was not appreciated and these eyes were likely to become blind. Permission confirmed from Arch Ophthalmol. 2005;123:991–9. Fig. 12a, p. 996

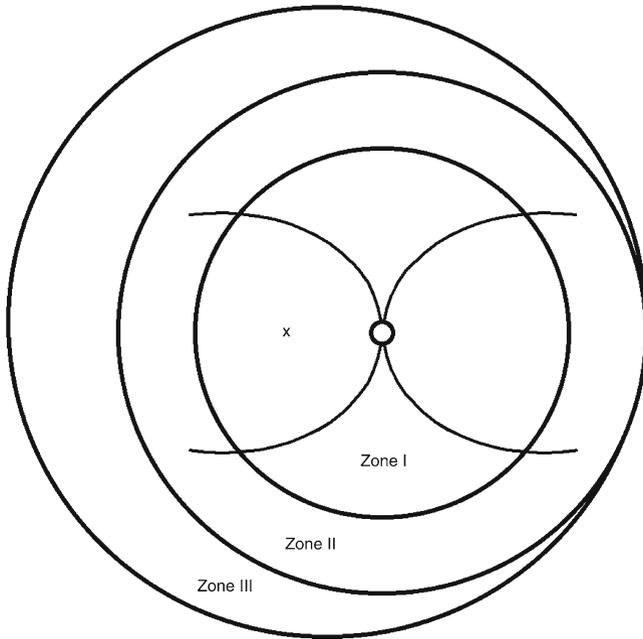


Fig. 75.4 Diagram showing the retinal zones. X marks the macula

b. ROP is recorded according to the following four criteria:

- (1) Severity by stages: 1–5 and *aggressive posterior ROP (AP-ROP)*.
- (2) Location by zones I–III. This is critical because the closer to zone I (posterior) the greater is the propensity to become severe, whereas ROP in zone III almost never causes visual disability (Fig. 75.4).
 - (a) Extent by clock hour involvement.
 - (b) Presence of “preplus” and “plus” disease.
 - (c) It is critical to record each of these criteria on every occasion and record the absence or presence of plus even if no ROP is observed. Sample form downloadable from <http://www.rcpch.ac.uk/ROP>.

V. Treatment

A. Principles

1. Most ROP is mild and will have no major visually disabling sequelae. Severe ROP is defined as prethreshold ROP, Types 1 and 2.

a. TYPE I PRETHRESHOLD ROP (should be treated):

- (1) Zone I, any ROP with plus disease
- (2) Zone I, stage 3 ROP without plus disease
- (3) Zone II, stages 2 or 3 with plus disease

b. TYPE 2 PRETHRESHOLD ROP (should be observed):

- (1) Zone I, stages 1 or 2 without plus
- (2) Zone II, stage 3 without plus

2. Type II ROP alerts the ophthalmologist that ROP is severe and may, if it progresses to Type I ROP, require treatment, as this is now the indication for treatment.
3. "Plus" disease is now the key criterion for treatment and is the critical difference between Type I that requires treatment and Type II ROP that does not.
4. Unfortunately, diagnosing "plus" disease is not always simple or robust, so it is recommended that all other ROP features are included in evaluating if treatment is needed.
5. It is recognized that the window of opportunity for treatment is not precisely defined and some eyes require intervention more urgently than others.

B. Treatment practicalities

1. Once prethreshold Type I has been diagnosed, treatment by laser (cryotherapy is used very infrequently) should be performed:
 - a. Within 48 for eyes with AP-ROP
 - b. Within 48 and 72 h for eyes which with less aggressive ROP but still requiring treatment
2. Bevacizumab (Avastin), an antivascular endothelial growth factor (anti-VEGF) agent, has very recently been used as a first line treatment. It has been reported to be beneficial for zone I, but not zone II, ROP. Caution is advised as concerns about possible systemic effects on the developing baby have yet to be determined. Current opinion is that this is still investigational intervention and should be reserved for use when laser has failed and not as a first line treatment.

VI. Long term follow-up

- A. All severe ROP requires ophthalmic follow-up, at least to 5 years of age because of the risk of reduced vision, refractive errors (especially myopia) and strabismus.
- B. The follow-up of very low birthweight babies who did not develop severe ROP is less well defined and is influenced by local protocols, but the likelihood of developing refractive errors and strabismus in childhood is much higher than in their full-term counterparts.

VII. Responsibilities and organization

- A. Effective and efficient screening for ROP, and its subsequent management requires multidisciplinary professional teamwork.
- B. National guidelines form the basis of protocols, which should be developed locally and jointly by the neonatal and ophthalmic teams.
- C. Identification of babies requiring screening is the responsibility of the neonatal team.
- D. Arrangement for follow-up need to be made for the baby who is transferred to another hospital and for any postexamination follow-up.

VIII. Information for parents

- A. Mild ROP is very common, but most babies do not develop severe ROP, so conversations and literature for parents need to convey this (sample downloadable from <http://www.rcpch.ac.uk/ROP>).
- B. For babies with, or close to, severe ROP that might require treatment, a personal discussion between the ophthalmologist and parents is important and this should involve also a member of the neonatal team (sample downloadable from <http://www.rcpch.ac.uk/ROP>).

IX. Future directions

- A. The retinovascular changes associated with ROP are not well defined. There is a need to develop automated vessel analysis from digital images to quantify precisely these changes. This will (hopefully) open opportunities for non-physician ROP screening in those countries with a high screening requirement, but where currently access to services is low.
- B. Data of babies at risk for severe ROP needs to be collected from all countries so that guidelines applicable to all countries can be developed.
- C. Now that the use of anti-VEGF agents is underway, it is important that their ophthalmic and systemic effects in preterm babies are understood.

Suggested Reading

- An International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. *Arch Ophthalmol.* 2005;123:991–9.
- Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity. *Arch Ophthalmol.* 2003;121:1684–96.
- Eriksson L, Haglund B, Ewald U, Odland V, Kieler H. Short and long-term effects of antenatal corticosteroids assessed in a cohort of 7,827 children born preterm. *Acta Obstet Gynecol Scand.* 2009;88:933–8.
- Fielder AR, Quinn GE. Retinopathy of prematurity. In: Taylor DSI, Hoyt CS, editors. *Pediatric ophthalmology and strabismus*. 4th ed. Elsevier Ltd. 2012, in press.
- Fielder AR, Reynolds JD. Retinopathy of prematurity: clinical aspects. *Semin Neonatol.* 2001;6:461–77.
- Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev.* 2008;84:77–82.

- Hård AL, Hellström A. On the use of antiangiogenetic medications for retinopathy of prematurity. *Acta Paediatr.* 2011;100(8):1063–5.
- Karna P, Muttineni J, Angell L, Karmaus W. Retinopathy of prematurity and risk factors: a prospective cohort study. *BMC Pediatr.* 2005;5(1):18.
- Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med.* 2011;364:603–15.
- Reynolds JD, Dobson V, Quinn GE, Fielder AR, et al. on behalf of the CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence-based screening for retinopathy of prematurity: natural history data from CRYO-ROP and LIGHT-ROP Studies. *Arch Ophthalmol.* 2002;120:1470–76.
- Section on Ophthalmology. American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics.* 2006;117(2):572–6. *Erratum in: Pediatrics.* 2006;118(3):1324.
- Tin W, Wariyar U. Giving small babies oxygen: 50 years of uncertainty. *Semin Neonatol.* 2002;7:361–7.
- Wilkinson AR, Haines L, Head K, Fielder AR. UK retinopathy of prematurity guideline. *Early Hum Dev.* 2008;84:71–4. Full guideline and sample downloadable forms available <http://www.rcpch.ac.uk/ROP>.

Chapter 76

Neurologic Complications of Mechanical Ventilation

Gillian Brennan and Jeffrey M. Perlman

I. Background

- A. The developing brain of the newborn, and in particular the premature infant, is at increased risk for hemorrhagic and/or ischemic injury (Table 76.1).
- B. The most frequent lesions noted are periventricular intraventricular hemorrhage (PV-IVH) and injury to white matter, often referred to as periventricular leukomalacia (PVL).
- C. These lesions are most likely to occur in the premature infant with respiratory distress syndrome requiring mechanical ventilation.
- D. The etiology of both lesions is likely multifactorial including the following:
 1. Perturbations in cerebral blood flow (CBF) which are considered to be of paramount importance.
 2. The cerebral circulation in the sick newborn infant appears to be pressure-passive, i.e., changes in CBF directly reflect similar changes in systemic blood pressure.
 3. The periventricular white matter at greatest risk for injury resides within arterial border and end zones of the long penetrating vessels. The terminations of these long penetrators result in distal arterial fields that are most sensitive to a reduction in cerebral blood flow. Since active development of this periventricular vasculature occurs predominantly in the last 16 weeks of human gestation, in the more immature the infant, even a lesser degree of hypoperfusion may cause cerebral ischemia.

G. Brennan, MB, BCh, BAO • J.M. Perlman, MB, ChB (✉)
Division of Newborn Medicine, Weill Cornell Medical Center,
New York-Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, USA
e-mail: jmp2007@med.cornell.edu

Table 76.1 Risk factors for cerebral injury in sick premature infants requiring mechanical ventilation

A.	Cerebral
	(1) Vulnerable capillary beds, e.g., germinal matrix, periventricular white matter
	(2) Pressure passive cerebral circulation
B.	Respiratory
	(1) Respiratory distress syndrome
	(2) Pneumothorax/pulmonary interstitial emphysema
C.	Vascular
	Perturbations in systemic hemodynamics: e.g., hypotension, hypertension, fluctuations in systemic blood pressure
D.	Consequences of mechanical ventilation
	(1) High mean airway pressure
	(2) Hypocapnia

4. Resting cerebral blood flow to white matter is low.
5. The cerebral circulation is also exquisitely sensitive to changes in PaCO₂ and to a lesser extent pH.
6. These factors increase the potential for cerebral injury during periods of systemic hypotension or hypertension.
7. Mechanical ventilation of the sick newborn infant can thus directly or indirectly affect CBF via systemic vascular or acid–base changes and increase the risk for cerebral injury (see below).

II. Mechanical ventilation and potential brain injury

A. Direct effects.

1. Infants breathing out of synchrony with the ventilator.
 - a. The sick infant with respiratory distress syndrome (RDS) may exhibit beat-to-beat fluctuations in arterial blood pressure. The arterial fluctuations that affect both the systolic and diastolic components of the waveform appear to be related to the infant's own respiratory effort, which invariably is out of synchrony with the ventilator breaths.
 - b. The fluctuations are increased with increasing respiratory effort and are minimized when respiratory effort is absent (Fig. 76.1).
 - c. The arterial blood pressure fluctuations are associated with similar beat-to-beat fluctuations in the cerebral circulation consistent with a pressure-passive state. The cerebral fluctuations if persistent have been associated with subsequent PV-IVH. Minimizing the fluctuation is associated with a reduction in hemorrhage.
 - d. Minimize fluctuations by:
 - (1) Increasing ventilator support
 - (2) Use of synchronized mechanical ventilation (e.g., assist/control or pressure support ventilation)

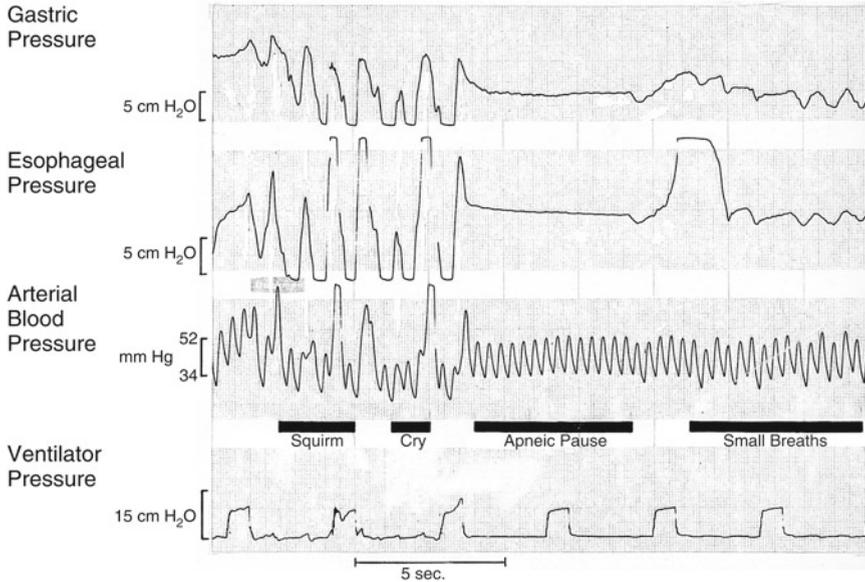


Fig. 76.1 Relationship of respiratory effort to other physiologic variables

(3) Use of sedatives

(4) Skeletal muscle paralysis (This has become less frequent in recent years with the increased tendency toward synchronized ventilation).

2. Impedance of venous return

a. Increase in mean airway pressure (P_{aw}) may impede venous return to the heart with two consequences:

- (1) An increase in central venous pressure and, as a result, an increase in intracranial venous pressure
- (2) Decreased cardiac output

b. A combination of an elevated venous pressure and a concomitant decrease in cardiac output markedly increases the risk for cerebral hypoperfusion within vulnerable regions of the brain (i.e., periventricular white matter).

c. High P_{aw} is often utilized with either conventional or high-frequency ventilation in the sick infant with respiratory failure. Cardiac output (CO) is affected by changes in P_{aw} during HFOV in a similar manner to conventional ventilation with increases in P_{aw} associated with decreases in CO.

d. An *association* between the use of high-frequency ventilation and PVL has been observed.

- e. Close monitoring of the vascular system is critical in the sick infant requiring high P_{aw} to support respiratory function.
 - f. Some of the primary determinants of P_{aw} with conventional ventilation include inspiratory time (T_I), PIP, PEEP, and gas flow rates. A long T_I has been associated with a significant increase in air leak.
3. Volume-targeted versus pressure-targeted ventilation. There is evidence that volume-targeted ventilation as opposed to pressure targeted ventilation in the premature infant may reduce the occurrence of pneumothorax, hypocapnia, and fluctuations in oxygen saturation, leading to a reduction in PVL and severe IVH.
 4. Effects of PaCO_2
 - a. The cerebral circulation is exquisitely sensitive to changes in PaCO_2 , (i.e., hypocapnia decreases CBF, and hypercapnia increases CBF). This relationship appears to be intact in the sick newborn infant.
 - b. Hyperventilation with a reduction in PaCO_2 has been utilized as a strategy to augment pulmonary blood flow. The resultant hypocapnia may significantly reduce CBF.
 - c. Hypocapnia in mechanically ventilated preterm infants, particularly during the first days of life has been shown to be to be an independent predictor of PVL, predisposing these infants to subsequent neurodevelopmental delay.
 - d. Conversely, hypercapnia, with an increase in CBF, has been associated with an increased risk for PV-IVH.
 - e. Provide a ventilation strategy to achieve normocapnia.
- B. Indirect effects: complications of RDS.
1. Ventilated infants with RDS are at increased risk for air leak, (i.e., pneumothorax and/or pulmonary interstitial emphysema).
 2. There is a strong association between pneumothorax and subsequent PV-IVH.
 3. At the time of pneumothorax there appears to be a marked increase in flow velocity within the anterior cerebral arteries, especially during diastole. This increase in flow velocity resolves some hours after resolution of the pneumothorax. These alterations on flow velocity within the anterior cerebral arteries likely result from the following:
 - a. Increase in mean systemic pressure, especially diastolic pressure
 - b. Decreased cardiac output
 - c. Impeded venous return
 - d. Increased PaCO_2
 - e. Hemodynamic changes that accompany evacuation of pleural air
- C. Other associations: Sensorineural hearing loss. Term infants with pulmonary hypertension subjected to hyperventilation are at increased risk for sensorineural hearing loss. The mechanism of such injury remains unclear.

D. Potential therapeutic strategies.

1. Reduce fluctuations in systemic hemodynamics
 - a. Synchronized ventilation
 - b. Sedation
 - c. Paralysis
2. Avoid systemic hypotension and/or hypertension
 - a. Consider inotropic support
 - b. Consider volume expansion
3. Avoid impedance of venous return by using P_{aw} (if feasible)
4. Avoid hypoxemia
5. Avoid hypercapnia
6. Avoid pneumothorax
 - a. Surfactant administration for RDS
 - b. Synchronized ventilation
 - c. Wean as rapidly as tolerated

Suggested Reading

- Altman DI, Powers WJ, Perlman JM, et al. Cerebral blood flow requirement for brain viability in newborn infants is lower than in adults. *Ann Neurol.* 1988;24:218–26.
- Fujimoto S, Togari H, Yamaguchi N, et al. Hypocarbia and cystic periventricular leukomalacia in premature infants. *Arch Dis Child.* 1994;71:F107–110.
- Greisen G, Munck H, Lou H. Severe hypocarbia in preterm infants and neurodevelopmental deficit. *Acta Paediatr Scand.* 1987;76:401–4.
- Gullberg N, Winberg P, Sellén H. Changes in stroke volume cause change in cardiac output in neonates and infants when mean airway pressure is altered. *Acta Anaesthesiol Scand.* 1999;43:999–1003.
- Gullberg N, et al. Changes in mean airway pressure during HFOV influences cardiac output in neonates and infants. *Acta Anaesthesiol Scand.* 2004;48(2):218–23.
- Hendricks-Munoz KD, Walter JP. Hearing loss in infants with persistent fetal circulation. *Pediatrics.* 1988;81:650–6.
- Hill A, Perlman JM, Volpe J. Relationship of pneumothorax to the occurrence of intraventricular hemorrhage in the premature newborn. *Pediatrics.* 1982;69:144–9.
- Kaiser JR, Gauss CH, Pont MM, Williams DK. Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. *J Perinatol.* 2006;26:279–85.
- Kamlin CO, et al. Long versus short inspiratory times in neonates receiving mechanical ventilation. *Cochrane Database Syst Rev.* 2004;18(4):CD004503.
- Mirro R, Busija D, Green R, Leffler CB. Relationship between mean airway pressure, cardiac output and organ blood flow with normal and decreased respiratory compliance. *J Pediatr.* 1987;111:101–6.
- Pape KE, Armstrong DL, Fitzhardinge PM. Central venous system pathology associated with mask ventilation in the very low birth weight infant. A new etiology for intracerebellar hemorrhage. *Pediatrics.* 1976;58:473–83.

- Perlman JM, McMenanim JB, Volpe JJ. Fluctuating cerebral blood flow velocity in respiratory distress syndrome: relationship to subsequent development of intraventricular hemorrhage. *N Engl J Med.* 1983;309:204–9.
- Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood flow velocity in preterm infants with respiratory distress syndrome. *N Engl J Med.* 1985;312:1353–7.
- Perlman JM, Volpe JJ. Are venous circulatory changes important in the pathogenesis of hemorrhagic and/or ischemic cerebral injury? *Pediatrics.* 1987;80:705–11.
- Pryds O, Greisen G, Lou H, Friis-Hansen B. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation. *J Pediatr.* 1989;115:638–45.
- Shalak L, Perlman JM. Hemorrhagic-ischemic cerebral injury in the preterm infant: current concepts. *Clin Perinatol.* 2002;29:745–63.
- Shankaran S, Langer JC, Kazzi SN, Laptook AR, Walsh M. Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants. *Pediatrics.* 2006;118:1654–9.
- Wheeler K et al. Volume-targeted versus pressure-limited ventilation in the neonate. *Cochrane Database Syst Rev.* 2010;(11):CD003666.
- Wiswell TE, Graziani LJ, Kornhauser MS. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high frequency jet ventilation. *Pediatrics.* 1996;98:918–24.

Part XIII
Other Considerations

Chapter 77

Nursing Care of the Ventilated Infant

Kimberly LaMar

- I. As nurses spend 24 h per day with the newborn in an intensive care nursery, nursing care is essential to the eventual recovery and discharge of these fragile patients.
- II. History taking assists in focusing on an area while keeping the mind open to other possibilities. It is also important to know environmental and community/epidemiological impacts (e.g., onset of Respiratory Syncytial Virus season).
 - A. Maternal, including past and existing medical conditions
 - B. Family
 - C. Social
 - D. Delivery room
 - E. Neonatal
- III. Normal physiology, pathophysiology, and embryology are key to understanding the concepts of respiratory disease in the neonate.
- IV. Assessment.
 - A. Observation
 1. General state
 - a. Sleeping, awake, alert, crying or motions of crying, if ventilated
 - b. Must be an objective assessment as patient cannot give subjective feedback
 - c. A number of pain scales and stress scales are available for use with neonates including preterm and ventilated babies

K. LaMar, ND, NPD-BC (✉)
Chamberlain College of Nursing, Phoenix Campus, 2149 W Dunlap Ave,
Phoenix, AZ 85021, USA
e-mail: Klamar@chamberlain.edu

2. Color

- a. Generalized color as well as central color determined by examining the mucous membranes and skin for ruddiness, intense redness, pallor, or cyanosis, as well as jaundice, although it is less likely to be related to a respiratory origin. In the first few minutes of life, the newborn may have acrocyanosis, a normal finding, making examination of the nail beds unreliable.
- b. Cyanosis results from the presence of >5 g/dL unsaturated Hgb.

3. Mouth and nose

- a. Secretions: amount, color, consistency. Usually clear or white. Excessive secretions may be associated with a tracheoesophageal fistula
- b. Nasal flaring to decrease resistance in upper airways
- c. Nasal stuffiness associated with maternal illicit drug use
- d. Nasal snuffles with copious amounts of nasal drainage seen with congenital syphilis

4. Chest

- a. Size and shape: normal chest size in a full term infant is 33 ± 3 cm, or 2 cm less than the head circumference
- b. Deviations include pigeon chest with protrusion of the sternum, or a funnel chest with an indented sternum. These may be seen in Marfan's syndrome or neonatal rickets
- c. Increased diameter or "barrel chest" in meconium aspiration syndrome
- d. Symmetry of chest, assess at the nipple line
- e. Synchrony of chest with ventilation, chest rises with ventilator breaths
- f. Rate of respirations counted for a full minute. Tachypnea is a rate >60 /min, apnea is cessation of respirations for 20 s or longer, and hypopnea is shallow spontaneous respiratory effort
- g. High-frequency ventilation assessed by amount of chest vibration or "wiggle"
- h. Retractions caused by infant's soft cartilage and muscle groups that draw in to augment respiration. May be intercostal, subcostal, sternal, suprasternal, and subxiphoid. May also exhibit "seesaw" pattern of chest and abdominal breathing
- i. Work of breathing is observed as comfortable, easy pattern or increased work of breathing when entire effort of infant is involved in respiration to the exclusion of all other activity

B. Auscultation

1. External.

- a. Grunting heard without the use of a stethoscope. It is the infant exhaling against a partially closed glottis in an attempt to slow the respiratory flow and maintain a higher functional residual capacity.
- b. Air leak may be heard in very small infants or those with higher ventilatory support as the endotracheal tubes are uncuffed. These may also be identified with graphic monitoring on the ventilator.
- c. Cry may be lusty, weak, absent, hoarse, shrill or high pitched. The high pitched cry is associated with Cri du chat syndrome.
- d. Stridor is a high pitched sound heard either at inspiration or expiration that indicates a partial obstruction of the airway. May be associated with post-extubation, edema, laryngomalacia, or damage to the vocal cords.

2. Internal.

- a. Assess with the warmed bell side of a neonatal stethoscope.
 - b. Compare and contrast side to side of chest on the anterior chest and posterior chest walls.
 - c. Crackles are fine, medium, or coarse and represent air or fluid moving in the small or large airways. Find crackles originate in the dependent lobes of the lungs and are heard at the end of inspiration and may be associated with respiratory distress syndrome (RDS) or bronchopulmonary dysplasia (BPD). Medium crackles originate in the bronchioles and may be associated with air moving through tenacious fluid, such as with pneumonia or transient tachypnea of the newborn. Coarse crackles are bubbly and are associated with fluid in the large airways and usually resolve with clearing the airway.
 - d. Rhonchi are musical and seldom heard in the neonate.
 - e. Wheezes may be heard on inspiration or expiration and are louder with expiration.
 - f. Rubs may be heard with inflammation of the pleura but are seldom heard in the neonate.
 - g. Must assess breath sounds for symmetry, diminished or absent sounds, tight sounds, and synchrony with the ventilator.
 - h. Imperative to listen to neonates on high-frequency ventilation both on and off the ventilator to gain full assessment of lungs. Should coordinate this time to coincide with care requiring brief pauses of the ventilator.
3. Palpation and percussion are not widely used in the neonate unless palpating for crepitus or percussing for dull sounds, such as those in congenital diaphragmatic hernia.

V. Monitoring (Chaps. 17 and 18).

A. Transcutaneous

1. May measure oxygen or carbon dioxide tensions through skin rather than arterial monitoring. Correlation is dependent upon the perfusion of skin.
2. May have a combination of transcutaneous carbon dioxide and pulse oximetry through a peripheral sensor for newborns.
3. Complications include ineffective readings secondary to technique, heat burns, requiring frequent changes with subsequent increase in nursing time for care. This is especially true for premature babies with very friable skin.

B. Pulse oximetry

1. Emits wavelengths to a receptor that measures oxygen saturation of Hgb.
2. Monitors continuously.
3. Accuracy depends on perfusion, body temperature, Hgb.
4. Has been used with a device to control inspired oxygen concentration with the ventilator (Chap. 53).
5. End tidal CO₂. Device that attaches to end of endotracheal tube adaptor to assure position of endotracheal tube in the airway. It has a filter paper sensitive to carbon dioxide, changes color from purple to yellow if exposed to carbon dioxide found in the trachea.

VI. Radiology: Radiology is a specialty of medicine but this is intended as a few general guidelines for nurses. It is important that nurses understand basic principles for assisting in a quality radiographic exam and to assist in the identification of emergency conditions.

- A. Anything placed on the neonate's skin should be carefully considered for absolute necessity and potential for interference of imaging exams. Items to consider include heat probe patches, any monitoring electrodes and wires, warming pads that can cause a "waffle" appearance on image. All lines and tubes must be kept from crossing the field being examined.
- B. Assure patient is positioned correctly in as symmetrical an alignment as possible with head in a neutral position in the midline. Must assist the radiography technician in accomplishing this successfully to avoid negative outcomes such as dislodging of tubes or lines.
- C. Assess the reason for the examination using a systematic approach.
 1. Soft tissue, bony structures, mediastinum, thymus
 2. Trachea, pulmonary vasculature
 3. Chest—lungs, heart, diaphragm
 4. Abdomen—stomach, bowel gas pattern, visible masses
 5. Lines/tubes—Endotracheal, umbilical catheters, peripherally inserted central catheters, chest drainage devices, naso/orogastric

VII. Pharmacotherapy (Chap. 52). Neonatal nurses should be well versed in the drug therapies that have impact on the neonate's respiratory system. There are many drugs in development continuously with new drugs being approved for use for neonates. This is a brief list of the more common drugs but is by no means all inclusive. Drugs may be delivered a number of ways including orally, intramuscularly, subcutaneously, intervenously, endotracheally, sublingually, or dermally. These include the following:

- A. Sedatives
- B. Analgesics
- C. Muscle relaxants
- D. Vasoactive agents
- E. Exogenous surfactants
- F. Diuretics
- G. Steroids
- H. Bronchodilators
- I. Anticipatory guidance. Caregivers should be aware of normal course of disease or treatments and anticipate the care required. Examples of these include:
 - 1. RDS—has a diuretic phase 48–72 h after birth that will generally coincide with increased compliance and improvement in condition.
 - 2. Surfactants—immediate increase in compliance after dosing, requires less ventilatory support. An inability to recognize this may result in pneumothorax.
 - 3. BPD—As lungs develop dependency on ventilation or oxygen, baby may have an increase in frequency and severity of desaturation spells.

VIII. Documentation (Chap. 83).

- A. Should be timely and accurate.
- B. American Nurses Association has set standards for nurses that they must document in the medical record to communicate with other health-care providers any information concerning their patient whether in flow-sheets, care plans, electronic medical records, patient teaching, incident reports, etc.
- C. The Standards for Nursing Practice in British Columbia has set the purpose of documentation as improving communication to other nurses and care providers, promoting good nursing care in determining the effectiveness of treatments and necessary changes to the plan of care and assisting in decision making about funding for nursing research and resource management. Finally, it meets professional and legal standards for nursing measured against a standard of a reasonable and prudent nurse with similar education and experience.

- D. Should include:
1. Assessment of the neonate
 2. Baseline vital signs, evidence of pain and response to treatment of pain, ventilatory settings and/or oxygen therapies, oxygen saturation and/or transcutaneous readings
 3. Need for any nursing procedure, outcome, tolerance, complications of procedure, if any
 4. Amount, type, color, consistency of secretions
 5. Any apneic, desaturation or bradycardic episodes not caused iatrogenically, such as associated with suctioning, positioning, tube placements
- E. Abbreviations
1. Use as little as possible
 2. Only use approved abbreviations
 3. Print, do not use cursive writing, for all abbreviations
 4. Use appropriate symbols
 5. Do not invent new ones
 6. Clarify unknown abbreviations with the writer
- IX. Nursing procedures for respiratory care of the newborn.
- A. Nursing procedures have been found to have an impact on the outcomes of newborns in the intensive care.
 - B. Pain management and developmentally appropriate care should gain particular attention during any nursing procedure related to respiratory care for newborns.
- X. Transport of neonates (Chap. 78).
- A. May be from one unit to another unit, such as transport from delivery room to NICU, or NICU to operating suite, or transition nursery to radiology. May be from one facility to another facility, city to city, or even country to country.
 - B. Regionalization of neonatal care has assisted in the establishment of facilities for levels of care and setting expectations for transport teams with expertise in this type of care.
- XI. Chest physiotherapy (CPT)/postural drainage (PD).
- A. No benefit in delivery room management.
 - B. PD rarely used secondary to concerns on neonate's lack of cerebral auto-regulation, especially if premature.
 - C. CPT may include vibration, although no evidence to support its use.
 - D. No evidence that routine CPT assists in clearing secretions or weaning from ventilator. Has been associated with an increase in intracranial hemorrhage in the first 24 h.

- E. Must monitor neonate's tolerance during CPT.
- F. Complications include hypoxia, bradycardia, rib fractures, and subperiosteal hemorrhage.

XII. Suctioning.

- A. Suctioning should never be performed on a routine schedule but rather according to need per an assessment with an understanding of the disease process. Studies have shown no increase in secretions or occlusion of endotracheal tubes when suctioning was extended to occur once every 12 h versus every 6 h in neonates ventilated for RDS.
- B. Indicators for suctioning may include visible secretions, coarse or decreased breath sounds, decrease in saturation, or acute change in blood gas results, agitation or change in vital sounds related to respiratory system. Graphic monitoring will show very irregular, noisy signals (Chap. 20, Fig. 20.19).
- C. Upper airways should be suctioned gently.
- D. Tracheal suctioning in the delivery room has been reserved for nonvigorous neonates or those requiring resuscitation in the immediate period after delivery regardless of the consistency of secretions or meconium.
- E. Endotracheal tube suctioning is performed only to maintain the patency of the endotracheal tube and never for attempts to clear actual airways beyond the endotracheal tube. In addition:
 1. Complications include hypoxemia, bradycardia, tachycardia, atelectasis, pneumonia, lability in blood pressure and intracranial pressure, trauma to airway, sepsis, tube blockage and dislodgement, and pneumothorax.
 2. Pre-oxygenation has been shown to result in a higher PaO₂ after suctioning with decreased recovery time.
 3. Endotracheal tube suctioning has theoretical concerns about deep suctioning, although there is no evidence to refute deep suctioning according to a recent Cochrane review.
 4. No clear evidence on how many passes should be made when suctioning but needs to be established each time suctioning is performed. One small study found no increase in secretion removal in two passes versus one pass.
 5. Saline should only be used as a lubricant for the catheter and never instilled in the endotracheal tube. Research has shown that it does not thin secretions, nor does it mobilize secretions.
 6. Head turning does not improve secretion removal and may be associated with intracranial pressure fluctuations and hemorrhage.
 7. A Cochrane review found utilization of a closed suctioning system that allows for suctioning without disconnection from the ventilator may have short term benefits such as decreased variability in oxygenation and heart rate. It was unable to assess the clinical relevance of

these benefits or to assess other outcomes and therefore is unable to make any implications for practice.

8. Neonate should be contained during suctioning to improve tolerance.
9. Nurse must stay at bedside and assure recovery from suctioning.

XIII. Artificial respirations through the use of assistive devices.

- A. Neonatal Resuscitation Program (NRP) certification is essential for any caregivers applying respirations through the use of assistive devices. Evidence exists for impact on peak pressure and tidal volume effects based upon handling of devices such as the anesthesia bag.
 1. Anesthesia bags that require an oxygen or air source to inflate
 2. Self inflating bags that do not require an oxygen or air source to inflate
 3. T-Piece devices to maintain PEEP
 4. May see use of these devices in the delivery room as well as the NICU, operating suites, or any areas delivering care to newborns
- B. Nurse has the responsibility to collaborate with respiratory therapy, physicians, ECMO technicians for the use of assistive devices.
- C. Nurse should check equipment at least once a shift to assure equipment is in proper working condition, has safety features such as pop-off valves that are functional and that equipment is easily accessible.

XIV. Transillumination (Chap. 22).

- A. As an adjunct to clinical assessment and radiographs
- B. May see a diameter larger than 1 cm around the light probe when placed on anterior chest or in midaxillary line with thoracic air leaks
- C. Edema, tape, equipment may decrease its usefulness

XV. Chest drainage devices (Chap. 72).

- A. Should be familiar with the set up and function of the drainage devices *before* they are needed as these are emergent procedures.
- B. Connections should be secured with tape.
- C. Tubing is typically very heavy and should be firmly secured to bed alleviating any tension.
- D. Drainage device should be assessed for air bubbling in water seal chamber in most devices.
- E. Chest tubes should be assessed for secretions and movement of air or secretions in the tubing.
- F. No benefit to milking chest tubes and may cause harm.
- G. Fluid removed should be assessed and documented at least once per 8 h shift unless clinical conditions call for increased monitoring.
- H. Dressing should be assessed for occlusiveness, drainage under dressing, condition of skin, and any foul odor or change in color of secretions.

- I. Should use a separate wall suction for clearing airway.
- J. Must have an alternate set up for emergent need of second set up or replacement of current set up ready at bedside. Should also have an emergent means available at the bedside for a qualified health-care professional to do a needle thoracentesis as a means to remove air quickly while setting up for tube thoracostomy.

XVI. Securing respiratory devices.

- A. Nurse must pay careful attention to the securing and maintenance of respiratory devices, such as the endotracheal tube, nasal prongs, chest tubes, monitoring devices, ECMO and other vascular catheters (such as venous and arterial access), and environmental control (such as probes for temperature).
- B. There are a number of devices on the market for the securing of ET tubes and nasal CPAP. Nurse must meet the goal of skin integrity and no accidental dislodging of tubes by newborn, caregivers, or family members.

XVII. Weighing.

- A. Need to establish frequency of weighing as part of daily plan of care.
- B. Need at least two personnel to weigh labile neonate; one person may weigh stable neonate.
- C. Preferable to disconnect ventilating devices while transferring to and from scale and reconnecting to ventilatory device while on scale and when returned to bed, if using a free standing scale. If in-bed scale, usually may leave connected to ventilator during weighing process.
- D. Assess neonate before and after weighing.

XVIII. Positioning.

- A. Much published data seems to favor prone positioning for optimizing respiratory performance of the neonate.
- B. May be additional benefit in raising head of bed slightly to allow gravity to contribute to expansion of lungs, although position should be changed to avoid pooling of secretions at base of lungs.
- C. Cochrane review of infant position during mechanical ventilation found prone positioning to slightly improve oxygenation. Remind parents that this facilitates respiratory care, and that infant is being continuously monitored. Once respiratory issues have resolved, "Back to Sleep" may be initiated (see below).
- D. Must reinforce American Academy of Pediatrics position that supine positioning during sleep is preferred for care *at home*, where there is no monitoring and 24-h bedside care.
- E. Massage therapy, touch therapy, stroke therapy have empirical reports of benefits.

- F. Kangaroo care may be beneficial as an adjunct for respiratory care.
 - 1. May kangaroo neonate receiving ventilation
 - 2. Must assist mother to transfer neonate to chest before mother sits in chair rather than handing neonate to mother who is sitting
- G. Co-bedding of multiples.
 - 1. Still in investigation, very limited data.
 - 2. Some limited anecdotal use in ventilated infants with improvement in respiratory status, weaning from ventilator, and no increase in spontaneous extubation, but must be approached cautiously until research is evident.

Suggested Reading

- Balaguer A, Escribano J, Roque M. Infant position in neonates receiving mechanical ventilation. *Cochrane Database Rev.* 2003. Taken from <http://www.nichd.nih.gov/cochrane/Balaguer/balaguer.htm>.
- Bassani M, Mezzacappa Filho F, Coppo M, Marba S. Peak pressure and tidal volume are affected by how the neonatal self-inflating bag is handled. *J Pediatr.* 2009;85(3):217–22.
- Chang Y, Anderson G, Dowling D, Lin C. Decreased activity and oxygen desaturation in prone ventilated preterm infants during the first postnatal week. *Heart Lung.* 2002a;31(1):34–42.
- Chang Y, Anderson G, Lin C. Effects of prone and supine positions on sleep state and stress responses in mechanically ventilated preterm infants during the first postnatal week. *J Adv Nurs.* 2002b;40(2):161–9.
- Claire N, Bancalari E, D’Ugard C, Nelin L, Stein M, Ramanathan R, Hernandez R, Donn SM, Becker M, Bachman T. Multicenter crossover trial of automated adjustment of inspired oxygen in mechanically ventilated preterm infants. *Pediatrics.* 2011;127:e76–83.
- Hodge D. Endotracheal suctioning and the infant: a nursing care protocol to decrease complications. *Neonatal Netw.* 1991;9(5):7–15.
- Loveless R, Demers B, Linn W. Approaching the RSV season with a nursing plan of action. *Pediatr Nurs.* 1995;21(6 Suppl):1–4.
- Pritchard M, Flenady V, Woodgate P. Preoxygenation for tracheal suctioning in intubated, ventilated newborn infants. *Cochrane Database Rev.* 2002. Taken from <http://www.nichd.nih.gov/cochrane/pritchard/pritchard.htm>.
- Solberg M, Hansen T, Bjork R. Nursing assessment during oxygen administration in ventilated preterm infants. *Acta Paediatr.* 2011;100(2):193–7.
- Spence K, Gillies D, Waterworth L. Deep versus shallow suction of endotracheal tubes in ventilated neonates and young infants. *Cochrane Database Rev.* 2003. Taken from <http://www.nichd.nih.gov/cochrane/Spence2/spence.htm>.
- Spence K, Smith J, Peat J. Accuracy of weighing simulated infants with in-bed and freestanding scales while connected and disconnected to a ventilator. *Adv Neonatal Care.* 2003b;3(1):27–36.
- Swinth J, Anderson G, Hadeed A. Kangaroo (skin to skin) care with a preterm infant before, during and after mechanical ventilation. *Neonatal Netw.* 2003;22(6):33–8.
- Wells D, Gillies D, Fitzgerald D. Positioning for acute respiratory distress in hospitalized infants and children. *Cochrane Database Syst Rev.* 2005;18(2):CD003645.

- Wielenga J, DeVos R, de Leeuw R, De Haan R. COMFORT scale: a reliable and valid method to measure the amount of stress of ventilated preterm infants. *Neonatal Netw.* 2004;23(2):39–44.
- Wilson G, Hughes G, Rennie J, Morley C. Evaluation of two endotracheal suction regimes in babies ventilated for respiratory distress syndrome. *Neonatal Netw.* 1992;11(7):43–5.
- Woodgate P. Tracheal suctioning without disconnection in intubated ventilated neonates. *Cochrane Database Rev.* 2001. Taken from <http://www.nichd.nih.gov/cochrane/Woodgate2/Woodgate.htm>.
- Wrightson D. Suctioning smarter: answers to eight common questions about endotracheal suctioning in neonates. *Neonatal Netw.* 1999;18(1):51–5.
- Yokum F. Nursing documentation. 2004. Taken from <http://www.awarenessproductions.com>.

Chapter 78

Transport of Ventilated Babies

Steven M. Donn and Molly R. Gates

I. Equipment

A. Goals of neonatal transport

1. Optimally, all infants requiring neonatal intensive care should be delivered at a facility capable of providing such services. Unfortunately, numerous circumstances arise which prevent this, including geographical and economic constraints, and unexpected complications of labor, delivery, or the neonatal period.
2. The next best option is maternal transport when time and circumstances permit the transfer of a mother with an identified high-risk pregnancy to a facility able to care for the infant.
3. When neither of these options is possible, transport of a critically ill newborn must be accomplished in a manner that maximizes safety and minimizes complications to the infant. Neonatal transport must be considered an extension of the Neonatal Intensive Care Unit, and the same philosophy of care delivered in the NICU should be delivered in the transport vehicle.

B. Transport vehicles

1. Ground ambulance

- a. The most frequently used vehicle
- b. Provides the most access to the patient during transport

S.M. Donn, MD, FAAP (✉)
Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonnmd@med.umich.edu

M.R. Gates, MA, MSN, RN-C
Perinatal Nursing, C.S. Mott Children's Hospital, University of Michigan
Health System, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5258, USA

- c. Enables the largest number of transport team members
 - d. Easy to stop vehicle in the event of patient deterioration and need for medical intervention
 - e. Subject to traffic delays, road conditions, and weather (though to a lesser extent than airborne vehicles)
 - f. Should be adaptable to special needs of neonatal transport
2. Helicopter
 - a. Provides a rapid means of transport
 - b. Not subject to traffic or road conditions, but weather conditions may preclude use
 - c. Size of vehicle may limit number of team members
 - d. Landing pad may not be adjacent to hospital, requiring extra time and possible ambulance use
 - e. Virtually no access to patient en route
 - f. Must land in event of patient deterioration
 - g. Requires special training of crew
 - h. Expensive
 3. Fixed wing aircraft
 - a. Enables long distance transport.
 - b. Subject to weather conditions.
 - c. Size of vehicle may limit number of team members.
 - d. Rapid, although travel time to/from airport and hospitals must be considered.
 - e. Intermediate access to patient en route; deterioration may be problematic.
 - f. Special problems at higher altitudes.
 - g. Expensive.
 4. Combination: At times, it may be advantageous to combine modes of transport, such as the “fly-drive” method. Transport team and only essential emergency equipment is flown to referring hospital, helicopter returns to tertiary facility immediately, while ambulance is dispatched with the remainder of transport equipment and possibly additional team members. This eliminates helicopter “down time” while infant is stabilized, and allows for use of a more stable environment for transport of infant.
- C. Transport incubator and related equipment
1. Several commercial types are available.
 - a. Self-contained types include virtually all necessary components as “built-ins,” which may offer a better price, although repairs may be costlier and may take the device out of service for a longer period of time.
 - b. More basic models are available, to which specific components can be added according to the specific needs of an institution.

2. Basic necessities

a. The incubator must be able to maintain the infant in a thermoneutral environment, and for small infants, infant servo-controlled heaters are recommended. This is especially important for winter climates that have a significantly low ambient temperature. Additional heat-conserving or heat-generating devices are necessary in colder climates.

- (1) Heat shield or thermal blanket
- (2) Exothermic chemical mattress

b. An electronic cardiorespiratory monitor, which should work well despite vehicle vibration or electrical interference.

c. A pulse oximeter with motion artifact correction.

d. A means of recording the temperature of the incubator and the baby.

e. A source of air and oxygen, including a blender and an analyzer, and the means to deliver increased FiO_2 to the infant.

f. A self-contained power source (battery) and the ability to be run by an external power source (e.g., wall electricity, vehicle generator or inverter).

g. Easy accessibility to the infant (e.g., portholes, front and side doors).

h. A means of securely anchoring the incubator within the transport vehicle.

i. All necessary resuscitative equipment, including:

- (1) Bag and masks (assorted sizes)
- (2) Laryngoscope and endotracheal tubes (assorted sizes)
- (3) Vascular access devices
- (4) Emergency medications and the means to deliver them

j. Adequate lighting, including a backup flashlight.

3. Recommended options

a. Transport ventilator, especially if transporting critically ill infants or transporting long distance

b. Communications device

- (1) Vehicle radio system
- (2) Cellular telephone

c. Vascular infusion pump(s)

d. Blood pressure monitoring device, either invasive or noninvasive

e. Transcutaneous $\text{TcPO}_2/\text{PCO}_2$ device or portable blood gas analyzer for long-distance transport of a critically-ill infant

D. Transport Equipment (Tables 78.1 and 78.2): Equipment should be readily available to treat any emergency that might occur at either the referring hospital or en route.

Table 78.1 Typical transport equipment

Adapters
Adhesive tape ½" and 1"
Alcohol wipes
Antiseptic ointment
Antiseptic swabs
Blood culture bottle
Blood supplies
BP transducer
Bulb syringe
Butterflies: 23, 25 g
Camera with film
Catheters: 22, 24 g
Chest tubes #10
Connectors
Cotton balls
DeLee suction tube
D ₁₀ W: 250 mL bag
Dressings, 4×4
Dressings, 2×2
Forceps, sterile
Gauze squares: see dressings
Gloves, sterile
Glucose screening strips
Heimlich valves
Hemostats, sterile
Labels
Lancets
Large bore tubing
Lubricating gel
Microbore tubing
Needles: 18, 21, 25 g
NG tubes: 5 and 8 Fr.
Occlusive dressing
Paperwork (extra)
Platelet infusion set
Pneumothorax aspiration set
Replegle tubes: 6 and 8 Fr.
Saline squirts
Scalpel
Scissors, sterile
Stopcocks
Stopcock plugs
Suction catheters: 6 and 8 Fr.
Suture: 4–0 silk
Syringes: TB
Syringes: 3 mL

(continued)

Table 78.1 (continued)

Syringes: 5 mL
 Syringes: 10 mL
 Syringes: 20 mL
 Syringes: 30 mL
 Syringes: 60 mL
 T-connectors
 Tape, plastic: ½" and 1"
 Tape measure, sterile
 Thermometer
 Toumey syringe: 60 mL
 UA catheters
 UA double lumen
 UAC tray
 Umbilical tape
 Waterproof adhesive tape

Table 78.2 Respiratory care transport equipment

Hood and aerosol tubing (include extra tubing)
 Venturi mask
 Stethoscope
 Infant restraints
 Chemical exothermic mattress
 Resuscitation bag
 Flashlight
 Cargo netting
 Wrench for medical gas "E" tanks
 Surfactant administration devices
 Electronic cardiorespiratory monitor
 ECG electrode patches and leads
 Blood pressure cable
 Neonatal mask
 Infant mask
 Manometer
 PEEP valve
 22 mm connectors (2)
 15 mm connectors (2)
 Rubber connector
 Endotracheal tubes
 2.5 mm (2)
 3.0 mm (2)
 3.5 mm (2)
 4.0 mm (2)
 Endotracheal tube adapters
 Endotracheal tube stylets (2)

(continued)

Table 78.2 (continued)

Pulse oximeter
Pulse oximetry probes with elasticized wrap (2)
Laryngoscope handle with spare batteries and bulb
Laryngoscope blades
Miller #0
Miller #1
Magill forceps
Hemostats and scissors
Adhesive tape
Adhesive solution
Cotton swabs
Adhesive remover
Nasal CPAP prongs, assorted sizes
Sterile water-soluble lubricant
Oxygen tubing (2)
Oxygen tubing connectors (2)
Flowmeter nipples (2)
Suction catheters, 6 Fr. (2)
Air and oxygen connectors
Nasal cannula, newborn
Nasal cannula, premature
Aluminum oxygen tank
Aluminum air tank
Inhaled nitric oxide and delivery system

- E. Transport Medications (Table 78.3): Medications should also be readily available, as well as the means to deliver them (e.g., syringes, diluents, catheter connectors). Medications must be secured and checked regularly for condition and expiration date.
- F. Miscellaneous issues
1. A digital camera is useful, both to give the parents a picture of the infant and to document any unusual physical findings.
 2. All necessary documents for the medical record as well as printed information given to the parents should be prepared in advance. Keeping them together by means of a clipboard works well.
 3. Team members must protect themselves at all times.
 - a. Dress appropriately for the weather.
 - b. Use flame-retardant clothing for air transport.
 - c. Use approved helmets for air transport.
 - d. Have provisions (e.g., snacks and drinks) for long-distance transports, especially if there is a likelihood of missing meals.
 - e. Always use seat belts.
 - f. Maintain current knowledge of transport supplies and procedures.
 4. Packs or containers for miscellaneous transport gear should be lightweight, sturdy, well-labeled, and secure. Housing all supplies needed for a given procedure in one compartment is useful.

Table 78.3 Typical transport medications

Adenosine 3 mg/mL
Ampicillin 250 mg
Aquamephyton 10 mg/mL
Atropine 0.1 mg/mL
Calcium gluconate 10%
Dexamethasone 4 mg/mL
Dextrose in water 25%
Diazepam 5 mg/mL
Digoxin 25 mcg/mL
Dobutamine
Dopamine 40 mg/mL
Epinephrine 1:10,000
Furosemide 10 mg/mL
Gentamicin 10 mg/mL
Glucagon and diluent
Heparin
Isoproterenol 1 mg/5 mL
Lidocaine 1%
Lidocaine 2%
Lorazepam 2 mg/mL
Midazolam 1 mg/mL
Narcan 0.4 mg/mL
Pancuronium 1 mg/mL
Potassium chloride
Prostaglandin E (PGE)
Sodium bicarbonate 4.2% (0.5 mEq/mL)
Sodium chloride
Sterile water
THAM
5% Albumin
Morphine 0.5 mg/0.5 mL
Phenobarbital 30 mg
Phenobarbital 60 mg
Surfactant

II. Stabilization of the transported newborn

A. Basic stabilization upon arrival

1. Respiratory

a. Assess the adequacy of gas exchange

(1) Clinical assessment

- (a) Breath sounds
- (b) Chest excursions
- (c) Skin color
- (d) Presence of distress

- (2) Laboratory assessment
 - (a) Blood gas analysis
 - (b) Chest radiograph
 - b. Airway management
 - (1) Patency (suction if necessary).
 - (2) If already intubated and tube position is satisfactory, secure tube adequately.
 - (3) If not intubated, consider elective intubation if there is any chance that this might become necessary en route. It is safer (and easier) to do this under controlled conditions at the referring hospital than in the back of an ambulance or while in flight.
 - c. Place an orogastric tube (especially important for air transport).
2. Cardiac
- a. Assess tissue perfusion, treat if inadequate.
 - (1) Blood pressure
 - (2) Capillary refill time
 - (3) Urine output
 - b. Auscultation
 - (1) Murmur
 - (2) Abnormal heart sounds
 - (3) Abnormal rhythm
 - c. Chest radiograph
 - d. If cyanotic congenital heart disease suspected, consider starting infusion of Prostaglandin E (consult with neonatologist or cardiologist before doing so)
3. Hematologic
- a. Check for sites of active bleeding.
 - b. Assure all vascular connections are secure.
 - c. Check hematocrit if not already done. Consider transfusion if low and infant is critical, and transport is anticipated to be long.
4. Metabolic
- a. Perform glucose screen. If low, check serum glucose and treat.
 - b. Assure adequate glucose load during transport. Stress may increase consumption.
 - c. Check baby's temperature and maintain thermoneutrality. Pre-warm transport incubator before transferring baby to it.

5. Vascular access

- a. It is generally best to achieve vascular access prior to departing the referring hospital in the event that an emergency arises en route.
- b. A well placed peripheral venous line is usually sufficient.
- c. If difficulty in securing peripheral venous access, consider placing an umbilical venous catheter. Confirm position radiographically before infusing medications through it (Chap. 15).
- d. An umbilical artery catheter (Chap. 15) is generally not needed for transport unless no other vascular access can be achieved. It is an elective procedure, which can be time-consuming and can significantly delay the departure and prolong the transport. Many community hospitals are ill-equipped to handle a complication. As a rule, this procedure is best left until the infant is admitted to the NICU.

6. Miscellaneous issues

- a. Make sure the infant is secured within the transport incubator. Retaining straps should be used but must not be too tight to impair thoracic excursions.
- b. Tighten all connections (e.g., endotracheal tube adapter, ventilator circuit, vascular catheter connections, power lines) before departing. Label all lines.
- c. Consider the use of infant “ear muffs” to decrease noise exposure for air transports.
- d. Always have spare batteries for equipment that requires them.
- e. Give the parents an opportunity to see and touch the infant before departing the referring hospital.
- f. Be sure baby is properly identified.
- g. Collect records from referring hospital to accompany infant.

B. Stabilization during transport

1. If the infant was well stabilized in the referring hospital, there should be little else necessary once underway.
2. Check to be sure all of the vehicle equipment is functioning at the time the switch from incubator to vehicle is made.
 - a. Power (generator or inverter)
 - b. Gas (air and oxygen) sources
 - c. Suction source
3. Be sure the transport incubator is securely anchored and that there is no loose equipment or tanks, which could cause a hazard en route.
4. Monitoring of the infant during the transport should be no different than that which is done in the NICU.
5. Should the infant unexpectedly deteriorate en route, it is generally best to stop the vehicle (this may mean landing if in a helicopter) while attending

to the infant. It is extremely difficult to perform resuscitative procedures and draw up and administer medications in a moving vehicle, and to do so places both the patient and the transport team members at risk for injury.

C. After the transport

1. A thorough transport note should be written in the medical record to document the events of the transport, as well as any treatments rendered, and how the baby tolerated any procedures.
2. All supplies should be promptly replenished.
3. Any mechanical problems (vehicle, equipment, or other) should be reported and corrected immediately.
4. Give feedback to the referring physician and notify the parents that the baby arrived safely.

III. Special considerations

A. Intensive care

1. Although transport vehicles are an attempt at extending intensive care services to referring hospitals, they are not intensive care units. One of the most difficult decisions during neonatal transport is deciding whether a specific procedure should be performed in the referring hospital/transport vehicle or deferred until admission to the NICU. Some aspects to consider include:
 - a. Urgency of the procedure in light of the patient's condition (i.e., elective, semi-elective, or emergent)
 - b. Availability of experienced personnel to assist
 - c. Suitability of available equipment
 - d. Ability to handle a major complication, if it occurs
 - e. Adequacy of monitoring the patient during the procedure
2. Some procedures which are of an elective nature should be considered in view of the difficulty with which they are performed in a transport vehicle.
 - a. Endotracheal intubation. Control of the airway in a baby with respiratory distress is crucial. Do not wait until the baby is in marked distress to intubate.
 - b. Vascular access. Placement of a peripheral intravenous catheter prior to departure from the referring hospital is strongly advised. This is an extremely difficult procedure in a dimly lit and moving vehicle, especially if the baby is hypotensive. It also enables prompt treatment of problems such as hypoglycemia.

3. If transport to an ECMO facility is being considered, remember the following:
 - a. Not all transport teams can provide inhaled nitric oxide during the transport. Do not delay transfer for PPHN if this is the case.
 - b. It is, at present, infeasible in most instances to transport a baby on high frequency ventilation. If a baby cannot be safely managed temporarily by conventional or manual ventilation, transport may be ill-advised.
- B. Effects of altitude
1. Impact on respiratory status
 - a. The partial pressure of oxygen decreases as altitude increases; thus, the availability of oxygen to the baby decreases and alveolar hypoxia increases. The baby must work harder to achieve satisfactory gas exchange.
 - b. The cabins of fixed-wing aircraft are either pressurized or nonpressurized. If nonpressurized, this effect of altitude will occur early. Pressurized cabins generally have a pressure equivalent to that at 8,000 ft rather than atmospheric pressure at sea level.
 - c. These effects must be appreciated in the management of respiratory insufficiency. They underscore the need for close monitoring (i.e., pulse oximetry) as well as anticipating the need for increasing support as altitude is increased.
 2. Impact on contained gases
 - a. As altitude increases, and thus barometric pressure decreases, the volume of contained gases also increases.
 - b. This effect must be taken into consideration in the management of the infant.
 - (1) Gas in the stomach and bowel will expand, potentially aggravating respiratory distress by impinging on the diaphragm. Be sure that an orogastric or nasogastric tube is in place to vent the stomach.
 - (2) Abnormal accumulations of gas in the chest (e.g., pulmonary interstitial emphysema, pneumomediastinum) can also expand, leading to pneumothorax. Observe closely and be ready to intervene.
 - c. The effects of altitude must also be considered in treatments.
 - (1) Medications and fluids are packaged at sea level, and thus are at higher pressure at altitude. Take caution when drawing up medications from vials.
 - (2) As the aircraft descends, carefully observe gravity drip infusions; external pressure may create a gradient which causes reversal of flow from the baby with subsequent blood loss.

C. Miscellaneous effects on the infant

1. Noise and vibration. While not totally avoidable, some measures can be taken to minimize their effects.
 - a. Muffle noise by using “ear muffs” or cotton inserts.
 - b. Make sure vehicle suspension is in good order.
 - c. Avoid excessive speed or poorly maintained roads, if possible.
2. Cold stress.
3. Position infant optimally for clinical support and to maximize caregivers’ ongoing assessment.

D. Miscellaneous effects on the transport team

1. Motion sickness, aversion to exhaust fumes
2. Stress
3. Safety issues

E. Effects on the family

1. Separation from the infant (especially for the mother)
2. Economic hardship
3. Psychosocial stress

F. Systems issues

1. Organized procedures must be in place and communicated to all potential participants for requesting, accepting, dispatching, and conducting neonatal transports.
2. Periodic review of transports enables identification and correction of system problems.
3. Contingency planning and prior consideration of unusual circumstances improves response and lessens stress.

Suggested Reading

- Bossley CJ, Cramer D, Mason B, Smyth J, et al. Fitness to fly testing in term and ex-preterm babies without bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed.* 2011, Sept 13 (epub ahead of print).
- Donn SM, Faix RG, Gates MR. Emergency transport of the critically ill newborn. In: Donn SM, Faix RG, editors. *Neonatal emergencies*. Mt. Kisco, NY: Futura Publishing Co; 1991. p. 75–86.
- Donn SM, Faix RG, Gates MR. Neonatal transport. *Curr Prob Pediatr.* 1985;15:1–63.
- Donn SM, Gates MR. Neonatal transports. In: Donn SM, editor. *Michigan manual of neonatal intensive care*. 3rd ed. Philadelphia: Hanley & Belfus; 2003. p. 447–55.
- Gates MR, Geller S, Donn SM. Neonatal transport. In: Donn SM, Fisher CW, editors. *Risk management techniques in perinatal and neonatal practice*. Armonk, NY: Futura Publishing Co; 1996. p. 563–80.
- Lilly CD, Stewart M, Morley CJ. Respiratory function monitoring during neonatal emergency transport. *Arch Dis Child Fetal Neonatal Ed.* 2005;90:F82–3.

Chapter 79

Home Ventilation

Wan Chong Tsai

- I. Home mechanical ventilation: assisted ventilation outside the hospital environment in the home
- II. Indications for long-term home mechanical ventilation
 - A. Recognition of chronic respiratory failure
 1. Result of an uncorrectable imbalance in the respiratory system, in which ventilatory muscle power and central respiratory drive are inadequate to overcome the respiratory load
 2. Leads to ventilator dependency
 3. Ventilator support normalizes gas exchange and alveolar ventilation through the following mechanisms:
 - a. Relieves respiratory load
 - b. Reduces respiratory muscle work
 - c. Improves O₂ and CO₂ sensitivity
 - B. Medical assessment for initiation of long-term mechanical ventilation
 1. Clinical characteristics of pediatric ventilator dependency
 - a. Child who has recovered from acute respiratory failure but remains incapable of sustaining normal gas exchange without mechanical ventilation support
 - b. Absence of spontaneous respiration
 - c. Failure to extubate after many attempts by skilled respiratory care team
 - d. Multiple hospitalizations for recurrent acute respiratory failure requiring mechanical ventilation
 - e. Disease states that benefit from home ventilation

W.C. Tsai, MD, MS (✉)

Department of Pediatric Pulmonology, Promedica Toledo Children's Hospital
and University of Toledo, 2121 Hughes Drive, Suite 640, Toledo, OH 43606, USA

2. Diseases that are progressive with resultant severe respiratory failure requiring support can be successfully controlled by assisted mechanical ventilation to sustain life
 - a. Restrictive lung diseases:
 - (1) Thoracic restrictive disorders
 - (2) Diffuse pulmonary fibrosis
 - b. Chronic obstructive lung diseases:
 - (1) COPD
 - (2) Cystic fibrosis
 - (3) Bronchiectasis
 - c. Mixed lung diseases:
 - (1) Bronchopulmonary dysplasia (BPD)
 - (2) Tracheobronchomalacia
 - d. Central hypoventilation syndromes:
 - (1) Congenital
 - (a) Idiopathic
 - (b) Anatomic (Arnold–Chiari malformation, myelo-meningocele)
 - (2) Acquired
 - (a) Traumatic
 - (b) Vascular
 - (c) Infectious
 - (d) Surgical diseases affecting the respiratory centers
 - e. Ventilatory muscle dysfunction
 - (1) CNS diseases
 - (2) Polyneuropathy, polyradiculopathy
 - (3) Myopathy, muscular dystrophy
 - (4) Chest wall diseases
 3. Adequate physiologic and clinical patient stability for home ventilation
 - a. Disease process does not fluctuate greatly for >1 month
 - b. Multiorgan coexisting conditions are well-controlled
 4. Alternate means of support considered (failed trial, deemed inadequate or undesirable)
 5. Ventilator dependency demonstrated in order to continue living or to improve the quality of life
- C. Best candidates for home ventilation
1. Young otherwise healthy

2. Except for isolated disorder of the respiratory tract (BPD)
3. Stable disorders (spinal cord injury, post polio)
4. Slowly progressive disorders (neuromuscular disorders)

III. Goals of long-term mechanical ventilation

- A. To provide medically safe assisted ventilation in the home while optimizing the quality of life without recreating the hospital environment
- B. To extend life
- C. To provide an environment, which enhances individual potential and quality of life
- D. To reduce morbidity
- E. To improve physical and physiologic function
- F. To be cost-effective

IV. Chronic ventilation strategy

- A. Use ventilator to provide enough support to normalize alveolar hypoventilation
- B. Wean as soon as respiratory status stabilizes and can maintain alveolar ventilation without support
 1. SaO₂ normal ± O₂ supplement (<4 LPM for home)
 2. End tidal CO₂ ~ normal
- C. Work of breathing is eliminated

V. Timing of modifications and weaning is dependent on disease state

- A. Stable disorders (spinal cord injury)—never weanable
- B. Slowly progressive disorders (neuromuscular disorders)—escalate support over years
- C. Slowly recovering disorders (BPD)—reducing support over 1–3 years but still long-term expectation

VI. Nonmedical assessment for initiation of long-term mechanical ventilation

- A. Available resources in outpatient medical team, home, and community
- B. Physical environment
- C. Attendant care needs

VII. Modes and types of portable home ventilators

- A. Performance of the ventilator and settings are more important than ventilator mode
- B. Delivery
 1. Volume
 - a. First mode for polio, fixed tidal volume, no leak compensation
 - b. Not tolerated in high airway resistance, low compliance, small children

2. Negative vs. positive pressure ventilation

- a. Positive pressure ventilators are the most commonly used for children
- b. Better triggering to overcome low flow or inappropriate spontaneous breath rate

C. Control, assist/control, IMV, and weaning modes

1. Choice of mode is determined by:

- a. Mechanisms of respiratory failure in each child
- b. Machine performance specifications
- c. Size of child, ability to trigger ventilator
- d. Cuffed vs. uncuffed tracheostomy tube and constancy or magnitude of leaks around the tracheostomy tube

VIII. Monitoring systems

A. Observation of clinical variables

1. Alleviation of signs
2. May be more important and more effective as invasive monitoring

B. Assessment of physiologic variables

1. Acute: 24 h for arterial blood gas normalization
2. Chronic:
 - a. Polysomnogram—critical for patient–ventilator asynchrony, air leaks
 - b. Arterial blood gas while awake
 - c. Nocturnal oximetry and capnometry
 - d. Respiratory muscle evaluation—work of breathing
 - e. Pulmonary function, if able to perform

IX. Complications of home mechanical ventilation

A. Tracheostomy tube

1. Obstruction of the tracheostomy tube is the most common early complication
 - a. Mucus plugging
 - b. Granulation tissue
2. Accidental decannulation
3. Increased respiratory infections (e.g., tracheobronchitis or pneumonia)
4. Airway injuries
 - a. Tracheal stenosis
 - b. Tracheal dilatation
 - c. Tracheomalacia

5. Stoma injuries
 - a. Tracheoinnominate fistula
 - b. Poor wound healing
- B. Acute respiratory exacerbations
 1. Respiratory exacerbations
 - a. Definition is nonspecific
 - b. Clinical signs of lower respiratory tract infection include fever, leukocytosis, purulent sputum, change in tracheal secretions, worsening respiratory parameters on baseline ventilator settings (desaturation is common)
 - c. Absence of infiltrate on chest X-ray (ventilator-associated tracheobronchitis)
 - d. Presence of infiltrate on chest X-ray (ventilator-associated pneumonia vs. health care-associated pneumonia vs. nosohusial pneumonia)
 2. Acute respiratory failure is expected during illnesses above baseline of chronic respiratory failure
 3. Patients have reduced pulmonary reserve to handle acute illness
 4. Management
 - a. Escalate support briefly and temporarily until recovery from acute illness
 - b. Escalate pulmonary inhaled regimen and pulmonary hygiene or clearance
- C. Prolonged mechanical ventilation
- D. Pulmonary hypertension, cor pulmonale

Suggested Reading

- Eigen H, et al. Home mechanical ventilation of pediatric patients. American Thoracic Society Position Paper. *Am Rev Respir Dis.* 1990;141(1):258–9.
- Johnston J, et al. Care of the Child with a Chronic Tracheostomy. American Thoracic Society Consensus Statement. *Am J Respir Crit Care Med.* 2000 Jan;161(1):297–308.
- Long-term invasive mechanical ventilation in the home. American Association for Respiratory Care clinical practice guideline. *Respir Care.* 2007;52(8):1056–62.
- Respiratory Care of the Patient with Duchenne Muscular Dystrophy. American Thoracic Society Consensus Statement. *Am J Respir Crit Care Med.* 2004;170(4):456–65.
- Wetmore R, et al. Tracheal suctioning in children with chronic tracheostomies: a pilot study applying suction both while inserting and removing the catheter. *Ann Otol Rhinol Laryngol.* 1999;108(7(Part 1)):695–9.

Chapter 80

Discharge Planning and Follow-Up of the NICU Graduate

Win Tin and Mithilesh Lal

I. Discharge planning of the NICU graduate

A. Introduction: Hospitalization of an ill newborn is not only costly, but also very stressful for the family. Discharging the neonatal intensive care unit (NICU) patient early has several advantages, including enhancement of family/infant bonding, provision of better environment for infant development, and reduction in cost. Discharging too early, on the other hand, can impose risk of deterioration of an infant's condition and can lead to hospital readmissions, thus adding further stress on the family. Therefore, an effective discharge planning is an important factor to make the discharge process as positive and stress free as possible.

B. Essential features of effective discharge planning:

1. Safe and effective transition from hospital to community care and preparation of caregivers from the early stages through education
2. Customizing needs of an individual infant and family
3. Involving multidisciplinary agencies, as appropriate
4. Avoiding duplication of services and minimizing disruption to the family
5. Providing good communication between the NICU and community-based primary care providers
6. Simplifying the care of an infant without risking major changes immediately prior to discharge
7. Identifying unresolved medical issues and making appropriate follow-up arrangements

W. Tin, FRCPCH (✉) • M. Lal, FRCPCH
Department of Neonatal Medicine, The James Cook University Hospital,
Middlesbrough, UK TS4 3BW
e-mail: win.tin@stees.nhs.uk

C. Assessment of readiness for discharge

1. Assessment of infant

- a. Healthy infants can be considered ready for discharge if they:
 - (1) Maintain temperature in an open bed
 - (2) Feed well orally and maintain appropriate growth
 - (3) Do not require cardiorespiratory monitoring
- b. Infants with specific ongoing problems need individualized discharge plans; they should be considered ready for discharge only when the specific needs can be provided at home by the parents, with the support of care providers in the community.
- c. Common problems among NICU graduates include bronchopulmonary dysplasia requiring home oxygen therapy, and long-term feeding problems requiring nasogastric tube feeding. Community nurse specialists/practitioners play a vital role in these circumstances.

2. Family assessment should in fact start from the time of the admission of an infant to the NICU and include:

- a. Parenting skills and their willingness to take responsibility
- b. Parental experience and understanding of routine infant care and ability to cope with specific problems
- c. Family structure and extended family support
- d. Parental medical and psychological history
- e. Home environment
- f. Financial concerns
- g. Cultural differences and language difficulties

D. Predischarge evaluation and examination

1. Specific evaluation and screening of NICU graduates

- a. Ophthalmologic examination
 - (1) Routine retinopathy of prematurity (ROP) screening for all infants with risk factors, according to guidelines (Chap. 75).
 - (2) Specific eye examination should be arranged for those with congenital infections, congenital eye abnormalities, chromosomal abnormalities, and absent red reflex.
- b. Hearing screening: Universal screening has become the standard of care; otherwise, a risk-based approach should include infants with neonatal meningitis or encephalitis, severe hyperbilirubinemia, congenital infection, congenital malformation of the ear, prolonged use of oto-toxic drugs (such as aminoglycosides), following hypoxic-ischemic injury, and with a family history of sensorineural hearing loss. Prematurity *per se* is also considered a high risk factor.

- c. Cranial ultrasound screening for hemorrhagic and/or ischemic brain injuries in high-risk infants according to individual NICU guidelines. *A structurally normal cranial sonogram does not rule out long-term neurodevelopmental problems* and parents need to be aware that follow-up of these infants remains the most important part of the ongoing assessment.
 - d. Immunizations: Preterm infants should receive immunizations based on chronological age using the same dosage as in term counterparts.
 - e. Candidates for RSV prophylaxis with palivizumab should be identified prior to discharge, and should preferably receive the first dose in the NICU in season.
2. PredischARGE examination is essential to ensure that good general health and growth are maintained in an infant who is ready for discharge. It also identifies problems requiring further evaluation (e.g., heart murmur, unstable hip). However, a normal predischARGE examination does not give complete reassurance and the parents need to be aware of this.
- E. Discharge summary (letter) and communication
1. Written information should be made available to the primary care providers and the parents.
 2. All medical terminology should be explained to the parents and the discharge letter must include:
 - a. Infant's particulars (name, date of birth, address, etc.)
 - b. Date of admission and discharge
 - c. List of important medical problems
 - d. Brief clinical summary
 - e. Ongoing problem(s) at the time of discharge
 - f. Medications, doses, concentrations, and administration times
 - g. Instruction on immunizations
 - h. Plans for follow-up and further assessments
- II. Follow-up of the NICU graduate
- A. NICU graduates are at high risk of adverse neurodevelopmental outcome and hence, carefully planned follow-up forms an essential part of NICU service.
- B. Importance of follow-up.
1. For the child
 - a. Early identification of major problems of perinatal origin (e.g., cerebral palsy, developmental delay, major hearing, or visual impairment): This facilitates any further diagnostic tests, assessment, and involvement of appropriate professionals and agencies.
 - b. Screening for other medical problems (e.g., strabismus, speech delay, growth failure) so that early remedial measures can be implemented.
 - c. Maintenance of optimum health in order to achieve better potential for growth and development.

2. For the parents/caregivers

- a. Support to families of children with special needs: It is important that one “lead” clinician coordinates the infant’s care with the help and support of other professional agencies and services to minimize confusion and to provide consistency of care and advice.
- b. Counseling to the caregivers regarding the child’s problems and its relationship to perinatal events, probable prognosis of the condition, appropriate investigations, and the results of various assessments.
- c. Advice on immunization, medications, diet, as well as the need for other specialists’/therapists’ involvement.
- d. Reassure caregivers and address concerns regarding the child’s condition and progress.

3. For the professionals/institutions

- a. Follow-up studies/programs (hospital based or population based) are very useful as an audit process:
 - (1) To evaluate and improve the standards of neonatal intensive care
 - (2) To monitor changing patterns of prognosis (mortality and morbidity) with time
 - (3) To evaluate newer treatment and interventions, where the long-term neurodevelopmental outcome is used as a primary outcome measure
 - (4) To provide reliable sources of data/information for counseling
- b. Follow-up programs/clinics also provide training opportunities for professionals.

C. Who should be followed?

1. This depends to a great extent on the resources available.
2. Commonly used categories of babies for follow-up include the following.
 - a. Very preterm and/or very-low-birth-weight infants (<32 weeks’ gestation and/or <1,500 g at birth): Accurately assessed gestation is a better predictor than birth weight for long-term morbidity. Outcome at 2 years is already part of National Neonatal Audit Program (NNAP) in the UK. This program requires 2-year outcome data on all infants <30 weeks’ gestation so that rates of normal survival can be compared across units (see Appendix).
 - b. All NICU graduates who required mechanical respiratory support.
 - c. Small-for-gestational-age babies (birth weight or head circumference more than two standard deviations below the mean for gestational age).
 - d. Babies with perinatal neurologic problems, such as hypoxic-ischemic encephalopathy, known ischemic and/or hemorrhagic brain lesions, persistent ventriculomegaly, microcephaly, and those with abnormal neurologic behavior (neonatal convulsion, hypotonia, etc.).

- e. Hydropic infants, from any cause.
- f. Babies who had intrauterine or severe perinatal infections.
- g. Babies who had metabolic derangements, such as persistent hypoglycemia or hyperbilirubinemia, requiring exchange transfusion, etc.
- h. Babies with congenital abnormalities.
- i. Babies exposed to toxic agents (e.g., drugs) in utero.

D. Who should follow NICU graduates?

1. This varies from one unit to another depending on the structure and resources, but the follow-up team should ideally consist of:
 - a. The “lead” clinician (usually, a developmental pediatrician), whose role is to coordinate between the families and other appropriate professionals/agencies
 - b. Community (visiting) nurse or nurse practitioner
 - c. Pediatric physiotherapist
 - d. Pediatric dietician
2. The NICU follow-up team may often need support and consultation from other specialties, such as ophthalmology, pediatric surgery, orthopedic surgery, neurosurgery, neurology, genetics, audiology, speech and language therapy, psychology, and occupational therapy. However, it is important that the family relies upon one named clinician who coordinates and communicates with other professionals involved in the care of the child.

E. Components of follow-up assessment

1. Listening to the parents/caregivers and addressing their concerns is probably the most important part of follow-up.
2. Anthropometric assessment: Weight, length, and head circumference should be regularly monitored.
3. System review, particularly any health problems; feeding and bowel habits.
4. Assessment of vision and hearing: Some children may need further referral for detail assessment.
5. Neurological/neurodevelopmental assessment:
 - a. Assessment of posture, tone, reflexes, and presence of primitive reflexes. Joint assessment may prove very useful.
 - b. Assessment of gait and detailed neurological examination in older children.
 - c. Achievement of developmental milestones: It is appropriate to correct for prematurity for children who are chronologically <24 months, especially if they were born extremely preterm.
 - d. Follow-up programs in some centers may also include more structured developmental assessments, such as the Bayley Scales of Infant Development, Griffiths Mental Developmental Scales, etc.

6. Systemic examination.
 7. Review of medications (including oxygen therapy); some may need to be discontinued, whereas others may need adjustment of dosage.
 8. Check whether all the immunizations have been given and all necessary screening tests have been completed.
 9. Infants with BPD may require additional follow-up by pediatric pulmonologists, with testing of lung function and mechanics where indicated.
- F. How often and how long should NICU graduates be followed up?
1. This depends on the needs of the child and family and also on the resources available. Problems, such as minor cognitive and learning problems, clumsiness, or poor attention span, are more common among NICU graduates than in the normal-term counterparts, and ideally NICU graduates should be followed until they are of school age or penultimate to adulthood.
 2. Most do not need follow-up regularly once their growth and development are satisfactorily progressing.
 3. Communication between the follow-up team and the community pediatrician/school is important if the child needs long-term follow-up, mainly because of potential education difficulties.
- G. In summary, follow-up of NICU graduates is essential to facilitate optimal care for the child and family, advancement of perinatal services, and to ensure the provision of appropriate support services for these children.

Appendix: NNAP 2-year Corrected Age Outcome Proforma

TRPG/SEND/NNAP 2-YEAR CORRECTED AGE OUTCOME FORM

PLEASE DO NOT COMPLETE THIS FORM IF THE CHILD IS ACUTELY ILL

Name & Designation of person completing form _____
 Hospital of Birth _____
 Infant's name _____ Infant's NHS No _____
 Date of Birth ____/____/____ Date of assessment ____/____/____
 Gestation at birth (completed weeks) _____ Sex: Male / Female
 Reason if child not assessed: Deceased post discharge / lost to follow up _____
 Full Current Post Code _____ Date of death if applicable ____/____/____
 Birth weight _____ Current hospital of follow up: _____

1. Neuromotor	No	Yes	Don't Know
a. Does this child have any difficulty walking?			
b. Is this child's gait non-natural or abnormal reducing mobility?			
c. Is this child unable to walk without assistance?			
d. Is this child unsteady or needs to be supported when sitting?			
e. Is this child unable to sit?			
f. Does this child have any difficulty with the use of one hand?			
g. Does this child have difficulty with the use of both hands?			
h. Is this child unable to use hands (i.e. to feed)?			
2. Malformations:			
a. Does this child have a malformation identified at birth within the first 2 yrs?			
b. Does this malformation impair daily activities despite assistance?			
3. Respiratory & CVS system:			
a. Does this child have limited exercise tolerance with or without treatment?			
b. Does child require supplemental oxygen or other respiratory support			
4. Gastro-intestinal Tract:			
a. Is this child on a special diet? If yes, what diet?			
b. Does this child have a stoma?			
c. Does this child require TPN, NG or PEG feeding?			
5. Renal:			
a. Does this child have renal impairment, no treatment?			
b. Is this child on dietary or drug treatment for renal impairment?			
c. Is this child having renal dialysis or awaiting renal transplant?			

1) Does this child have Cerebral Palsy? Yes No

If yes, please classify:

Spastic bilateral: 2 limb involvement	
Spastic bilateral: 3 limb involvement	
Spastic bilateral: 4 limb involvement	
Hemiplegia: Right sided	
Hemiplegia: left sided	
Dyskinetic/ dystonic/ choreo-athetoid	
Not classifiable	

2) Please give diagnosis: _____

Bayley III (if performed) – please enter RAW scores	
Cognitive	
Receptive language	
Expressive language	
Fine Motor	
Gross motor	
Social emotional	
Adaptive behaviour (enter sum of scaled scores)	
Notes	

6. Neurology:	No	Yes	Don't Know
a. Has this child had a fit or seizure in the past 12 months?			
b. Is this child on any anticonvulsants?			
c. Has this child had more than 1 seizure a month despite treatment?			
d. Has this child ever had ventriculo-peritoneal shunt inserted?			
7. Growth: Give date of measurements if different from date of assessment _____			
Weight _____ kg Date _____			
Length _____ cm Date _____			
Head circumference _____ cm Date _____			
8. Development	No	Yes	Don't Know
a. Is the child's development between 3-6 months behind corrected age?			
b. Is the child's development between 6-12 months behind corrected age?			
c. Is the child's development more than 12 months behind corrected age?			
d. Will you be referring the child for a detailed neurodevelopmental assessment?			
e. If child had detailed neurodevelopmental assessment, provide name of the test:			
9. Neurosensory:			
a. Does this child have a hearing impairment?			
b. Does this child have hearing impairment corrected by aids?			
c. Does this child have hearing impairment not correctable with aids?			
d. Does this child have any visual problems (including albinism)?			
e. Does this child have visual deficit that is not fully correctable?			
f. Is this child blind or sees light only?			
10. Communication			
a. Does this child have any difficulty with communication?			
b. Does this child have difficulty with speech (<10 words/phrases)?			
c. Does the child have <5 meaningful words, vocalisations or signs?			
d. Does this child have difficulty with understanding outside of familiar context?			
e. Is this child unable to understand words or signs?			
Special Questions:			
a. Is this child on at-risk register, fostered or adopted?			
b. Was this child difficult to test? If yes, circle appropriate below: (1) tired, (2) poor attention, (3) difficult to engage, (4) other			

Note: If answering 'yes' to questions 1a - 1h, 2b or 3e please classify/enter score on the reverse of this form

Griffiths (if performed) – please enter RAW scores	
A Locomotor	
B Personal and social	
C Hearing and Language	
D Eye and hand coordination	
E Performance	
F Practical reasoning	
Notes	

Schedule of Growing Skills (if performed) – please enter RAW scores	
Locomotor	
Manipulative	
Interactive Social	
Self-care social	
Hearing and Language	
Speech and Language	
Visual	
Notes	

This proforma was developed by the TRPG Outcome Group: it is used with their permission

Suggested Reading

- AAP policy statement. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2006;117(2):572–6.
- Allen MC. The high risk infant. *Pediatr Clin North Am*. 1993;40:479–90.
- Damato EG. Discharge planning from the neonatal intensive care unit. *J Perinat Neonatal Nurs*. 1991;5:43.
- Edwards M. Discharge planning. In: Avery G, Fletcher M, MacDonald M, editors. *Neonatology: pathophysiology and management of the newborn*. Philadelphia: J.B. Lippincott; 1994. p. 1349–54.
- Johnson S, Fawke J, Hennessy E, Rowell V, Trikic R, Wolke D, Marlow N. Neuro-developmental disability through 11 years of age in children born before 26 weeks of gestation. *Pediatrics*. 2009;124:e249–57.
- Marlow N, Wolke D, Bracewell M, Samara M. Neurologic and developmental disability at 6 years of age following extremely preterm birth. *N Engl J Med*. 2005;352(1):9–19.
- McCormick MC, Stuart MC, Cohen R, et al. Follow up of NICU graduates: why, what and by whom. *J Intensive Care Med*. 1995;10:213–25.
- Royal College of Paediatrics and Child Health; National Neonatal Audit Programme (NNAP): <http://www.rcpch.ac.uk/nnap>.
- Tin W, Wariyar U, Hey E. Changing prognosis for babies of less than 28 weeks' gestation in the north of England between 1983 and 1994. *BMJ*. 1997;314:107–11.
- Wood NS, Marlow N, Costeloe K, et al. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med*. 2000;343:378–84.

Part XIV
Ethical and Legal Considerations

Chapter 81

Initiation of Life Support at the Border of Viability

Naomi Laventhal, Joanne Lagatta, and William Meadow

- I. Important considerations regarding resuscitation of infants at the borderline of viability
 - A. Evidence regarding resuscitation techniques in this population
 - B. Guidelines for who should be resuscitated in the delivery room
 - C. Considerations regarding withdrawal of resuscitative efforts
- II. Recent evidence for resuscitation techniques at the borderline of viability
 - A. Regulation of supplemental oxygen.
 - 1. Resuscitation with 100% oxygen has been shown to lead to hyperoxemia even in extremely preterm infants; conversely, extremely preterm infants respond poorly to resuscitation with room air.
 - 2. Pulse oximetry and the use of blended oxygen in the delivery room have been used safely in extremely preterm infants and are now recommended for use.
 - B. Ventilation strategies.
 - 1. An initial sustained inflation by nasal CPAP compared to face mask ventilation has been shown in some (but not all) studies to decrease the need

N. Laventhal, MD, MA (✉)
Department of Pediatrics, University of Michigan C.S. Mott Children's Hospital, 8-621 Mott
Hospital SPC 4254, 1540 E. Medical Center Drive 4, Ann Arbor, MI 48109-4254, USA
e-mail: naomilav@med.umich.edu

J. Lagatta, MD, MS
Department of Pediatrics, Medical College of Wisconsin, 999 N. 92nd St. Suite C410,
Milwaukee, WI 53226, USA

W. Meadow, MD, PhD
Department of Pediatrics, The University of Chicago, 5815 South Maryland Ave,
Chicago, IL 60637, USA

for intubation in the first 72 hours; no studies have enrolled infants <25 weeks to test this strategy.

2. For extremely preterm infants overall (<28 weeks), no significant difference in outcome between the use of early CPAP with selective intubation and prophylactic surfactant for surfactant has been shown.
 - a. In post hoc analysis of one large trial, infants 24 0/7–25 6/7 weeks treated with CPAP had lower rates of death during hospitalization and at 36 weeks than those who received early surfactant.
 - b. This has not been further studied.
 3. No studies have compared ventilation strategies in the delivery room for infants <24 weeks; most infants <24 weeks who are actively resuscitated require intubation.
- C. Ventilation equipment: Limited evidence exists to recommend the preferential use of self-inflating bags, flow-inflating bags, or pressure-limited T-piece resuscitators, regardless of gestational age.

III. Considerations in deciding whether to offer delivery room resuscitation to preterm infants

- A. International consensus guidelines in industrialized countries are generally based upon gestational age.
1. Resuscitation is not indicated for infants ≤ 22 weeks' gestation, as death or severely impaired outcome is very likely (futility).
 2. Resuscitation is generally recommended for infants ≥ 25 weeks' gestation, as an acceptably high rate of relatively intact survival is expected (best interest standard).
 3. Infants of 23–24 weeks are considered the “gray zone” of viability; in these cases, local guidelines, and caregiver and family preferences should apply.
 - a. Parents, physicians, and other caregivers may differ in their beliefs.
 - (1) What constitutes a reasonable chance of survival?
 - (2) What constitutes a good/poor outcome?
 - b. Available guidelines within this gray zone are often conceptual in nature and may not be specific for gestational-age thresholds or definitions of “good” or “bad” outcomes.
- B. Besides gestational age, estimated weight, gender, administration of prenatal corticosteroids, and singleton status have been shown to be of important prognostic value.

- C. Extremely premature infants appear to represent a unique patient population.
 - 1. Physicians may prioritize parental autonomy above the best interest of the infant
 - a. In a series of international surveys, neonatal care providers do not appear to base decisions to resuscitate consistently for different patient groups with a similar prognosis.
 - b. Compared to cases describing older patients, for premature babies, physicians were more likely to withhold resuscitation at the parents' request, despite stating that resuscitation would be in the infant's best interest.
 - 2. Balance of best interest assessment and parental wishes
 - a. Some may consider the best interest of the family unit in deciding whether to resuscitate an infant at the margin of viability.
 - b. Existing literature offers little guidance about this practice.
- IV. Considerations regarding withdrawal of resuscitative efforts at the borderline of viability
 - A. In the delivery room
 - 1. Discontinuation of resuscitation in the delivery room
 - a. Observations of an infant's status and the response to resuscitative efforts are quantified by the Apgar score.
 - b. In general, infants with a 10-minute Apgar score of zero despite 10 minutes of adequate resuscitation are believed to have a minimal chance of intact survival, and discontinuation of resuscitation can be considered acceptable.
 - 2. Limitations of physician assessment in the delivery room
 - a. However, beyond 10-min Apgar scores of zero, it is not clear that Apgar scores are significantly associated with outcome at the borderline of viability.
 - b. Apart from Apgar scores, clinical assessment of extremely preterm infants in the delivery room has been shown to poorly predict survival.
 - B. Early in the NICU
 - 1. Information gathered over the course of treatment in the NICU may alter the prognosis of an individual infant from the original prognosis based on gestational age and/or other factors available prior to delivery.
 - 2. Withdrawal of intensive care treatments can occur based on an assessment of an individual infant's prognosis, after discussion of the risks and benefits to continued treatment.

3. Evidence to guide discussions regarding withdrawal of treatment. Some neonatologists may include:
 - a. Severe physiologic instability
 - b. High likelihood of severe neurologic impairment based upon known congenital defects or acquired brain injury
 - c. Physician assessment of nonsurvival
 - d. Combinations of the above
 4. Limitations to evidence regarding withdrawal of intensive care treatment
 - a. Measurements of physiologic instability, such as Score for Neonatal Acute Physiology (SNAP scores), are useful for risk adjustment in a large population but have poor discrimination for predicting individual outcomes.
 - b. Severely abnormal brain ultrasound findings in the first weeks of life have not been shown to universally predict poor outcomes; conversely, normal brain ultrasounds do not universally predict intact outcomes.
 - c. Clinician intuitions of infant nonsurvival tend toward being overly pessimistic; at least half of the time that clinicians predict an infant's nonsurvival, that infant, in fact, survives to discharge.
 5. Possible strategies for use of evidence regarding withdrawal of intensive care treatment
 - a. Infants predicted by medical caregivers to die before discharge have a high likelihood of either death or severe neurologic morbidity.
 - b. Combinations of clinical intuitions of nonsurvival and objective measurements of neurologic morbidity, specifically, an abnormal brain ultrasound, predict death or severe neurologic impairment with positive predictive value >95%.
 - c. Conversely, the sensitivity of all recognized strategies to predict poor outcome in ELBW infants is poor—that is, nearly 40% of ELBW infants who have *no* recognized risk factors for poor outcome have significant impairments nonetheless.
- V. In determining whether to offer or discontinue (see Chap. 82) intensive care treatments for extremely preterm infants:
- A. Neonatologists should review available prognostic information
 1. Epidemiologic data (likely outcomes as suggested by large cohort studies)
 2. Local outcomes data
 3. Individual prognostic markers (that may be known before birth or, with increasing accuracy, become available after a trial of intensive care therapy in the NICU)

- B. The degree of confidence in prognostic estimates should be considered; when the prognosis is highly uncertain, parents should be informed that physicians will likely act in accordance with parental values and preferences.
- C. Conversely, when the probability of an adverse outcome (either death or significant neurologic disability) is very high (e.g., >95%), parents should be fully informed about the likely outcome and afforded the option of palliative care.
- D. Institution-specific experience and preferences should be reviewed to encourage consistency across caregivers.

Suggested Reading

- Armstrong K, Ryan C, Hawkes C, Janvier A, Dempsey E. Life and death decisions for incompetent patients: determining best interests - the Irish perspective. *Acta Paediatr.* 2010 Nov 11. doi: 10.1111/j.1651-2227.2010.02084.x. [Epub ahead of print] PubMed PMID: 21070357.
- Bastek TK, Richardson DK, Zupancic JA, Burns JP. Prenatal consultation practices at the border of viability: a regional survey. *Pediatrics* 2005; 116: 407–13.
- Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The epicure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics.* 2000;106:659–71.
- De Leeuw R, Cuttini M, Nadai M, Berbic I, Hansen G, Kucinkas A, Lenoir S, Levin A, Persson J, Rebagliato M, Reid M, Schroell M, de Vonderweid U. Treatment choices for extremely pre-term infants: an international perspective. *J Pediatr.* 2000;137:608–16.
- Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994–9 compared with 2000–5. *BMJ.* 2008;336:1221–23.
- Haward MF, Murphy RO, Lorenz JM. Message framing and perinatal decisions. *Pediatrics.* 2008; 122:109–18.
- Janvier A, Bauer KL, Lantos JD. Are newborns morally different from older children? *Theor Med Bioeth.* 2007;28(5):413–25. PubMed PMID: 17985104.
- Janvier A, Barrington MB. The ethics of neonatal resuscitation at the margins of viability: informed consent and outcomes. *J Pediatr.* 2005;147:579–85.
- Janvier A, Leblanc I, Barrington KJ. The best-interest standard is not applied for neonatal resuscitation decisions. *Pediatrics.* 2008 May;121(5):963–9. PubMed PMID: 18450900.
- Janvier A, Leblanc I, Barrington KJ. Nobody likes premies: the relative value of patients' lives. *J Perinatol.* 2008 Dec;28(12):821–6. Epub 2008 Jul 17. PubMed PMID: 18633422.
- Kaempf JW, Tomlinson MW, Campbell B, Ferguson L, Stewart VT. Counseling pregnant women who may deliver extremely premature infants: medical care guidelines, family choices, and neonatal outcomes. *Pediatrics.* 2009;123:1509–15.
- Kopelman LM, Irons TG, Kopelman AE. Neonatologists judge the 'Baby Doe' regulations. *N Engl J Med.* 1988;318:677–83.
- Payot A, Gendron S, Lefebvre F, Doucet H. Deciding to resuscitate extremely premature babies: how do parents and neonatologists engage in the decision? *Soc Sci Med* 2007;64:1487–500.
- Paris JJ. What standards apply to resuscitation at the borderline of gestational age? *J Perinatol.* 2005;25:683–84.
- Sanders MR, Donohue PK, Oberdorf MA, Rosenkrantz TS, Allen MC. Perceptions of the limit of viability: neonatologists' attitudes toward extremely preterm infants. *J Perinatol.* 1995; 15:494–502.

- Singh J, Fanaroff J, Andrews B, Caldarelli L, Lagatta J, Peshya-Troyke S, et al. Resuscitation in the “gray zone” of viability: determining physician preferences and predicting infant outcomes. *Pediatrics*. 2007;120:519–26.
- Skupski DW, Chervenak FA, McCullough LB, Bancalari E, Haumont D, Simeoni U, Saugstad O, Donn S, Arabin B, Greenough A, Donzelli G, Levene M, Sen C, Carbonell X, Dudenhausen JW, Vladareanu R, Antsaklis A, Papp Z, Aksit M, Carrapato M. Ethical dimensions of periviability. *J Perinat Med*. 2010;38:579–83.
- Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity—moving beyond gestational age. *N Engl J Med*. 2008;358:1672–81.

Chapter 82

Withdrawal of Ventilatory Support

Malcolm L. Chiswick

I. Introduction

- A. Assisted ventilation should be viewed as a temporary support measure for infants with *potentially reversible* respiratory failure. In effect, it is a *trial of life*, and the desired outcome is survival with a reasonable chance of an independent existence free of disability in later childhood.
- B. Physicians who start assisted ventilation have *a duty* to consider with parents the withdrawal of ventilatory support if it seems likely that the desired outcome will not be achieved.
- C. The idea that life support must be continued as long as an infant is alive and that no one has the right to terminate assisted ventilation is an extremist view that few would defend.
- D. The withdrawal of life support and the redirection of care towards a peaceful death is widely practiced and featured in recommendations of professional paediatric organizations.

II. Withdrawing ventilatory support

- A. A robust and coherent code of practice is needed to define the circumstances that justify the withdrawal of assisted ventilation. Otherwise, *ad hoc* standards will be applied to each case and a decision will be justified only *after* it has been made.
- B. The code of practice should be derived from medical, logical and moral concepts, based on a respect for human life that can be applied consistently across a broad range of individual circumstances. We should not have to change the rules for each infant.

M.L. Chiswick, MD, FRCP(Lond), FRCPC, FRCOG, DCH (✉)
University of Manchester, Manchester, UK

Newborn Intensive Care Unit, St. Mary's Hospital, Oxford Road, Manchester M13 9WL, UK
e-mail: m.chiswick@btinternet.com

- C. In practice, there are two main circumstances, where withdrawal of ventilatory support is a consideration:
1. When it is considered that the infant has already entered the process of dying and that ventilatory support is prolonging death rather than offering a reasonable hope of survival. The concept of futility applies here.
 2. Where the continuation of assisted ventilation might well allow the infant to survive but with a significant risk of severe neurodevelopmental disability.

III. The dying infant and futility of treatments

- A. Physicians are not obliged to continue with treatments that serve no purpose, especially when the treatment is associated with prolonged distress for the infant.
- B. The problem for the physician is to decide when assisted ventilation has ceased to become a trial of life and is simply prolonging the process of dying.
- C. The infant's state is generally one of multiple organ impairments, where specific treatments directed towards affected organ systems have been offered without success. In effect, the decision to withdraw ventilatory support is based on *medical indications* that further ventilatory support is futile.
- D. Withdrawal of ventilatory support in this situation gives some control over the timing and circumstances of the death rather than parents and staff presiding over an infant who is surrounded by the technological trappings of failed intensive care and who will die from cardiac standstill at an unpredictable time.
- E. Severe and prolonged bronchopulmonary dysplasia (BPD) presents special problems, as the course is often characterized by repeated episodic deterioration, with the infant never quite gaining ground after each episode. The notion of futility may take a long time to dawn because of the difficulty in stepping off the therapeutic roller coaster once it has started. For the parents, each therapeutic intervention encourages hope, so it is important to engage them early and realistically about their infant's future.
- F. Infants in whom ventilatory support has been withdrawn because of advanced BPD are ethically challenging because their survival for days or even weeks is not uncommon. The redirection of their care includes a firm understanding that re-ventilation is rarely an option, whereas the infant's comfort certainly is. In particular, parents need to be involved in decisions about their infant's hydration, nutrition and the use of supplemental oxygen.

IV. The "quality of life" decision

- A. Here, the judgment is that an infant might well survive as a result of continuing ventilatory support, but the quality of life is seriously called into question.
- B. There are circumstances, albeit rarely, when it is ethically acceptable to withdraw assisted ventilation from an infant whose life might be saved only

by further prolonged discomfiture of neonatal intensive care and in whom it is probable that substantial neurodevelopmental or physical handicap will radically limit the child's ability to participate in human experience and will render him or her forever dependent on a caregiver for everyday living. The arguments surrounding quality of life decisions have been well-rehearsed and include the following concepts.

1. "Quality of life" is a subjective notion.
2. We can rarely be certain about the extent of any predicted handicap.
3. The infant cannot take part in the decision making.
4. No one has the right to "act like God" and to judge whether death or survival with severe handicap is the better of the two.
5. The concept of acting "in the best interests" of the infant readily rolls off the tongue but is fraught with uncertainty (see "Acting in the Infant's Best Interests").
6. On the other hand, faced with an intolerable existence, responsible adults may exercise their right to end their own lives, and someone has to speak out on behalf of the infant.

V. Acting in the infant's best interests

A. General concepts

1. The idea of acting in a patient's best interests is enshrined in medical practice but is rarely of *practical help* in decision making.
2. Of course, the infant's interests are paramount compared to the interests of others. However, the infant's interests are intimately linked with those of the parents, who carry a duty of care after the infant is discharged.
3. The concept of best interests implies that *we know* what those interests are, but faced with complex medical challenges we often do not.
4. Perhaps, the best "test" in these circumstances is the balance between the burden of treatments and the likely outcome. We may have a reasonable understanding of pain, suffering and distress, and to some extent these can be controlled. However, *neurodevelopmental outcomes* for individual infants and their potential *impact* are often impossible to assess in a helpful way.
5. That is why the "best interests" concept is often used as a *conclusion* after a decision about care has been made, as in "I *acted* in the infant's best interests". Sadly, it is only with hindsight that we may realize that a decision was not necessarily in the infant's best interests.

- B. Probably, the most common scenario for withdrawing ventilatory assistance on the basis of a quality of life decision is when an infant has persisting abnormal neurological signs associated with a brain scan that shows severe bilateral abnormalities. A trusting relationship built up over time between the parents and the designated senior physician together with a consensus view among experienced staff caring for the infant, often obviates the need for involvement of an ethics committee, although local practices do vary.

- C. It is rare for parents to request thoughtfully and consistently that assisted ventilation should be withdrawn against medical advice. On those occasions, the physician's duty of care is primarily towards the infant.
- D. It is more common for parents to request that ventilation should be *continued* contrary to medical advice. Here, the physician's duty to the infant is to ensure that the parents understand the facts and arguments, and that they are capable of acting on behalf of the infant. Coercing parents to agree to withdrawing ventilatory support can cause regret and guilt that may remain with them long after their baby dies. Instead, counselling should be continued with an emphasis on the notion of compassionate care and support rather than the focus on "pulling the plug."

VI. Engaging parents in decision making

- A. Parents of seriously ill infants need time to make their views known. When it is clear that their infant is seriously ill, parents should be led into the discussion early rather than later.
- B. Do not shoulder the burden of decision making on parents. (*"These are the facts, what do you want us to do?"*).
- C. Instead, *make clear your medical view* and indicate that you are seeking the parents' support.
- D. Most decisions center around infants in whom the continuation of ventilatory assistance is merely prolonging the process of dying, and it is unfair in those cases to burden and confuse parents with the complex issues surrounding quality of life decisions.

VII. Deceptive signals

- A. We need to guard against "giving up" on sick infants prematurely. There are deceptive signals that might erroneously persuade care providers that continuing ventilatory support is not justified:
 - 1. Despair
 - 2. Adverse appearance of the infant:
 - a. Under-nutrition and dehydration
 - b. Cholestatic jaundice
 - c. Multiple skin trauma from infusion sites ("war wounds")
 - d. Hydrops
 - 3. Biased impression of prognosis based on unthoughtful comparisons with other infants who have passed through the neonatal unit
 - 4. Non-visiting parents

VIII. Engaging staff in decision making

- A. Problems arise on neonatal units, where there is no proper leadership, where the staff does not work together as a team and where there is no proper forum for discussing ethical issues. Staff may feel unable to discuss the possibility of withdrawing assisted ventilation from an infant and instead unspoken signals occur.
1. *Standing off on clinical rounds:* Disgruntled staff turn away and show a lack of interest in discussing the infant and contributing to further management.
 2. *Exaggeration of clinical signs:* An infant with pallor might be described as appearing “white as a sheet;” skin peeling might be referred to as “peeling off in layers”.
 3. *Therapeutic nihilism:* All suggested treatments are rejected on the basis of their side effects.
 4. *Incongruous search for the expert:* Paradoxically, staff may suggest calling in an “expert,” such as a nephrologist or cardiologist, to advise on organ system failure. This may be a “cry for help” in the hope that the specialist will indicate that nothing further can be done for the infant.
 5. *Group formation among staff:* Small groups form among the staff and discuss among themselves the apparent futility of continuing ventilatory support.
 6. *“The parents do not realize how sick the infant is:”* In spite of the physician discussing the infant’s progress with the parents at frequent intervals, the staff may insist that the parents do not understand how ill the infant is.
- B. These unspoken signals reflect desperation and despair among staff, who cannot communicate their feelings to the senior physician. They are cries for help. It is essential that this situation is recognized and steps taken to improve the organization and communication on the neonatal unit. Unless this happens, decisions about withdrawing assisted ventilation generate a crisis each time and provoke additional suffering for parents and indeed for infants.

IX. Care following withdrawal of assisted ventilation

- A. Parents need to be counselled that withdrawing assisted ventilation is not simply a matter of “turning off the switch.” They should be prepared for events and offered a choice of how they would like their infant to be cared for during and after withdrawal.
- B. A minority of parents simply want to bid farewell to their infant, depart from the neonatal unit and leave the details to the staff. Their wishes should be respected.

- C. At the other extreme, some parents wish to remove the endotracheal tube and intravascular lines themselves.
- D. Facilities should be made available to allow parents to remain with their infant in a secluded room immediately after withdrawal. Some wish to bathe and dress their infant, even if death has already occurred.
- E. There are some uncomfortable facts that must be faced together with parents:
 - 1. After withdrawal of assisted ventilation, parents often want to know how long it will be before their baby dies. If the indication was that the baby had “already entered the process of dying,” death may occur very soon after withdrawal, but this is not always the case, and parents should be made aware beforehand of the inherent uncertainty. They should also be advised that their baby may gasp or show other reflex activities before expiring.
 - 2. The use of drugs in palliative care is based on the principle that the *primary intent* is to relieve discomfort, distress or pain. It is treading on a legal tightrope initially to prescribe sedatives or analgesics well in excess of recommended dosages, as the primary intent may be readily perceived as one of hastening death.
 - 3. Normally, the action of muscle relaxants, if used, has already been reversed shortly before ventilation was withdrawn in order to assess spontaneous breathing activity. The use of muscle relaxants as part of palliative care probably amounts to falling off that legal tightrope, as it is difficult to see this as anything other than an intention to promote death. However, the problem of managing “agonal gasping” continues to create dilemmas.
 - 4. Even more challenging is the palliative care of infants in whom ventilation has been withdrawn because of quality of life considerations. Sometimes, by the time agreement has been reached that ventilation should be withdrawn, the infant is no longer dependent on the ventilator and may well survive without it. In effect, the time taken for a quality of life decision may exceed the narrow window of opportunity to effect withdrawal of ventilation, and parents need to be made aware of this in a sensitive way.
 - 5. Withholding fluids, nutrition and warmth is not a reasonable option for these infants. The logic behind this statement is that the use of assisted ventilation is an *extraordinary measure* of medical care—a temporary support measure for infants with *potentially reversible* respiratory failure. In contrast, all babies are *normally dependent* on a caregiver for the provision of fluid, nutrition and warmth and so it is reasonable to continue to provide them.

- X. Requesting a post-mortem examination after withdrawal of ventilatory support
- A. It is not appropriate to subject parents at the same time to the dual burden of deciding about withdrawing assisted ventilation and consenting to a post-mortem examination.
 - B. Having withdrawn assisted ventilation to relieve unnecessary pain and suffering, they may be unwilling to subject their infant to what they perceive as further suffering through a post-mortem examination.
 - C. When requesting post-mortem consent, parents should not be given the impression that it is “to establish the cause of death” because it raises doubts that the decision to withdraw ventilatory support was made in ignorance about the infant’s problems.
 - D. Instead, it provides an opportunity to confirm with parents that the disease was so severe that survival was not possible. They can be reassured that having faced a most difficult parenting challenge they acted in the best interests of their baby.

Suggested Reading

- American Academy of Pediatrics, Committee on Fetus and Newborn. Non-initiation or withdrawal of intensive care for high-risk newborns. *Pediatrics*. 2007;119:401–3.
- Campbell AGM. Quality of life as a decision making criterion I. In: Goldworth A, Silverman W, Stevenson DK, Young EWD, editors. *Ethics and perinatology*. Oxford: Oxford University Press; 1995. p. 82–98.
- Chiswick ML. Withdrawal of life support in babies: deceptive signals. *Arch Dis Child*. 1990;65:1096–7.
- Chiswick M. End of life decisions in chronic lung disease. *Semin Fetal Neonatal Med*. 2009;14:396–400.
- Dyer O. Doctor cleared of act “tantamount to euthanasia”. *BMJ*. 2007;335:67.
- Delaney-Black V. Delivering bad news. In: Donn SM, Fisher CW, editors. *Risk management techniques in perinatal and neonatal practice*. Armonk, NY: Futura Publishing Co.; 1996. p. 635–49.
- Hawryluck L. Neuromuscular blockers – a means of palliation? *J Med Ethics*. 2002;28:170–2.
- Kraybill EN. Ethical issues in the care of extremely low birth weight infants. *Semin Perinatol*. 1998;22:207–15.
- Kuhse H. Quality of life as a decision making criterion II. In: Goldworth A, Silverman W, Stevenson DK, Young EWD, editors. *Ethics and perinatology*. Oxford: Oxford University Press; 1995. p. 104–20.
- Perkin RM, Resnik DB. The agony of agonal respiration: is the last gasp necessary? *J Med Ethics*. 2002;28:164–9.
- Pierce SF. Neonatal intensive care decision making in the face of prognostic uncertainty. *Nurs Clin North Am*. 1998;33:287–97.
- Royal College of Paediatrics and Child Health. *Withholding or withdrawing life sustaining treatment in children. A framework for practice*. London: RCPCH; 2004.
- Roloff DW. Decisions in the care of newborn infants. In: Donn SM, Faix RG, editors. *Neonatal emergencies*. Mt. Kisco, NY: Futura Publishing Co.; 1991. p. 635–43.
- Weil Jr WB, Benjamin M. *Ethical issues at the outset of life. Contemporary issues in fetal and neonatal medicine*. Boston: Blackwell Scientific Publications; 1987.

Chapter 83

Medical Liability, Documentation, and Risk Management

Steven M. Donn and Jonathan M. Fanaroff

I. Medical liability

A. Definition: Liability arising from delivery of medical care

B. Legal bases of medical malpractice

1. Negligence
2. Intentional misconduct
3. Breach of contract
4. Defamation
5. Divulgence of confidential information
6. Insufficient informed consent
7. Failure to prevent foreseeable injury to third parties

C. Tort: A civil wrong in which a person has breached a legal duty with harm caused to another

1. Can be intentional or negligent
2. Defined roles of plaintiff v. defendant(s)

S.M. Donn, MD, FAAP (✉)

Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital,
F5790 Mott Hospital/5254, University of Michigan Health System, 1500 E. Medical Center Dr.,
Ann Arbor, MI 48109-5254, USA
e-mail: smdonmd@med.unich.edu

J.M. Fanaroff, MD, JD

Division of Neonatology, Department of Pediatrics, Rainbow Babies & Children's Hospital,
11100 Euclid Avenue, Cleveland, OH 44106, USA

D. Medical negligence

1. Predominant theory of medical negligence
2. Plaintiff must establish each of the following four elements by a preponderance of the evidence (more likely than not/>50% chance):
 - a. Duty of defendant to plaintiff: Supervising residents or nurse practitioners may be enough to establish a duty even if a physician has never seen the patient.
 - b. Breach of standard of care (what a reasonable health care provider would do under similar circumstances): Generally, established by expert testimony.
 - c. Proximate cause (breach directly led to injury).
 - d. Damages:
 - (1) Economic—medical expenses, costs of care. Lifetime care costs can be very high in neonatal cases.
 - (2) Non-economic—pain and suffering, emotional distress. Limited in some states.
 - (3) Punitive—malicious or egregious conduct.

E. Areas of malpractice risk in neonatology

1. Delivery room management/resuscitation
2. Medication errors—wrong medicine, wrong dose, wrong patient
3. Delay in diagnosis/treatment—acidosis, hypotension, sepsis, congenital heart disease, seizures, hypoglycemia, meningitis, jaundice, others

II. Documentation

A. Importance of the medical record

1. Memorialization of the hospital course
2. Communication among physicians and other health care professionals
3. Key piece of evidence in litigation

B. Legal issues associated with medical records

1. Confidentiality
2. Record retention
3. Patient rights
4. Release of records
5. Electronic medical records
6. Fraud and abuse
7. Spoliation—altering of records

C. Communicating via the medical record

D. Effective documentation

1. Meets guidelines for evaluation and management (coding and billing)
2. Employs risk management skills (see below)

3. Complete, factual, and accurate
4. Timely (date and time all notes and orders)
5. Original (avoid “cut and paste”)
6. Must be legible
7. Objective
8. Discussions with parents, including evidence of informed consent and refusal

E. Things to avoid

1. Language that accepts or assigns blame
2. Superlative modifiers (e.g., “profound,” “severe,” “emergent,” etc.)
3. Offensive language
4. Judgmental language
5. Speculation

F. Procedure notes

1. List indication(s)
2. Describe procedure and equipment used
3. Note patient tolerance and complications, if any
4. Document appropriate follow-up study (e.g., chest radiograph) *and response* (“X-ray obtained → UVC pulled back 2 cm”)

III. Risk management: A systematic process to identify, evaluate, and address problems which may injure patients, lead to malpractice claims, and cause financial loss to health care providers

A. Key elements

1. Identification of potential risk
 - a. External—legal action, patient complaints
 - b. Internal (preferred method)—incident reporting, occurrence, screening
2. Calculation of probability of adverse effect from risk
3. Estimation of impact of adverse effect
4. Establish risk prevention

B. Risk management success depends upon:

1. Attitude
 - a. Awareness of potential liability
 - b. Commitment to effective communication
 - c. Appreciation of impact of “other forces” (e.g., business decisions)
2. Knowledge
 - a. Unique neonatology/family relationship
 - b. Informed consent

- c. Communication systems and skills
 - d. Documentation requirements
 - e. Neonatal malpractice claims
3. Culture
- a. Culture of blame and finger-pointing lead to silence and repeated mistakes
 - b. Culture of safety allows caregivers to openly discuss barriers to safer care
- C. Root cause analysis (RCA)—Evaluating the causative factors after things go wrong
- 1. RCA team members
 - a. Individuals with knowledge of the issues involved in the incident
 - b. Risk management members
 - c. Quality improvement members
 - 2. Key questions
 - a. What happened?
 - b. Why did it happen?
 - c. What are we going to do to prevent it from happening again?
 - d. How will we know that the changes we make actually improve the safety of the system?
 - 3. Potential actions to decrease the likelihood of an event after an RCA
 - a. Train staff
 - b. Write new policies
 - c. Decrease workload
 - d. Checklists
 - e. Standardize equipment
 - f. Redesign process to improve safety

Suggested Reading

- Donn SM, McDonnell WM. When bad things happen: adverse event reporting and disclosure as patient safety and risk management tools in the neonatal intensive care unit. *Am J Perinatol.* 2011, Aug10 (epub ahead of print).
- McAbee GN, Donn SM, editors. *Medicolegal issues in pediatrics.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011.

Part XV
Research and the Literature

Chapter 84

Interpreting Medical Literature

Omar Kamlin and Peter Davis

I. Introduction

- A. Clinical research helps improve patient outcomes
- B. Keeping up to date is difficult because of the rate at which new research is published
- C. Clinicians need strategies to:
 - 1. Identify what is worth reading in detail
 - 2. Determine whether the results should change their practice
 - 3. When interpreting clinical research, the reader should ask
 - a. Is it *valid*—can we trust the results?
 - b. Is it *important*—if true, is it worthwhile?
 - c. Is it *applicable*—can the results be used to help my patients?

II. Clinical research

- A. At the outset, the reader should identify the aims of the study and ask “what is this research about?” Is it:
 - 1. Evaluating a new therapy (e.g., does nitric oxide reduce mortality and morbidity of ventilated preterm infants?)
 - 2. Evaluating a new diagnostic test (e.g., does procalcitonin improve the accuracy of diagnosis of neonatal sepsis?)

O. Kamlin, MRCP, MRCPCH, FRACP
The Royal Women’s Hospital, Neonatal Services, 20 Flemington Road,
Parkville, VIC 3052, Australia

P. Davis, MBBS, MD, FRACP (✉)
Newborn Research, The Royal Women’s Hospital, 20 Flemington Road,
Parkville, VIC 3052, Australia
e-mail: pgd@unimelb.edu.au

3. Assessing causality (e.g., do postnatal steroids cause cerebral palsy?)
4. Determining the natural history or prognosis of a condition (e.g., what is the respiratory function in adulthood of infants with BPD?)

B. Therapy

1. Possible study designs, in decreasing order of validity
 - a. Randomized controlled trial (RCT)
 - b. Cohort study (e.g., comparing groups from different places or different periods of time)
 - c. Case control study
 - d. Case series
2. Checklist for evaluation (validity, importance, and applicability) of a study on therapy
 - a. Were treated and untreated infants at equal risk of a bad outcome before therapy? Best achieved by random allocation of patients.
 - b. Was there a prespecified primary outcome, and was there an estimate of the sample size required to detect a clinically important difference in this outcome? Was the trial registered?
 - c. Were both groups treated equally apart from the therapy being evaluated? Best achieved by masking of caregivers.
 - d. Were important outcomes assessed (e.g., death, neurodevelopment in infancy versus short-term physiological changes)?
 - e. Were the groups assessed equally for the outcome of interest? Best achieved by masking of those assessing outcomes.
 - f. Were the study infants similar to those you treat?
 - g. If a *statistically* significant difference in outcomes was reported, was the difference *clinically* important?
 - h. Is the therapy available and affordable in your practice?
 - i. Were all the enrolled patients accounted for at the end of the study?

C. Diagnostic tests

1. Criteria for evaluation of a study on diagnostic tests
 - a. Was there a blind comparison with a “gold standard”?
 - b. Were the patients similar to those in your practice?
 - c. Was the “normal” range defined?
 - d. Is the diagnostic test precise (reproducible), free of bias, and applicable in your clinical area?
 - e. To determine importance of the results, draw up a 2×2 table (Tables 84.1 and 84.2).

Table 84.1 2x2 Table for diagnostic tests

	Gold standard result		
	Disease (+)	No disease (-)	
Test positive (+)	<i>a</i>	<i>b</i>	Positive predictive value $a/(a+b)$
Test negative (-)	<i>c</i>	<i>d</i>	Negative predictive value $d/(c+d)$
	Sensitivity $a/(a+c)$ Specificity $d/(b+d)$		

Sensitivity refers to the proportion of subjects with disease that have a positive test [$a/(a+c)$]
 Specificity refers to the proportion of subjects free of disease that have a negative test [$d/(b+d)$]
 Positive predictive value is the proportion of subjects with a positive result who have the disease [$a/(a+b)$]

Negative predictive value is the proportion of subjects with a negative result who are disease free [$d/(c+d)$]

The accuracy of the test can be calculated by examining proportion of true results (true positives and true negatives) of all results [$(a+d)/(a+b+c+d)$]

Table 84.2 Using a 2x2 table

	Outcome	
	Yes (+)	No (-)
Exposed (+)	<i>a</i>	<i>b</i>
Not exposed (-)	<i>c</i>	<i>d</i>

In an RCT or cohort study, the relative risk of the exposure causing the outcome is $(a/a+b)/(c/c+d)$; in a case control study, the relative odds are ad/bc

D. Causality

1. Types of Study (in decreasing order of validity)*

- a. RCT
- b. Cohort
- c. Case control
- d. Case series

*Although an RCT is the most robust test of causality, other designs may be more useful, particularly when looking for rare events.

2. Checklist for evaluation of a study investigating causation

- a. Was an inception cohort (i.e., a group assembled prior to exposure) formed with exposed and nonexposed groups similar in all important baseline characteristics, other than exposure to the factor(s) being investigated?
- b. Were exposures and clinical outcomes measured the same way in both groups?

- c. Was follow-up long enough and complete?
- d. Is the association strong and biologically plausible? Did the exposure predate the outcome?

E. Prognosis

1. Criteria for evaluation of a study investigating prognosis

- a. Was an inception cohort assembled?
- b. Was follow-up long enough and complete?
- c. Were the outcomes assessed by individuals masked to the subject's history/and or interventions?
- d. Was the assessment objective?
- e. Are the results applicable to your own practice and how will the evidence affect what you tell your patient/parents?

III. Statistical considerations

- A. A good Methods section simply describes the statistical tests used.
- B. Inappropriate choice of statistical tests may lead to misleading interpretation of results. (Was the test chosen only because it yielded a “significant *P* value?”).
- C. A statistical test provides the reader with a probability, a *P* value, of the results (a difference between two groups) resulting from chance alone. The arbitrary (but widely accepted) cutoff is 0.05 (1 in 20). When the *P* value is <0.05, then the null hypothesis (no difference between two interventions) can be rejected, and we may conclude that one intervention is better than the other.
- D. Confidence intervals (CIs) are an alternative way of assessing the play of chance. The 95% CI gives the range of values, within which we can be 95% certain the true value lies. The advantage of a CI over a *P* value is that it can quantitate the size of the difference, and the width of the interval provides an indication of precision of the estimate of that difference.

IV. Where to search for the evidence?

- A. Library—physical and online. With ready availability of computers and handheld devices, searching the Internet to access primary articles has become much easier using search engines, such as PubMed, Ovid, etc.
- B. Searching for pre-appraised evidence
 - 1. Cochrane database of systematic reviews, TRIP database (UK)
 - 2. Review articles
 - 3. Clinical practice guidelines, including consensus opinion statements

V. Some recognized pitfalls

- A. Do not assume that statistical significance is the same as clinical significance (importance).

- B. Do not assume that results from a published study are necessarily applicable to your patients.
- C. Do not forget to consider potential harms and economic effects of an intervention.

VI. Conclusion

- A. “Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values.”
- B. A sound, structured approach to reading journal articles helps determine the best course of action to take with your own patients in a time-effective manner.

Suggested Reading

Crombie IK. Pocket guide to critical appraisal. 2nd ed. London: John Wiley and Sons, Ltd; 2008.
Haynes RB, Sackett DL, Guyatt GH, Tugwell P. Clinical epidemiology: how to do clinical practice research. 3rd ed. Lippincott, PA: Williams and Wilkins; 2005.
The Cochrane Library: <http://www.thecochranelibrary.com/view/0/index.html>; <http://neonatal.cochrane.org/>.

Chapter 85

Contemporary Classics in Neonatal Respiratory Care

Rachel L. Chapman and Lorelei Woody

The following articles have been chosen as the top 100 peer-reviewed articles related to neonatal respiratory care and published in the last 10 years:

1. Ahmed SJM, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics*. 2010;125:e115–21.
2. Ambalavanan N, Van Meurs KP, Perritt R, et al. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. *J Perinatol*. 2008;28:420–6.
3. Angus DC, Clermont G, Watson RS, et al. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States. *Pediatrics*. 2003;112:1351–60.
4. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med*. 2003;340:959–67.
5. Baird R, MacNab YC, Skarsgard ED, et al. Mortality prediction in congenital diaphragmatic hernia. *J Pediatr Surg*. 2008;43:783–7.
6. Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med*. 2006;355:343–53. Erratum in: *N Engl J Med*. 2007;357:1444–5.
7. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev*. 2007;1:CD000509.

R.L. Chapman, MD (✉)

Division of Neonatal-Perinatal Medicine, Department of Pediatrics,
C.S. Mott Children's Hospital, University of Michigan School of Medicine,
F5790 Mott Hospital, 1500 E Medical Center Dr. SPC 5254, Ann Arbor, MI 48109-5254, USA
e-mail: rachellc@umich.edu

L. Woody, MLIS

Alfred A. Taubman Health Sciences Library, University of Michigan, 1135 E Catherine St.,
Ann Arbor, MI 48109, USA

8. Beardsmore CS, Westaway J, Killer H, et al. How does the changing profile of infants who are referred for extracorporeal membrane oxygenation affect their overall respiratory outcome? *Pediatrics*. 2007;120:e762–8.
9. Been JV, Rours IG, Kornelisse RF, et al. Chorioamnionitis alters the response to surfactant in preterm infants. *J of Pediatr*. 2010;156:10–5.
10. Bhandari V, Finer NN, Ehrenkranz RA, et al. Synchronized nasal intermittent positive-pressure ventilation and neonatal outcomes. *Pediatrics*. 2009;124:517–26.
11. Bloom BT, Clark RH, for the Infasurf Survanta Clinical Trial Group. Comparison of Infasurf (calfactant) and Survanta (beractant) in the prevention and treatment of respiratory distress syndrome. *Pediatrics*. 2005;116:392–9.
12. Boloker J, Bateman DA, Wung J-T, Stolar CJH. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. *J Pediatr Surg*. 2002;37:357–66.
13. Bose C, for the Extremely Low Gestational Age Newborn Study Investigators. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. *Pediatrics*. 2009;124:e450–8.
14. Breatnach C, Conlon NP, Stack M, et al. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. *Pediatr Crit Care Med*. 2010;11:7–11, 164–6.
15. Checkley W, West KP, Wise RA, et al. Maternal vitamin A supplementation and lung function in offspring. *N Engl J Med*. 2010;362:1784–94.
16. Cools F, Askie LM, Offringa M, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet* 2010;375:2082–91. Erratum in: *Lancet*. 2011;377(9777):1572.
17. Consortium on Safe Labor. Respiratory morbidity in late preterm births. *JAMA*. 2010;304(4):419–25.
18. Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med*. 2002;347:643–52.
19. Crowther CA, Haslam RR, Hiller JE, et al. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. *Lancet*. 2006;367:1913–9.
20. Dargaville PA, Copnell B, Mills JF, et al. Randomized controlled trial of lung lavage with dilute surfactant for meconium aspiration syndrome. *J Pediatr*. 2011;158:383–9.
21. Davis PG, Schmidt B, Roberts RS, et al. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr*. 2010;156:382–7.
22. De Visser YP, Walther FJ, Laghmani EH, et al. Phosphodiesterase-4 inhibition attenuates pulmonary inflammation in neonatal lung injury. *Eur Respir J*. 2008;31:633–44.
23. Doyle AU, Davis LW, Morley PG, et al. Outcome at 2 years of age of infants from the DART study: a multicenter, international, randomized, controlled trial of low-dose dexamethasone. *Pediatrics*. 2007;119:716–21.

24. Ehrenkranz RA, Walsh MC, Vohr BR, et al. Validation of the National Institute of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics*. 2005;116:1353–60.
25. Engel WA and the Committee on Fetus and Newborn. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. *Pediatrics*. 2008;121:419–32.
26. Farhath S, He Z, Nakhla T, et al. Pepsin, a marker of gastric contents, is increased in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. *Pediatrics*. 2008;121:e253–9.
27. Field D, Elbourne D, Hardy P. Neonatal ventilation with inhaled nitric oxide vs. ventilatory support without inhaled nitric oxide for infants with severe respiratory failure born at or near term: the INNOVO multicentre randomised controlled trial. *Neonatology*. 2007;91:73–82.
28. Finer NN, Rich W, Wang C, et al. Airway obstruction during mask ventilation of very low birth weight infants during neonatal resuscitation. *Pediatrics*. 2009;123:865–9.
29. Filippone M, Sartor M, Zacchello F, Baraldi E. Flow limitation in infants with bronchopulmonary dysplasia and respiratory function at school age. *Lancet*. 2003;361:753–4.
30. Friedrich AU, Pitrez L, Stein PMC. Growth rate of lung function in healthy preterm infants. *Am J Resp Crit Care Med*. 2007;176:1269–73.
31. Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database Syst Rev*. 2008;1:CD000456.
32. Gupta S, Sinha SK, Tin W, Donn SM. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus infant flow driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. *J Pediatr*. 2009;154:645–50, e2.
33. Håland G, Carlsen KC, Sandvik L, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med*. 2006;355(16):1682–9.
34. Hamutcu R, Nield TA, Garg M, et al. Long-term pulmonary sequelae in children who were treated with extracorporeal membrane oxygenation for neonatal respiratory failure. *Pediatrics*. 2004;114:1292–6.
35. Hansen AU, Wisbork K, Ulbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *BMJ*. 2008;336:85–7.
36. Harrison MR, Keller RL, Hawgood SB, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med*. 2003;349:1916–24.
37. Henderson-Smart DJ, Cools F, Bhuta T, Offringa M. Elective high-frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev*. 2007;18:CD000104.
38. Hibbs AM, Walsh MC, Martin RJ, et al. One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to prevent) Chronic Lung Disease trial. *J Pediatr*. 2008;153:525–9.

39. Higgins RD, Bancalari E, Willinger M, Raju TNK. Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. *Pediatrics*. 2007;119:790–6.
40. Hintz SR, Van Meurs KP, Peritt R, et al. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. *J Pediatr*. 2007;151:16–22.
41. Hofmeyr GJ, Xu H. Amnioinfusion for meconium-stained liquor in labour. *Cochrane Database Syst Rev*. 2010;1:CD000014.
42. Huddy CL, Bennett CC, Hardy P, et al. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4–5 years. *Arch Dis Child Fetal Neonatal Ed*. 2008;93:F430–5.
43. Hülskamp G, Lum S, Stocks J, et al. Association of prematurity, lung disease and body size with lung volume and ventilation inhomogeneity in unsedated neonates: a multicentre study. *Thorax*. 2009;64:240–5.
44. Kattwinkel J, Stewart C, Walsh B, et al. Responding to compliance changes in a lung model during manual ventilation: perhaps volume, rather than pressure, should be displayed. *Pediatrics*. 2009;123:e465–70.
45. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med*. 2006;355(4):354–64.
46. Konduri GG, Solimano A, Sokol GM, et al. A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. *Pediatrics*. 2004;113:559–64.
47. Konduri GG, Vohr B, Robertson C, et al. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. *J Pediatr*. 2007;150:235–40.
48. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? *Pediatrics*. 2008;121:82–88.
49. Kugelman A, Feferkorn I, Riskin A, et al. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized, controlled, prospective study. *J Pediatr*. 2007;150:521–6.
50. Lally KP, Lally PA, Lasky RE, et al. Defect size determines survival in infants with congenital diaphragmatic hernia. *Pediatrics*. 2007;120:e651–7.
51. Laughon M, Alldred EN, Bose C, et al. Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. *Pediatrics*. 2009;123:1124–31.
52. Lavoie PM, Pham C, Jang KL. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the National Institutes of Health. *Pediatrics*. 2008;122:479–85.
53. Litmanovitz I, Carlo WA. Expectant management of pneumothorax in ventilated neonates. *Pediatrics*. 2008;122:e975–9.

54. Lista G, Castoldi F, Bianchi S, et al. Volume guarantee versus high-frequency ventilation: lung inflammation in preterm infants. *Arch Dis Child*. 2008;93:F252–6.
55. Logan JW, Rice HE, Goldberg RN, Cotton CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. *J Perinatol*. 2007;27:535–49.
56. Mahut B, De Blic J, Emond S, et al. Chest computed tomography findings in bronchopulmonary dysplasia and correlation with lung function. *Arch Dis Child*. 2007;92:F459–64.
57. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed*. 2006;91:F320–6.
58. McEvoy C, Schilling D, Spitale P, et al. Decreased respiratory compliance in infants less than or equal to 32 weeks' gestation, delivered more than 7 days after antenatal steroid therapy. *Pediatrics*. 2008;121:e1032–8.
59. Mercier JC, Hummler H, Durrmeyer X, et al. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. *Lancet*. 2010;376:346–54.
60. Mestan KKL, Marks JD, Hecox K, et al. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med*. 2005;353:23–32.
61. Miller TL, Zhu Y, Altman AR, et al. Sequential alterations of tracheal mechanical properties in the neonatal lamb: effect of mechanical ventilation. *Pediatr Pulm*. 2007;42:141–9.
62. Moretti C, Giannini L, Fassi C, et al. Nasal flow-synchronized intermittent positive pressure ventilation to facilitate weaning in very low birth weight infants: unmasked randomized controlled trial. *Pediatr Int*. 2008;50:85–91.
63. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358:700–8. Erratum in: *N Engl J Med*. 2008;358:1529.
64. Murphy KE, Hannah ME, Willan AR, et al. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomized controlled trial. *Lancet*. 2008;372:2143–51.
65. Nixon PA, Washburn LK, Schechter MS, O'Shea TM. Follow-up study of a randomized controlled trial of postnatal dexamethasone therapy in very low birth weight infants: effects on pulmonary outcomes at age 8 to 11 years. *J Pediatr*. 2007;150:345–50.
66. Patel DS, Rafferty GF, Lee S, et al. Work of breathing during SIMV with and without pressure support. *Arch Dis Child*. 2009;94:434–6.
67. Patel DS, Sharma A, Prendergast M, et al. Work of breathing and different levels of volume-targeted ventilation. *Pediatrics*. 2009;123:e679–84.
68. Perlman JM, Wyllie J, Kattwinkel J, et al. Neonatal resuscitation: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Pediatrics*. 2010;126:e1319–44.

69. Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. *Cochrane Database Syst Rev.* 2007;4:CD006069.
70. Rabi Y, Rabi D, Yee W. Room air resuscitation of the depressed newborn: a systematic review and meta-analysis resuscitation. 2008;72:353–63.
71. Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics.* 2009;123:137–42.
72. Sai Sunil Kishore M, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. *Acta Paediatr.* 2009;98:1412–5.
73. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med.* 2006;354:2112–21.
74. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med.* 2007;357:1893–902.
75. Schreiber MD, Gin-Mestan K, Marks JD, et al. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med.* 2003;349:2099–107.
76. Scopesi F, Calevo MG, Rolfe P, et al. Volume targeted ventilation (volume guarantee) in the weaning phase of premature newborn infants. *Pediatr Pulm.* 2007;42:864–70.
77. Sharma A, Greenough A. Survey of neonatal respiratory support strategies. *Acta Paediatr.* 2007;96:1115–7.
78. Sharma A, Milner AD, Greenough A. Performance of neonatal ventilators in volume targeted ventilation mode. *Acta Paediatr.* 2007;96:176–80.
79. Singh J, Sinha SK, Alsop E, et al. Long term follow-up of very low birth-weight infants from a neonatal volume versus pressure mechanical ventilation trial. *Arch Dis Child Fetal Neonatal Ed.* 2009;94:F360–2.
80. Stenson B, Brocklehurst P, Tarnow-Murdi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med.* 2011;364:1680–2.
81. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev.* 2007;4:CD003063.
82. Straustrup A, Trasande L. Epidemiological characteristics and resource use in neonates with bronchopulmonary dysplasia: 1993–2006. *Pediatrics.* 2010;126:291–6.
83. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med.* 2010;362:1970–9. Erratum in: *N Engl J Med.* 2010;362:2235.
84. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362:1959–69.

85. Sweet D, Bevilacqua G, Carnielli V, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome. *J Perinat Med*. 2007;35:175–86.
86. Tingay DG, Mills JF, Morley CJ, et al. Trends in use and outcome of newborn infants treated with high frequency ventilation in Australia and New Zealand, 1996–2003. *J Paediatr and Child Health*. 2007;43:160–6.
87. Telford K, Waters L, Vyas H, et al. Outcome after neonatal continuous negative-pressure ventilation: follow-up assessment. *Lancet*. 2006;367:1080–5.
88. Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med*. 2009;360:111–20.
89. Vain NE, Szlyd EG, Prudent LM, et al. Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: multicenter randomized controlled trial. *Lancet*. 2004;364:597–602.
90. van den Hout L, Reiss I, Felix JF, et al. Risk factors for chronic lung disease and mortality in newborns with congenital diaphragmatic hernia. *Neonatology*. 2010;98:370–80.
91. Van Meurs KP, Wright LL, Ehrenkranz RA, et al. Inhaled nitric oxide for premature infants with severe respiratory failure. *N Engl J Med*. 2005;353:13–22.
92. Vargas-Origel A, Gomez-Rodriguez G, Aldana-Valenzuela C, et al. The use of Sildenafil in persistent pulmonary hypertension of the newborn. *Am J Perinatol*. 2010;27:225–30.
93. Ventolini G, Neiger R, Mathews L, et al. Incidence of respiratory disorders in neonates born between 34 and 36 weeks of gestation following exposure to antenatal corticosteroids between 24 and 34 weeks of gestation. *Am J Perinatol*. 2008;25:79–83.
94. Verlato G, Cogo PE, Balzani M, et al. Surfactant status in preterm neonates recovering from respiratory distress syndrome. *Pediatrics*. 2008;122:102–8.
95. Walsh MC, Hibbs AM, Martin CR, et al. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. *J Pediatr*. 2010;156:556–61.
96. Walsh MC, Laptook A, Kazzi SN, et al. A cluster-randomized trial of benchmarking and multimodal quality improvement to improve rates of survival free of bronchopulmonary dysplasia for infants with birth weights of less than 1250 grams. *Pediatrics*. 2007;119:876–90.
97. Watson RS, Clermont G, Kinsella JP, et al. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. *Pediatrics*. 2009;124:1333–43.
98. Wintermark P, Tolsa JF, Van Melle G, et al. Long-term outcome of preterm infants treated with nasal continuous positive airway pressure. *Eur J Pediatr*. 2007;166:473–83.
99. Yeh TF, Lin YJ, Lin HC, et al. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. *N Engl J Med*. 2004;350:1304–13.
100. Zupancic JAF, Hibbs AM, Palmero L, et al. Economic evaluation of inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *Pediatrics*. 2009;124:1325–32.

Appendix

Conversion Table A torr → kPa

torr	kPa
20	2.7
25	3.3
30	4.0
35	4.7
40	5.3
45	6.0
50	6.7
55	7.3
60	8.0
65	8.7
70	9.3
75	10.0
80	10.7
85	11.3
90	12.0
95	12.7
100	13.3
105	14.0
110	14.7
115	15.3
120	16.0
125	16.7
130	17.3
135	18.0

Conversion Table B kPa → torr

kPa	torr
2.5	19
3.0	22.5
3.5	26
4.0	30
4.5	34
5.0	37.5
5.5	41
6.0	45
6.5	49
7.0	52.5
7.5	56
8.0	60
8.5	64
9.0	67.5
9.5	71
10.0	75
10.5	79
11.0	82.5
12.0	90
12.5	94
13.0	97.5
13.5	101
14.0	105

Index

A

- Abbasi, S., 70
- Acetaminophen, 455–456, 480
- Adamkin, D., 425
- Adler, B.H., 70
- Adrenaline, 462
- Aggressive nutrition therapy, 427, 430
- Air leaks
 - description, 651
 - incidence of, 651
 - pathophysiology, 652
 - pneumomediastinum
 - diagnosis, 658
 - pathophysiology, 652
 - patient management, 658
 - pneumopericardium, 658–659
 - pneumoperitoneum, 659–660
 - pneumothorax
 - diagnosis, 652–653
 - etiology, 652
 - pathophysiology, 652
 - patient management, 653–657
 - prevention, 653
 - pulmonary interstitial emphysema
 - diagnosis, 657
 - management of, 658
 - risk factors, 651
 - subcutaneous emphysema,
 - 652, 659
- Air leak syndrome
 - adverse cardiopulmonary interaction, 334
 - ECMO, 334
 - mucostasis, 334–335
 - PIE, 333
 - pneumothorax, 334
 - severe persistent air leak, 336
- Airway lining
 - respiratory tract functions, 100
 - structure, 99–100
- Albuterol, 458
- Alveolar capillary dysplasia, 22
- Ambalavanan, N., 73, 87, 93
- Aminophylline, 457
- Analgesia
 - assessing adequacy of, 481
 - clinical implications of, 482–483
 - short-term consequences of, 482
 - use of, 478
- Andy, 70
- Aoyag, T., 155
- Apgar score, 122, 123
- Apnea, 45
 - AOP and AOI, 593
 - definition of, 593
 - diagnostic considerations, 597–600
 - etiology, 594, 595
 - medical conditions, 594, 595
 - periodic breathing, 593
 - risk groups
 - ALTE, 595–596
 - central alveolar hypoventilation syndrome, 596
 - infantile pathologic gastroesophageal reflux, 595
 - neurologic birth injury, 596
 - premature infants, 594
 - SIDS victims, siblings of, 596
 - term infants, 595
 - treatment, 600–605
- Apnea of prematurity (AOP), 457, 593, 600–602
- Apnea ventilation, 383–384

- Apparent life-threatening episode (ALTE), 593, 595–596
- Artificial airway compensation (AAC), 349
- Artificial noses, 104–105
- Asselin, J.M., 407
- Assist/control ventilation, weaning, 273, 612
- Atelectasis, 333–335
- Atracurium, 462–463
- Attar, M.A., 17
- Attention deficit hyperactivity disorders (ADHD), 645–646
- Auscultation, 115
- AVEA ventilator
 - alarms/limits, 350
 - features, 349–350
 - management, 353
 - monitoring, 350
 - nomenclature, 350–351
 - proximal flow sensor, 349
 - ventilation modality
 - pressure, 351–352
 - volume, 352–353
 - weaning and extubation, 354
- B**
- Babylog VN500 ventilator
 - alarms, 381–382
 - automatic tube compensation, 380
 - management, 384–385
 - nomenclature, 382
 - O₂ suctioning, 380–381
 - unit, 379
 - ventilation mode, 382–384
 - ventilator functions and monitor system, 379
 - volume measurement, 380
- Ballard, R.A., 494
- Bancalari, E., 469, 633
- Barrington, K.J., 417
- Bear Cub 750_{PSV} ventilator
 - alerts and alarms, 360–361
 - assist sensitivity, 359
 - breath types, 357
 - infant ventilator, 357
 - manual breath, 359
 - modes and modality, 358–359
 - monitor, 360
 - optional features, 361
 - overpressure relief valve, 359
 - oxygenation, 359
 - ventilation control, 359
- Becker, M.A., 341, 349
- Beck, J., 387
- Berglund, 70
- Bhatt-Mehta, V., 455
- Bhutani, V.K., 3, 27, 39, 61, 70
- Biphasic pressure release ventilation (BPRV), 370, 371, 373
- Bird VIP gold ventilator
 - alarm, 342
 - assist/control vs. SIMV/PS, 343
 - flow-cycling, 343–344
 - management, 346
 - monitoring
 - graphic monitor, 342
 - internal, 341
 - pressure vs. volume ventilation, 342
 - ventilation modality, 344–346
 - weaning and extubation
 - extubation, 348
 - pressure mode, 346–347
 - VAPS, 347
 - volume mode, 347
- Blood gases
 - air bubble, 163
 - arterial and venous, 162
 - arterial puncture/capillary stick, 163
 - capillary, 162
 - capillary blood gas values, 163
 - clinical interpretation, 164
 - dilution of, 163
 - gas exchange
 - physiology of, 159–160
 - mixed venous oxygen saturation, 161–162
 - noninvasive estimation of, 163
 - oxygen content, 160–161
 - oxygen delivery, 161–162
 - SaO₂, 163
 - target ranges, 164–165
 - UAC, 137
 - ventilator parameters, 97
- Blood urea nitrogen (BUN), 427, 430
- Blum-Hoffman, E., 334
- Borderline of viability
 - delivery room resuscitation, preterm
 - infants, 738–739
 - intensive care treatments, 740–741
 - regulation of supplemental oxygen, 737
 - ventilation strategies and equipment, 737–738
 - withdrawal of resuscitation
 - delivery room, 739
 - NICU, 739–740
- Boyle, E.M., 473
- BPD. *See* Bronchopulmonary dysplasia (BPD)
- BPRV. *See* Biphasic pressure release ventilation
- Brennan, G., 689
- Brockway, J., 51

- Bronchodilators, 457–458
- Bronchomalacia, 19
- Bronchopulmonary dysplasia (BPD)
- arterial oxygen saturation, 58
 - blood gases, clinical interpretation, 164
 - case study, 637–640
 - dead space volume, 35
 - definition of, 625–626
 - health consequences of, 625
 - HFV, optimal frequency, 303–304
 - home mechanical ventilation, 722
 - incidence of, 626
 - management
 - bronchodilators, 635–636
 - corticosteroids, 636
 - fluid management, 635
 - mechanical ventilation, 634–635
 - oxygen therapy, 633–634
 - pulmonary vasodilators, 637
 - neonatal morbidity, 643–644
 - newborns, long-term outcomes of
 - cognitive and academic consequences, 645–646
 - motor development, 645
 - nephrocalcinosis, 646
 - neurodevelopmental disability, 645
 - neurosensory impairment, 645
 - nutrition, 644
 - pulmonary hypertension, 646
 - respiratory abnormalities, 646
 - oxygen toxicity, 55
 - pathogenesis of
 - antioxidants, 627
 - fluids/PDA, 629
 - infection, 628
 - inflammation, 627–628
 - nutrition, 628
 - oxidative lung injury, 627
 - ventilator induced lung injury, 626–627
 - pathophysiologic changes, 629–630
 - postnatal maturation, 12
 - radiography, 184–185
 - smooth muscle hyperplasia, 10
 - surfactant replacement therapy, 444, 452
 - ventilation/perfusion mismatch, 514
 - withdrawal of assisted ventilation, 744
- Bronchopulmonary sequestration, 22
- Bronchoscopy
- clinical hints, 227
 - equipment, 225
 - indications, 226
 - intubated and nonintubated patient, 227
 - laryngotracheoesophageal cleft, 18
 - neonatal diagnoses, 227
 - patient preparation, 225–226
 - tracheal stenosis, 19
- Bumetanide, 459
- BUN. *See* Blood urea nitrogen
- Bunnell, J.B., 301
- Bunnell Life-Pulse high-frequency jet ventilator
- alarm, 404, 405
 - displayed parameter, 404
 - endotracheal tube adaptor, 403
 - functional button, 405
 - PIE treatment, 406
 - servo pressure, 404, 405
 - set variable, 403
 - suctioning, 405–406
- C**
- Caffeine, 457–458
- Campbell, D.M., 233
- Cardiac supportive therapy, 419
- Cardiogenic shock, 421–422
- Cardiopulmonary resuscitation, 462
- Cardiorespiratory system, clinical examination, 110
- Carlo, W.A., 73, 87, 93
- Carter, 334
- CDH. *See* Congenital diaphragmatic hernia (CDH)
- CDP. *See* Continuous distending pressure
- Central alveolar hypoventilation syndrome, 596
- Central venous pressure (CVP), 421, 571
- Chapman, R.L., 763
- Chatburn, R.L., 73, 87, 93, 363
- Chest physiotherapy (CPT), 557–558, 702–703
- Chest wall movements, 152–153
- Chiswick, M.L., 743
- Chlamydia trachomatis*, 547–548
- Chloral hydrate, 466
- Chlorothiazide, 459
- Chronic lung disease (CLD), 184, 333, 638
- Cis-atracurium*, 463
- Clark, R.H., 327, 332, 333
- Claure, N., 469
- Clinical examination
- abdomen, 113
 - air entry, 115
 - apnea, 112
 - auditory observations, 114
 - auscultation, 115
 - blood pressure, 110, 117–119
 - bowel sounds, 116

- Clinical examination (*cont.*)
- cardiac auscultation, 116–117
 - cardiorespiratory system, 110
 - central nervous system, 113
 - clubbing, 113
 - crepitations, 116
 - dyspnea, 111
 - gaspings, 112
 - general appearance, 112–113
 - heart sounds, 110
 - murmurs, 110
 - palpation, 114
 - percussion, 114–115
 - positive pressure ventilation, 111–112
 - pulse rate, 109–110
 - respiratory rate, 109, 111
 - rhonchi, 116
 - transillumination, 117
 - venous pressure, 113
- Clubbing, 113
- Congenital bronchiolar cysts, 21
- Congenital bronchogenic cysts, 19
- Congenital cystic adenomatoid malformation (CCAM), 21–22
- Congenital diaphragmatic hernia, 21
- Congenital diaphragmatic hernia (CDH), 201–203
- delivery, 580
 - ECMO, 571, 581
 - embryology, 577
 - FETO, 579–580
 - gastroesophageal reflux, 582
 - high-frequency ventilation, 314
 - incidence of, 577
 - infants, postnatal management of, 581
 - liquid ventilation, 207
 - neonatal respiratory failure, HFOV, 331
 - NICU, pre-operative, 580–581
 - pathophysiology, 577–578
 - postdischarge follow-up guidelines, 582
 - postoperative care, 581
 - prenatal fetal surgery, 579–580
 - presentation and diagnosis, 578
 - pulmonary morbidity, 582
 - surfactant replacement therapy, 452
 - surgical repair, 581
 - syndromic and nonsyndromic, 577
 - ventilatory case study, 583–585
- Congenital high airway obstruction syndrome (CHAOS), 18–19, 144
- Congenital lobar emphysema (CLE), 20, 200
- Congenital lobar overinflation, 200, 201
- Congenital pneumonia
- cytomegalovirus, 535–536
 - herpes simplex virus, 536
 - toxoplasmosis, 534–535
 - Treponema pallidum*, 537–538
- Congenital pulmonary airway malformation (CPAM), 198, 200
- Congenital pulmonary lymphangiectasis (CPL), 22–23
- Continuous distending pressure (CDP), 330
- Continuous positive airway pressure (CPAP)
- alveolar collapse, 237–239
 - apnea of prematurity, 601–602
 - apneic and bradycardic, 243
 - AVEA ventilator, 352
 - bear Cub 750_{psvr}, 359
 - biotrauma, 302
 - bird VIP Gold ventilator, 346
 - definitions of, 237
 - face mask, 240–241
 - hazards/complications, 244
 - indications for, 240
 - meconium aspiration syndrome, 558–559
 - postextubation, 243
 - preterm baby, 243
 - pulmonary hypoplasia, 589
 - SERVOi ventilator, 391
 - short binasal prongs, 241–242
 - surfactant, 448
 - weaning babies, 244
- Cook, 70
- Cools, F., 333
- Courtney, S.E., 332
- Cytomegalovirus, 535–536
- D**
- Dalton, J., 651
- Davis, J.M., 625
- Davis, P., 757
- Dexamethasone, 464–465
- Dipalmitoyl phosphatidylcholine (DPPC), pulmonary surfactant, 444
- Diuretics, 459–460
- Dobutamine, 460–461
- Documentation
- medical records, 752–753
 - nursing care, 701–702
 - resuscitation, 126
 - transport of newborns, 714
- Donn, S.M., 129, 137, 143, 211, 261, 267, 271, 275, 281, 285, 341, 455, 523, 565, 609, 651, 709, 751
- Dopamine, 461
- Dowd, S.A., 234
- Durand, D.J., 159, 407

Dyspnea

- analgesics, 456
- clinical examination, 111
- sildenafil, 467

E

Ebstein, 485, 567

Echocardiography

- accuracy and reproducibility, 223–224
- apical four chamber, 214, 216
- cardiac assessment, 214
- cardiac function, 218
- cardiovascular adaptation
 - newborn, 213
 - prematurity and respiratory disease, 213
- indications for, 218
- left ventricular assessment, 218–220
- long-axis parasternal, 214
- M-mode, 214, 216
- patent ductus arteriosus assessment, 222–223
- pulsed-wave Doppler cursor, 215, 217, 218
- right ventricular assessment, 221
- short-axis parasternal mitral, 214, 215
- short-axis parasternal pulmonary, 214, 215
- subcostal, 214
- stysolic function, Doppler assessment
 - cardiac output, 220–221
 - diastolic function, 222
 - ductal flow, 222
 - foramen ovale, 222
 - stroke volume, 220
 - time to peak velocity (TPV), 222
 - tricuspid regurgitation, 222

ECMO. *See* Extracorporeal membrane oxygenation (ECMO)

EFAD. *See* Essential fatty acid deficiency

Elastic unloading gain, 291, 292, 295

ELBW. *See* Extremely low birth weight (ELBW)

Electrocardiography (ECG), 153

Endotracheal intubation

- indications for, 129
- premedication, 130
- replacement, 134–135
- tube diameter, 130
- tube position, 134

Endotracheal tube (ETT), 205

End-tidal carbon dioxide (ETCO₂) monitoring, 152

Epinephrine, 458

Escherichia coli, 539

Esophageal atresia, 17, 114, 203, 204

Essential fatty acid deficiency (EFAD), 430

Expiratory reserve volume (ERV), 35

Extracorporeal membrane oxygenation (ECMO), 206, 207, 334

- circuit, 497
- circuit problems, 501–502
- congenital diaphragmatic hernia, 581
- daily management, patient protocols, problems, 500–501
- decannulation, 502–503
- description of, 497
- initial bypass problems, 499
- initial management, 499–500
- meconium aspiration syndrome, 560–561
- patient selection, 498
- post-ECMO follow-up, 503
- PPHN, 571
- pulmonary hypoplasia, 590
- transport of newborns, 719
- trial off, 502
- weaning, 502

Extremely low birth weight (ELBW)

- amino acids administration, 430
- glucose intolerance, 427
- intravenous lipid emulsions, 431
- milk fortification, 434
- nutrition of ventilated infants, 426
- oxygen toxicity, 55
- postdischarge nutrition, 436

Ex utero intrapartum treatment (EXIT) procedure, 144–145

F

Fanaroff, A.A., 109

Fanaroff, J.M., 109

FCV. *See* Flow control valve

Feather, 70

Feeding disorder

- GER, 441
- oropharyngeal hypersensitivity, 438, 440, 441
- swallowing disorder, 441

Fentanyl, 456

Fetal endoscopic tracheal occlusion (FETO), 579–580

Field, D., 577, 587

Fielder, A.R., 679

Filiano, J.J., 594

Finer, N.N., 225

Flow control valve (FCV), 349

Flow-volume (V-V) loop

- high airway resistance, 177
- inadequate flow, 176
- pulmonary graphics, 178
- suctioning, 178, 179

Flynn, 51
 Fractional oxygen extraction (FOE), 517
 Fraction of inspired oxygen (FiO_2)
 advantages of, 470
 arterial oxygen saturation, 469
 description, 469–470
 hyperoxemia and hypoxemia, 470–472
 tissue oxygenation, 49
 workload, 470
 Fuentes, L., 387
 Furosemide, 459–460

G

Gas exchange
 I:E ratio, 95
 liquid ventilation, 506
 PEEP, 94
 physiology of, 159–160
 PIP, 93
 tissue oxygenation, 49
 transition at birth, 40
 transition to extrauterine life, 76–77
 weaning strategies, 611
 Gastroesophageal reflux (GER), 441
 Gates, M.R., 709
 Gerhardt, T., 70
 Gerstmann, D.R., 332
 Ghavam, S., 255
 Glucose infusion rate (GIR), 427
 Graphical user interfaces (GUIs), 168–169
 Greenough, A., 513, 517, 521
 Gupta, S., 155

H

Hay, W.W., 51
 Hemodynamics
 cardiogenic shock, 421–422
 fetal circulation, 418
 hypotension, 422–423
 hypovolemic shock, 421
 neonatal cardiovascular physiology,
 417–418
 PPHN, 418–419
 septic shock, 419–421
 Henner, N., 625
 Herpes simplex virus (HSV), 536
 HFOV. *See* High-frequency oscillatory
 ventilation (HFOV)
 HFV. *See* High-frequency ventilation (HFV)
 High-frequency jet ventilation (HFJV), 531
 benefit, 319–320
 Bunnell Life-Pulse, 403

clinical application
 acute abdominal distention, 324
 airway disruption, 324
 disease pathophysiology, 321
 floppy airway, 325
 gas exchange control, 320–321
 low pressure strategy, 322
 MAS treatment, 323
 optimal volume strategy, 322–323
 patient selection, 320
 PPHN treatment, 324
 principles, 321
 weaning, 325
 complications, 320
 indication, 319
 NICU (*see* High-frequency ventilation)
 rheotrauma, 302

High-frequency oscillatory ventilation (HFOV)

advantages, 328
 alveolar recruitment, 312–313
 amplitude frequency, 408–409
 animal and human trials, 413
 breaths, 407
 vs. CMV, 328
 conventional ventilation, 412
 definition, 327
 development, 327–328
 disadvantages, 328–329
 general indications, 413
 limitations, 315
 lung inflation, 312–313
 minute ventilation
 air leak syndrome, 333–335
 animal studies, 333
 atelectasis, 333–335
 clinical trials, 331–333
 lung hypoplasia syndromes, 336
 MAS, 335
 oxygenation, 330
 physiology, 330–331
 Taylor dispersion, 330
 tidal volume, 329

NICU

exhalation and gas trapping, 308–309
 frequency, 309–310
 gas delivery and inspiration, 308
 inspiratory times and I:E, 310
 intrapulmonary gas distribution,
 310–311
 pressure waveforms, 310–311
 spontaneous breathing, 311
 oxygenation and ventilation, 408
 pulmonary hemorrhage, 675, 677

- rheotrauma, 302
 - types, 329
 - viscous shear and airway velocity profiles, 306
 - weaning and extubating, 411
 - High-frequency ventilation (HFV)
 - benefits, 315–316
 - BPD, 314
 - cardiac surgery patients, 314
 - CDH patients, 314
 - dead space reduction, 304–306
 - direct alveolar ventilation, 304–306
 - disruptive technology, 302–303
 - flow-streaming, 304–306
 - limitations, 315
 - lung protective ventilation
 - air leaks, 313–314
 - alveolar recruitment, 312–313
 - atelectrauma, 302
 - barotrauma, 301
 - biotrauma, 302
 - definition, 301
 - lung volume, maintenance of, 312–313
 - mechanical ventilation, lung injury, 301
 - preterm infants, 313
 - rheotrauma, 302
 - volutrauma, 302
 - meconium aspiration syndrome, 559
 - NICU
 - device similarities, 307
 - exhalation and gas trapping, 308–309
 - frequency, 309–310
 - gas delivery and inspiration, 307–308
 - HFJV, 306–307
 - hybrid devices, 307
 - inspiratory times and I:E, 310
 - intrapulmonary gas distribution, 310–311
 - pressure waveforms, 310–311
 - spontaneous breathing, 311
 - obstructive lung disorders, 314
 - optimal frequency, 303–304
 - pulmonary hyperinflation/gas trapping, 314
 - resonant frequency phenomena, 303
 - upper airway leaks and fistulas, 314
 - Hirschl, R.B., 505
 - Holleman-Duray, D., 234
 - Home mechanical ventilation
 - bronchopulmonary dysplasia, 722
 - chronic ventilation strategy, 723
 - complications of, 724–725
 - goals of, 723
 - indications
 - candidates, 722–723
 - chronic respiratory failure, 721
 - medical assessment, 721–722
 - modes and types of, 723–724
 - monitoring systems, 724
 - nonmedical assessment, 723
 - Human metapneumovirus (hMPV), 551–552
 - Humidification
 - aerosol application, 105
 - airway irrigation, 105
 - artificial noses, 104–105
 - basic physics of
 - nebulized water, 100
 - relative humidity (RH), 101
 - total heat content, 101–102
 - vaporized water, 101
 - heated humidifiers, 102–104
 - humidifier malfunction, 99
 - inadequate, 99
 - inspiratory gas conditioning, 106
 - nosocomial infection risk, 106
 - Humidified high-flow nasal cannula (HFNC)
 - clinical applications, 233–234
 - mechanisms of action, 232
 - risks and benefits of, 232–233
 - Hydrocortisone, 465
 - Hygroscopic condenser humidifiers (HCH), 104
 - Hypercapnia, 45, 81
 - Hyperoxia
 - brain, 57
 - lungs, 58
 - monitoring oxygen therapy, 52
 - prevention of, 59
 - retina, 57–58
 - transcription factors, 57
 - vitamin A derivatives, 628
 - Hyperviscosity syndrome, 567
 - Hypotension, 422–423
 - Hypoxemia, 45, 46
 - diffusion limitation, 80
 - hypoventilation, 80
 - shunt, 79
 - ventilation-perfusion ratios, 78
 - V/Q mismatch, 79
- I**
- IMV. *See* Intermittent mandatory ventilation (IMV)
 - Inhaled nitric oxide (iNO) therapy
 - candidates, 490–492
 - clinical benefits of, 486
 - cyanotic newborn
 - echocardiography, 489, 490

- Inhaled nitric oxide (iNO) therapy (*cont.*)
- history, 486–487
 - laboratory and radiologic evaluation, 488
 - physical examination, 487
 - pulse oximetry measurements, 487–488
 - supplemental oxygen, 489
 - diagnostic value of, 486
 - meconium aspiration syndrome, 560
 - physiologic rationale, 485
 - PPHN, 485–486
 - preterm newborn, 494–495
 - pulmonary hypoplasia, 589
 - treatment strategies
 - dosage and duration, 492
 - monitoring, 493
 - ventilator management, 493
 - weaning, 492–493
- Inotrope, 460–462
- Inspiratory reserve volume (IRV), 35
- Intermittent mandatory ventilation (IMV)
- bear Cub 750_{PSV}, 358
 - breath controls, 263–264
 - characteristics of, 261–262
 - complications, 262–263
 - definition of, 261
 - indications, 262
 - patient management, 265–266
 - PAV, 295
 - positive end-expiratory pressure, 264–265
 - weaning, 266, 613
- Intraventricular hemorrhage (IVH)
- HFJV, 320
 - HFOV, 332
- Ipratropium, 458
- J**
- Javier, M.-C., 443
- Johnson, A.H., 333
- K**
- Kamlin, O., 757
- Karlberg, 70
- Keszler, M., 319, 332, 403
- Kinney, H.C., 594
- Kinsella, J.P., 334, 485, 494
- Kirpalani, H., 247, 255
- L**
- Lagatta, J., 737
- Lal, M., 727
- LaMar, K., 697
- Lampland, A.L., 231
- Laryngoscopy, oral intubation, 131–133
- Laryngotracheoesophageal cleft, 18
- Laventhal, N., 737
- Leach, C.L., 508
- Lemyre, B., 247
- Liquid ventilation
- CDH, 207
 - description, 505
 - perfluorocarbon ventilation, physiology of, 505–507
 - PILG, 509
 - PLV, 507–508
 - TLV, 508
- Listeria monocytogenes*, 539–540
- Lorazepam, 466
- Lung anomalies
- categorizations, 18
 - distal lung parenchyma malformations
 - alveolar capillary dysplasia, 22
 - bronchopulmonary sequestration, 22
 - CCAM, 21–22
 - congenital bronchiolar cysts, 21
 - congenital diaphragmatic hernia, 21
 - CPL, 22–23
 - interstitial lung disease, 23
 - pulmonary agenesis, 20
 - pulmonary hypoplasia, 20
 - tracheobronchial tree malformations, 18–20
- Lung compliance
- bronchopulmonary dysplasia, 65
 - definition of, 63
 - hysteresis, 62
 - pressure-volume curve, 62
 - pressure-volume relationship, 63
 - surface-active substance, 63
 - tissue elasticity, 63
 - young healthy newborn, 63
- Lung hypoplasia syndromes, 336
- M**
- Mammel, M.C., 231
- Mandatory minute ventilation, 288
- MAS. *See* Meconium aspiration syndrome (MAS)
- McGrath, 70
- McIntosh, N., 473
- Meadow, W., 737
- Mechanical ventilation
- absolute indications, 521
 - apnea of prematurity, 602
 - blood gas analysis
 - arterial blood gas values, 81, 83

- classifications, 81, 82
 - metabolic acidosis and alkalosis, 84
 - respiratory acidosis and alkalosis, 83, 84
 - bronchopulmonary dysplasia, 634–635
 - CO₂ elimination, 81, 82
 - compliance, 73–74
 - control variables
 - equation of motion, 87, 88
 - flow controller, 87
 - pressure controller, 87
 - time controller, 88
 - volume controller, 87
 - equation of motion, 76
 - gas exchange, 76
 - extrauterine life, 76–77
 - hypercapnia, 81
 - hypoxemia, 78–80
 - inspired and alveolar gases composition, 77
 - lung injury, 301
 - mixed venous blood, 77–78
 - neurologic complications of
 - arterial blood pressure fluctuations, 690–691
 - cerebral injury, sick premature infants, 689, 690
 - effects of PaCO₂, 692
 - impedance of venous return, 691–692
 - PVL and PV-IVH lesions, 689, 690
 - RDS, complications of, 692
 - sensorineural hearing loss, 692
 - skeletal muscle paralysis, 691
 - therapeutic strategies, 693
 - use of sedatives, 691
 - volume-targeted vs. pressure-targeted ventilation, 692
 - oxygenation, 80–81
 - phase variables
 - baseline (PEEP), 90
 - cycle, 89–90
 - limit, 89
 - trigger, 89
 - ventilator-supported breath, 88, 89
 - PPHN, 569–570
 - pulmonary gas exchange, determinants, 77
 - pulmonary mechanics, 73
 - relative indications
 - delivery room, 521
 - NICU, 522
 - resistance, 74
 - time constant
 - incomplete inspiration and expiration, 75, 76
 - neonatal acid-base map, 74
 - ventilatory modes, 90
- Meconium aspiration syndrome (MAS), 335
 - conventional management of
 - chest physiotherapy, 557–558
 - continuous positive airway pressure, 558–559
 - mechanical ventilation, 559
 - nasal cannula, 558
 - oxygen, 558
 - therapies, 559
 - definition of, 555
 - HFJV treatment, 323
 - meconium-stained amniotic fluid, 555
 - neonatal respiratory failure, HFOV, 331
 - nonconventional management
 - bolus exogenous surfactant, 559–560
 - ECMO, 560–561
 - high-frequency ventilation, 559
 - inhaled nitric oxide, 560
 - steroid therapy, 560
 - pathophysiology, 556
 - PPHN, 566
 - prevention of, 556–557
 - pulmonary air leak, risk of, 651
 - pulmonary hemorrhage, 670
 - radiographic finding, 557
 - radiography, 187, 188
 - surfactant replacement therapy, 451
 - ventilation/perfusion mismatch, 514
 - ventilatory case study, 561–563
 - Meconium-stained amniotic fluid (MSAF), 555
 - Medical liability
 - definition, 751
 - legal bases of, 751
 - medical negligence, 752
 - neonatology, 752
 - tort, 751
 - Medical literature
 - clinical research
 - causality, 758
 - diagnostic tests, 758, 759
 - prognosis, 759
 - therapy, 758
 - evidence, search engines, 760
 - statistical tests, 760
 - Mercier, J.C., 494
 - Midazolam, 466
 - Migdal, 70
 - Migliori, C., 508
 - Miller, C., 369
 - Miller, S.M., 234
 - Miller, T.L., 234
 - Milner, A.D., 513, 517, 521
 - Milrinone, 461

- Morley, C.J., 237
 Morphine, 456–457
 Mortola, 70
 Moya, F., 443
 Murthy, P., 643
- N**
- Nakajima, S., 155
 Nasal cannula therapy. *See* Humidified high-flow nasal cannula
 Nasal intermittent positive pressure ventilation (NIPPV)
 definition of, 247–248
 evidence of, 248–249
 physiological mechanism, 248
 Nasotracheal intubation, 133–134
 National Neonatal Audit Programme (NNAP), 733
 Nelson, D.B., 70
 Neonatal cardiovascular physiology
 cardiac function, 417
 shunts, 418
 vascular response, 417–418
 Neonatal intensive care unit (NICU)
 borderline of viability, withdrawal of resuscitation, 739–740
 discharge planning
 advantages, 727
 assessment of infant, 728
 discharge letter and communication, 729
 family assessment, 728
 features of, 727
 predischARGE evaluation and examination, 728–729
 follow-up of, 729–732
 high-frequency ventilation
 device similarities, 307
 effective frequency, 309–310
 exhalation and gas trapping, 308–309
 gas delivery and inspiration, 307–308
 HFJV, 306–307
 hybrid devices, 307
 inspiratory times and I:E, 310
 intrapulmonary gas distribution, 310–311
 pressure waveforms, 310–311
 spontaneous breathing, 311
 mechanical ventilation
 absolute indications, 521
 relative indications, 522
 NNAP 2-year corrected age outcome proforma, 733
 pulmonary hypoplasia, 589–590
 transportation, 718–719
- Neonatal pneumonia, radiography, 187, 189, 190
 Neonatal resuscitation. *See* Resuscitation
 Neurally Adjusted Ventilatory Assist (NAVA), 390–391
 Newport e360 ventilator
 alarms, 377–378
 control variables, 370
 cycle variables, 371–372
 exhalation system, 373
 features, 369
 inhalation system, 373
 input, 370
 operator-set control, 372–376
 output, 376
 phase variables, 371
 Newport wave ventilator
 alarms, 367
 classification, 363
 clinical feature, 367
 control subsystem
 circuit, 365–366
 drive mechanism, 366
 output control valve, 366
 control variable, 363
 input, 363
 mode, 365
 output, 366–367
 phase variable, 364–365
 Nicks, J., 167, 357
 NICU. *See* Neonatal intensive care unit (NICU)
 Noninvasive ventilation (NIV)
 apnea, 250
 complications of, 251
 nasal interface, 249
 NIPPV (*see* Nasal intermittent positive pressure ventilation)
 non-synchronized nasal ventilation, 249
 post-extubation, 250
 putative benefits, 251
 respiratory distress syndrome, 250
 SERVOi ventilator, 387, 388, 395–396
 settings, 250–251
 synchronized nasal ventilation, 249–250
 Noradrenaline, 461–462
 Northway, W.H. Jr., 643
 Null, D.M. Jr., 379
 Nursing care
 assessment
 auscultation, 699
 observation, 697–698
 chest drainage devices, 704–705
 chest physiotherapy/postural drainage, 702–703

- documentation, 701–702
- history taking, 697
- infant positioning, 705–706
- monitoring, 700
- newborns, respiratory care of, 702
- pharmacotherapy, 701
- radiology, 700
- respiratory disease, 697
- securing respiratory devices, 705
- suctioning, 703–704
- transillumination, 704
- transport of newborns, 702
- use of assistive devices, 704
- weighing, 705
- Nutrition of ventilated infants
 - aggressive strategy, 425
 - ELBW, 426
 - enteral requirement
 - caloric density strategy, 435–437
 - feeding, 438–440
 - feeding practicum, 433–434
 - fetal growth, 432–433
 - human milk, 433–435
 - PDF, 437
 - time of discharge, 437, 438
 - feeding disorder
 - GER, 441
 - oropharyngeal hypersensitivity, 438, 440, 441
 - swallowing disorder, 441
 - neonatal intensive care unit, 425
 - optimize neurodevelopmental, 425–426
 - protein and energy requirement
 - aggressive nutrition therapy, 427, 430
 - EFAD, 430
 - estimation method, 426, 427
 - GIR, 427
 - TPN, 427–429
 - TPN, 431, 432
- O**
- Oxygenation index (OI), 50
- Oxygen inhalation, 45, 46
- Oxygen therapy
 - alveolar-arterial oxygen pressure difference (A-aDO₂), 50
 - arterial-to-alveolar oxygen tension ratio (a/A ratio), 50
 - clinical evidence, 52–53
 - continous noninvasive and invasive monitoring, 52
 - fetal oxygen transport, 49–50
 - intermittent monitoring, 52
 - OI, 50
 - oxygen saturation (SaO₂), 50–51
 - oxygen saturation targeting trials, 53
 - PaO₂, 50–51
 - tissue oxygenation, 49
- Oxygen toxicity
 - clinical implications
 - oxygenation, beyond delivery room, 59
 - oxygenation, in delivery room, 58–59
 - hyperoxia
 - brain, 57
 - lungs, 58
 - prevention of, 59
 - retina, 57–58
 - in newborn period, 55–57
- P**
- Pain
 - analgesia and sedation
 - assessing adequacy of, 481
 - use of, 478
 - assessment of
 - acute distress, 475
 - clinical tools, 475, 476
 - research tools, 475
 - sub-acute distress, 475
 - ventilatedpreterm infants, 477
 - behavioral changes, 473, 474
 - causes of, 473, 474
 - definition of, 473
 - inadequate analgesia, effects of, 482–483
 - non-pharmacologic interventions, 477
 - pharmacologic interventions
 - local anesthetics, 481
 - non-opioids, 480
 - opioids, 477, 479–480
 - sedative drugs, 480–481
 - sucrose, 477
 - pharmacologic management, 477, 478
 - physiologic changes, 475
 - preterm infant, 481–482
 - sources of, 482
 - therapeutic interventions and outcome, 483
- Pancuronium, 463
- Paranka, M.S., 334
- Parravicini, E., 533
- Partial liquid ventilation (PLV)
 - gas exchange, hybrid method of, 507
 - neonatal respiratory failure, 508
 - respiratory distress syndrome, 507–508

- Patent ductus arteriosus (PDA)
 assessment of, 222, 223
 bronchopulmonary dysplasia, 629
 clinical effects of, 664
 clinical features, 664–665
 diagnosis, 665–666
 fetal circulation, 663
 furosemide, 459
 incidence, 663
 persistent ductal patency, 664
 physiologic effects of, 664
 postnatal closure, 663–664
 pulmonary hemorrhage, 674
 treatment, 666
- Patient-triggered ventilation (PTV), 271, 291
- PAV. *See* Proportional assist ventilation (PAV)
- PDA. *See* Patent ductus arteriosus (PDA)
- PDF. *See* Postdischarge formula
- PEEP. *See* Positive end-expiratory pressure (PEEP)
- Percussion, 114–115
- Perfluorocarbon-induced lung growth (PILG), 509
- Perfluorocarbon (PFC) ventilation
 biodistribution, elimination, and toxicology, 507
 neonatal respiratory failure
 gas exchange, 506
 lung injury, reduction of, 506–507
 pulmonary compliance, 506
 physical properties, 505–506
 PILG, 509
 uptake, 507
- Peripheral artery catheterization, 139–140
- Peripheral intravenous catheters, 140–141
- Periventricular intraventricular hemorrhage (PV-IVH), 689
- Periventricular leukomalacia (PVL), 689
- Perlman, J.M., 689
- Persistent fetal circulation (PFC), 565
- Persistent pulmonary hypertension (PPHN)
 description of, 565
 diagnosis
 echocardiography, 569
 hyperoxia-hyperventilation test, 568–569
 hyperoxia test, 568
 hypoxemia, differential diagnoses of, 567
 initial work-up, 567–568
 pre- and postductal oxygenation, evaluation of, 568
 hemodynamics, 418–419
 HFJV treatment, 323
 iNO therapy, 485–486
- pathogenesis
 abnormal pulmonary vascular morphology, 567
 normal pulmonary vascular morphology, 566–567
 structurally abnormal heart disease, 567
- PFC, 565
- pulmonary vascular development, 566
- radiography, 187, 188
- treatment
 ECMO, 571
 general supportive measures, 569
 mechanical ventilation, 569–570
 pharmacotherapy, 571
 prenatal and postnatal, 569
 ventilatory case study, 572–575
- Pharmacologic agents
 analgesics, 455–457
 bronchodilators and respiratory stimulants, 457–458
 diuretics, 459–460
 inotropes, 460–462
 pulmonary vasodilator, 466–467
 sedative, 466
 skeletal muscle relaxant, 462–464
 steroids, 464–465
- PIE. *See* Pulmonary interstitial emphysema
- Pleural effusion, radiography, 189, 191–193
- Pneumomediastinum
 diagnosis, 658
 pathophysiology, 652
 patient management, 658
- Pneumonia
 acquired before, duringFTER BIRTH
 bacterial pathogens, 539–540
 clinical history and manifestations, 540
 diagnosis, 541–544
 epidemiology, 538–539
 lung injury, pathophysiology of, 538
 management, 544–546
 pathogenesis, 539
 pathology, 538
 prevention, 546
Chlamydia trachomatis, 547–548
 congenital pneumonia
 cytomegalovirus, 535–536
 herpes simplex virus, 536
 toxoplasmosis, 534–535
Treponema pallidum, 537–538
 human metapneumovirus, 551–552
 lung host defenses, 533–534
 neonatal respiratory failure, HFOV, 331
 newborn infants, 533
 PPHN, 566–567

- pulmonary air leak, risk of, 651
 - respiratory syncytial virus, 550–551
 - surfactant replacement therapy, 452
 - Ureaplasma urealyticum*, 546–547
 - ventilation/perfusion mismatch, 514
 - ventilator-associated pneumonia, 548–550
- Pneumopericardium, 652, 658–659
- Pneumoperitoneum, 659–660
- Pneumothorax
 - diagnosis, 652–653
 - etiology, 652
 - pathophysiology, 652
 - patient management
 - needle aspiration, 653–654
 - nitrogen washout, 653
 - pigtail catheter technique, 656–657
 - straight chest tube technique, 654–656
 - prevention, 653
- Poets, C.F., 149
- Polgar, G., 70
- Polin, R.A., 533
- Positive end-expiratory pressure (PEEP), 94
 - airway pressure, 257
 - alveolar collapse, 237–239
 - application, 258–259
 - AVEA ventilator, 353
 - definition of, 255
 - determination, 257–258
 - evaluation, 258
 - evidence, 255–256
 - extubation criteria, 259
 - hazards, 259
 - indications for, 257
 - PAV, 292, 293
 - physiology, 256
- Postdischarge formula (PDF), 437
- PPHN. *See* Persistent pulmonary hypertension (PPHN)
- Pranikoff, T., 508
- Prenatal fetal surgery, 579–580
- Pressure control (PC), 352
- Pressure control ventilation
 - advantages and disadvantages, 282
 - clinical applications, 282
 - clinician-set parameters, 282
 - features of, 281
 - pressure-targeted modalities comparison, 282
- Pressure regulated volume control (PRVC),
 - SERVOi ventilator, 389
- Pressure support ventilation (PSV)
 - advantages of, 288
 - bear Cub 750_{psv}, 358
 - clinical applications, 287
 - cycling mechanisms, 285
 - mandatory minute ventilation, 288
 - patient management, 286–287
 - PAV, 291
 - premature termination, 287
 - pressure overshoot, 287
 - SLE5000 and SLE4000 ventilator, 401
 - trigger failure, 287
 - trigger mechanisms, 285–286
 - volume-assured, 288
- Proportional assist ventilation (PAV)
 - flow-proportional assist, 293, 294
 - patient management
 - ETT leak flow, 296
 - indication, 294
 - initiation in infants, 295
 - sensor malfunction, 296
 - weaning, 295–296
- PEEP, 292, 293
- PSV, 291
- PTV, 291
 - respiratory center activity, 292
 - safety limits, 293
 - volume-proportional assist, 292–293
- PSV. *See* Pressure support ventilation (PSV)
- PTV. *See* Patient-triggered ventilation
- Pulmonary agenesis, 20
- Pulmonary gas exchange
 - apnea, 45
 - birth transition, 40
 - cardiopulmonary adaptations, 40–42
 - gas laws, 40–41, 43
 - hypercapnia, 45
 - hypoxemia, 45, 46
 - maladaptations delay transition, 45
 - neonatal, 45, 46
 - oxygenation/ventilation failure, 45
 - oxygen inhalation, 45, 46
 - physiologic principle, 47
 - physiologic process, 44–45
 - pulmonary vasculature development, 43–44
- Pulmonary graphics
 - dynamics measurements/calculations, 179
 - flow waveform
 - exhalation, 171, 172
 - flow cycling, 171
 - higher resistance, 172
 - volume-and pressure-limited breath types, 170
 - graphical user interfaces, 168–169
 - graphic loops
 - flow-volume (V-V) loop, 175–179
 - pressure-volume (P-V) loop, 174–176
 - indications, 167–168

- Pulmonary graphics (*cont.*)
 - pressure waveform, 169–170
 - volume waveform
 - inspiration representation, 172, 173
 - leak, 172, 173
 - mechanical volumes vs. spontaneous volumes, 172, 173
 - patient-ventilator interaction, 173, 174
 - Pulmonary hemorrhage
 - clinical features, 672, 673
 - description, 669
 - incidence
 - autopsy, 670
 - gestational age, 669–670
 - infants, ECMO therapy, 670
 - NICU population, 669
 - investigations
 - blood tests, 674–675
 - chest radiograph, 673–674
 - PDA, 674
 - mortality and morbidity, 676
 - pathology, 671–672
 - pathophysiology, 670, 671
 - prevention, 676–677
 - risk factors, 670
 - treatment, 675–676
 - Pulmonary hypertension
 - BPD infants, 646
 - bronchopulmonary dysplasia, 625
 - Pulmonary hypoplasia, 20
 - classification, 587–588
 - counselling, future pregnancies, 590
 - diagnosis, 588
 - pathophysiology, 588
 - patient management, 589–590
 - prognosis, 590
 - pulmonary air leak, risk of, 651
 - utero intervention, 582
 - Pulmonary interstitial emphysema (PIE), 195–197, 333
 - Bunnell Life-Pulse treatment, 406
 - diagnosis, 657
 - management of, 658
 - pulmonary hemorrhage, 670
 - Pulmonary mechanics
 - BPD probabilities, 71
 - elastic properties
 - chest wall compliance, 65–66
 - definition, 62
 - lung compliance, 62–65
 - lung parenchyma, 61–62
 - total respiratory system compliance, 65
 - visceral pleura, 62
 - inertial properties, 68
 - neonatal pulmonary function parameters, 70
 - PMA, 71
 - postnatal alterations, 61
 - resistive properties, 66–68
 - respiratory parameters, 70
 - surfactant replacement, 71
 - work of breathing, 68–69
 - Pulmonary sequestration, radiography, 200, 201
 - Pulmonary vasodilator, 466–467
 - Pulse oximetry
 - abnormal hemoglobins, 156
 - advantages of, 155
 - anemia, 157
 - calibration and accuracy, 157
 - delay of response, 157
 - disadvantages of, 155–156
 - effect of dyes, 157
 - electrical/magnetic interference, 158
 - factors influencing measurements, 149–150
 - hypoxemia and hyperoxemia detection, 150
 - light sources interference, 158
 - motion artifact, 157
 - operation principles, 149
 - optimal use, rules, 158
 - oxyhemoglobin dissociation curve, 156
 - reduced perfusion states, 157
 - terminology, 156
 - venous pulsations, 157
 - Pulse oxygen saturation, 52. *See also* Oxygen therapy
- R**
- Radiography
 - air leaks
 - pneumomediastinum, 194, 195
 - pneumothorax, 192–194
 - pulmonary interstitial emphysema (PIE), 195–197
 - atelectasis, 189, 191
 - bronchopulmonary dysplasia, 184–186
 - CDH, 201–203
 - chest wall deformities, 206, 208
 - computed tomography, 182
 - congenital cardiovascular anomalies, 196–199
 - congenital lobar overinflation, 200, 201
 - conventional, 181–182
 - CPAM, 198, 200
 - esophageal atresia, 203, 204
 - fluoroscopy, 184
 - magnetic resonance imaging, 182–183

- meconium aspiration syndrome., 187, 188
- neonatal pneumonia, 187, 189, 190
- persistent pulmonary hypertension (PPHN), 187, 188
- pleural effusion, 189, 191–193
- pulmonary sequestration, 200, 201
- respiratory distress syndrome, 184, 185
- tracheal stenosis, 203, 205
- tracheoesophageal fistula, 203, 204
- transient tachypnea, 185–187
- tubes and catheters assessment
 - ECMO, 206, 207
 - endotracheal tube (ETT), 205
 - vascular catheters, 205
- ultrasound, 183
- Radiology, nursing care, 700
- Raju, T.N.K., 669
- RDS. *See* Respiratory distress syndrome (RDS)
- Recombinant factor VIIa (rFVIIa), 675–676
- Rennie, J.M., 121
- Residual volume (RV), 35, 37
- Resistance unloading gain, 293, 294
- Respiratory distress syndrome (RDS), 447–449
 - biochemical abnormalities, 523–524
 - clinical manifestations of, 525
 - complications, 527–528
 - definition, 523
 - diagnosis, 525
 - differential diagnoses, 525–526
 - functional abnormalities, 524
 - HFOV, 331–332
 - HFV, optimal frequency, 303–304
 - histopathologic abnormalities, 524
 - incidence and severity of, 523
 - laboratory abnormalities, 525
 - management algorithm, 96, 97
 - mechanical ventilation and brain injury, 692
 - morphologic/anatomic abnormalities, 524
 - neonatal respiratory failure
 - HFOV, 331
 - partial liquid ventilation, 507–508
 - neonatal respiratory failure, HFOV, 331
 - prenatal treatments, 528
 - pulmonary air leak, risk of, 651
 - pulmonary hemorrhage, 673
 - pulmonary interstitial emphysema, 657
 - radiographic findings, 525
 - radiography, 184, 185
 - reduced respiratory compliance, 514
 - treatment
 - adjunctive measures, 527
 - gas exchange, 526
 - surfactant replacement therapy, 526–527
 - ventilation/perfusion mismatch, 514
 - ventilatory case study
 - chest radiographs, 529–530
 - clinical course, 529
 - denouement, 531
 - diagnosis, 531
 - laboratory values, 530–531
 - physical finding, 529
 - prenatal and patient data, 529
 - therapies, 531
- Respiratory failure
 - high-frequency jet ventilation, 319
 - intubation, 129
 - liquid ventilation
 - description, 505
 - perfluorocarbon ventilation, physiology of, 505–507
 - PILG, 509
 - PLV, 507–508
 - TLV, 508
 - lung development, 4
 - mechanisms of
 - alveolar-capillary interface, 515
 - gas exchange, abnormality of, 513
 - hypoventilation, 514
 - hypoxemia, 513–514
 - ventilatory pump failure, 514–515
 - optimal pulmonary gas exchange, 45
 - volume-targeted ventilation, 277
- Respiratory gas conditioning
 - aerosol application, 105
 - airway irrigation, 105
 - artificial noses, 104–105
 - basic physics of, 100–102
 - heated humidifiers, 102–104
 - humidifier malfunction, 99
 - inadequate, 99
 - inspiratory gas conditioning, 106
 - nosocomial infection risk, 106
- Respiratory syncytial virus (RSV), 550–551
- Respiratory system development
 - alveolarization, 5
 - amniotic leak, 4
 - branching morphogenesis, 5
 - descriptive embryology, lung, 12–14
 - factors, 5
 - functional areas, 3
 - fundamental process, 6–7
 - human developmental stages, 14–15
 - lower airway, 9–10
 - lung
 - factors influencing, 8
 - fetal lung fluid and variations, 8
 - functional anatomy, 7
 - mechanical property, 7

- Respiratory system development (*cont.*)
- magnitude, 6
 - mammalian lung, 4
 - neonatal, 3
 - physical forces, 5–6
 - prenatal development, 6
 - pulmonary vasculature, 6
 - thoracic and muscle
 - anatomy, 10–11
 - postnatal maturation, 11–12
 - respiratory contractile function, 11
 - upper airway, 8–9
- Resuscitation
- with 100% oxygen, 126–127
 - airway, 123
 - apgar score, 122, 123
 - breathing, 123, 125
 - ceasing, 126
 - circulation, 125
 - documentation, 126
 - drugs, 125
 - equipment needed, 121–122
 - failure to respond, 126
 - ILCOR algorithm, 123, 124
 - infant assessment, 122
 - initiation, 122
 - meconium-stained fluid, 127
 - normal postnatal transition, 121
 - preterm babies, 127
 - response monitoring, 125
 - sodium bicarbonate, 127
 - therapeutic hypothermia, 127
- Retinopathy of prematurity (ROP)
- anti-VEGF agents, 687
 - childhood blindness, 679
 - examination protocol, 681–685
 - international classification of, 679, 680
 - low birthweight babies, follow-up of, 686
 - ophthalmic follow-up, 686
 - ophthalmologic examination, 728
 - parents, 687
 - prophylaxis, 679–681
 - responsibilities and organization, 687
 - retinovascular changes, automated vessel
 - analysis, 687
 - screening, 681
 - treatment, 685–686
- Risk management
- attitude, 753
 - culture, 754
 - knowledge, 753–754
 - risk, identification of, 753
 - root cause analysis, 754
- Röhler, 28, 29
- Röhler equation, 28
- Ronchetti, 70
- Root cause analysis (RCA), 754
- ROP. *See* Retinopathy of prematurity (ROP)
- Russell, 70
- S**
- Saigal, S., 643
- Salbutamol, 458
- Sanchez, R., 181
- Sarkar, S., 17
- Saslow, J.G., 234
- Saugstad, O.D., 55
- Schulze, A., 99, 291
- Schumacher, R.E., 565
- Sedative, 466
- Sensorineural hearing loss, 692
- SensorMedics 3100
- amplitude, 410
 - animal and human trials, 413
 - conventional ventilation, 412
 - FiO₂, 410
 - flow, measured in liters per minute (LPM), 410
 - frequency, measured in Hz, 410
 - general indications, 413
 - mean airway pressure, 409
 - optimizing settings, 411
- Septic shock, 419–421
- SERVOi ventilator
- active expiratory valve, 387
 - automode, 391–392
 - capability, 387
 - control panel and display, 392–395
 - CPAP, 391
 - NAVA, 390–391
 - NIV, 387, 388
 - noninvasive ventilation, 395–396
 - pressure support, 390
 - ventilation combination, 391
 - ventilation control, 388–389
 - volume support, 389–390
- Shoemaker, M.T., 234
- Sildenafil, 467
- SIMV. *See* Synchronized intermittent mandatory ventilation (SIMV)
- Sinha, S.K., 261, 267, 271, 275, 285, 397, 523, 609
- Sivieri, E.M., 27, 61, 70
- Skeletal muscle paralysis, 691
- Skeletal muscle relaxant, 462–464
- SLE5000 and SLE4000 infant ventilators
- electronic system, 398

- feature, 397
 - modality, 397
 - pneumatic system
 - advanced mode, ventilation, 401–402
 - alarm, 400
 - blending, 398
 - conventional ventilation, 399
 - HFO ventilation, 399–400
 - LCD screen display, 400
 - pressure generation, 398
 - targeted tidal volume, 401
 - trigger mechanism, 400
 - Spironolactone, 460
 - Spitzer, A.R., 593
 - Spontaneous breathing
 - driving pressure
 - intrapleural and alveolar, 29–30
 - intrapleural pressure, elastic component, 31–32
 - mechanical ventilation, 32
 - slow static inflation, 31
 - tidal breathing, 31
 - lung volumes
 - ERV, 35
 - FRC, 37
 - graphic representation, 35, 36
 - IRV, 35
 - RV, 35, 37
 - TGV, 37
 - TLC, 36
 - VC, 36
 - ventilatory volume, 34–35
 - mechanics of airflow
 - pathophysiologic states, 34
 - physical factors, 33
 - physiologic factors, 34
 - signals of
 - graphic representation, respiratory cycle, 27, 28
 - linear, first-order model, 28–29
 - Röhrer equation, 28
 - Sreenan, C., 234
 - Steroids, 464–465
 - Strang, 70
 - Streptococcus agalactiae*, 539
 - Strouse, P.J., 181
 - Subcutaneous emphysema, 652, 659
 - Sudden infant death syndrome (SIDS)
 - postneonatal infant mortality, 596
 - protective strategies, 603–605
 - risk factors, 596, 597
 - triple-risk model, 594
 - Surfactant replacement therapy
 - clinical ascertainment, 450
 - clinical response, 447
 - development, 450–451
 - exogenous
 - effective, 444–445
 - synthetic preparation, 445
 - types, 445, 446
 - head-to-head comparison, 449–450
 - intubation, 451
 - neonatal indication, 451–452
 - pulmonary
 - associated protein, 444
 - synthesis, 443–444
 - RDS treatment, 447–449
 - respiratory distress syndrome, 526–527
 - Suxamethonium, 463–464
 - Swyer, P.R., 70
 - Synchronized intermittent mandatory ventilation (SIMV), 332
 - autocycling, 269
 - bear Cub 750_{PSV}, 358
 - breathing time, 268
 - cycling mechanisms, 267
 - false triggering, 269
 - inadequate inspiratory time and tidal volume delivery, 269
 - newport wave, 365
 - parameters for, 287
 - patient management, 268–269
 - spontaneous breath, 268
 - trigger failure, 269
 - trigger mechanisms, 267
 - weaning, 269, 612–613
- T**
- Tausch, H.W., 70
 - Taussig, 70
 - Taylor, 330
 - Theophylline, 457
 - Thomas, S., 643
 - Thoracic gas volume (TGV), 37
 - Time-cycled, pressure-limited (TCPL), AVEA ventilator, 352
 - Tin, W., 49, 155, 727
 - Tissue hypoxia
 - blood lactate levels, 517
 - consequences of, 520
 - definition, 517
 - fractional oxygen extraction, 517
 - mixed venous saturation, 517
 - oxygen extraction, 519
 - oxygen transport, 518–519
 - reduced oxygen transport, 519
 - Tissue oxygenation, 49

Tolazoline, 467
 Total liquid ventilation (TLV), 508
 Total lung capacity (TLC), 36
 Total parenteral nutrition (TPN), 431, 432
 Toxoplasmosis, 534–535
 TPN. *See* Total parenteral nutrition
 Tracheal agenesis, 19
 Tracheal stenosis, 19
 Tracheal stenosis, radiography, 203, 205
 Tracheoesophageal fistula (TEF), 18
 Tracheoesophageal fistula, radiography, 203, 204
 Tracheomalacia, 19
 Tracheostomy
 EXIT procedure, 144–145
 indications, 143
 patient preparation, 143–144
 postoperative care, 144
 technique, 144
 Transcutaneous partial pressure of carbon dioxide (TcPCO₂) monitoring, 151–152
 Transcutaneous partial pressure of oxygen (TcPO₂) monitoring, 150–151
 Transient tachypnea, radiography, 185–187
 Transillumination
 clinical applications, 211
 dark adaptation, 211
 light source preparation, 211
 nursing care, 704
 pneumomediastinum, 212
 pneumopericardium, 212
 pneumothorax, 212
 Transport of newborns
 digital camera, 714
 documents, 714
 effects of altitude, 719–720
 fixed wing aircraft, 710
 fly-drive method, 710
 goal of, 709
 ground ambulance, 709–710
 helicopter, 710
 incubator, 710–711
 maternal transport, 709
 medications, 714, 715
 NICU, 718–719
 nursing care, 702
 respiratory care transport equipment, 713–714
 stabilization of, 715–718
 team members protection, 714
 typical transport equipment, 711–713
Treponema pallidum, 537–538
 Tsai, W.C., 721

U

Ultrasound, 183
 Umbilical artery catheterization (UAC), 137–138
 Umbilical vein catheterization, 138–139
 Universal mode translator, 274–276
Ureaplasma urealyticum
 diagnosis, 547
 manifestations, 546–547
 pathology, 546
 transmission, 546
 treatment and prognosis, 547

V

Van Meurs, L.J., 494
 VAP. *See* Ventilator-associated pneumonia
 Vascular access
 peripheral artery catheterization, 139–140
 peripheral intravenous catheters, 140–141
 UAC, 137–138
 umbilical vein catheterization, 138–139
 Vasudev, D.K., 577, 587
 Vaucher, Y.E., 334
 Vecuronium, 464
 Ventilation
 autocycling, 273
 borderline of viability, 737–738
 breath assistance, 272
 breath control, 272
 cycling mechanisms, 271
 false triggering, 273
 IMV (*see* Intermittent mandatory ventilation)
 inadequate inspiratory time and tidal volume delivery, 273
 mechanical (*see* Mechanical ventilation)
 metabolic acidosis, 273
 non-invasive (*see* Noninvasive ventilation)
 patent ductus arteriosus, 666
 patient management, 272–273
 pressure control
 advantages and disadvantages, 282
 clinical applications, 282
 clinician-set parameters, 282
 features of, 281
 pressure-targeted modalities comparison, 282
 PTV, 271
 SIMV (*see* Synchronized intermittent mandatory ventilation)

- transport of newborns, 711
 - trigger failure, 273
 - trigger mechanisms, 271
 - volume-targeted
 - advantages of, 276
 - characteristics of, 276
 - clinical indications, 277
 - minimal tidal volume delivery, 277
 - modes of, 275–276
 - weaning infants, 278
 - weaning, 612
 - withdrawal of assisted ventilation
 - “best interests” concept, 745–746
 - circumstances, 743–744
 - deceptive signals, 746
 - dying infant and futility of treatments, 744
 - medical care, 747–748
 - parents and staffs, decision making, 746, 747
 - post-mortem examination, 749
 - “quality of life” decision, 744–745
 - Ventilator-associated pneumonia (VAP)
 - bacterial and fungal pathogens, 548
 - diagnosis, 549
 - management, 549
 - prevention, 549–550
 - risk factors, 548
 - Ventilator induced lung injury (VILI),
 - bronchopulmonary dysplasia, 626–627
 - Ventilator parameters
 - blood gas goal, 96, 97
 - flow, 97
 - frequency, 94–95
 - I:E ratio, 95
 - inspired oxygen concentration, 95
 - management algorithm, RDS, 96, 97
 - PEEP, 94
 - PIP, 93–94
 - Vital capacity (VC), 36
 - Volsko, T.A., 363
 - Volume-targeted ventilation
 - advantages of, 276
 - characteristics of, 276
 - clinical indications, 277
 - minimal tidal volume delivery, 277
 - modes of, 275–276
 - weaning infants, 278
- W**
- Weaning, 287
 - adjunctive treatments
 - bronchodilators, 614
 - corticosteroids, 614–615
 - diuretics, 613–614
 - methylxanthines, 613
 - anemia, 615
 - assist/control ventilation, 273, 346, 347, 354, 612
 - congestive heart failure, 615
 - CPAP, 244
 - ECMO, 502
 - electrolyte disturbances, 615
 - elements of, 610–611
 - extubation
 - AVEA ventilator, 354
 - bird VIP Gold ventilator, 346–348
 - extubation and post-extubation care, 616–617
 - gas exchange, 611
 - general principles, 611
 - HFJV, 325
 - HFOV, 411–412
 - IMV, 266, 613
 - infection, 615
 - iNO therapy, 492–493
 - metabolic alkalosis, 615
 - minute ventilation, maintenance of, 610
 - neuromuscular disease, 615
 - nutrition, 616
 - oxygenation, 611–612
 - PAV, 295–296
 - PEEP, 259
 - pharmacologic agents, 615
 - pressure support ventilation, 287, 347, 354, 613
 - reduced respiratory system load, 610
 - respiratory drive, 609–610
 - SIMV, 269, 612–613
 - ventilatory case study, 617–620
 - volume-controlled ventilation, 278
 - work of breathing, 609
 - Wiseman, K., 129
 - Wiswell, T.E., 555
 - Wohl, 70
 - Woodhead, D.D., 233
 - Woody, L., 763
 - Wyllie, J., 213, 663