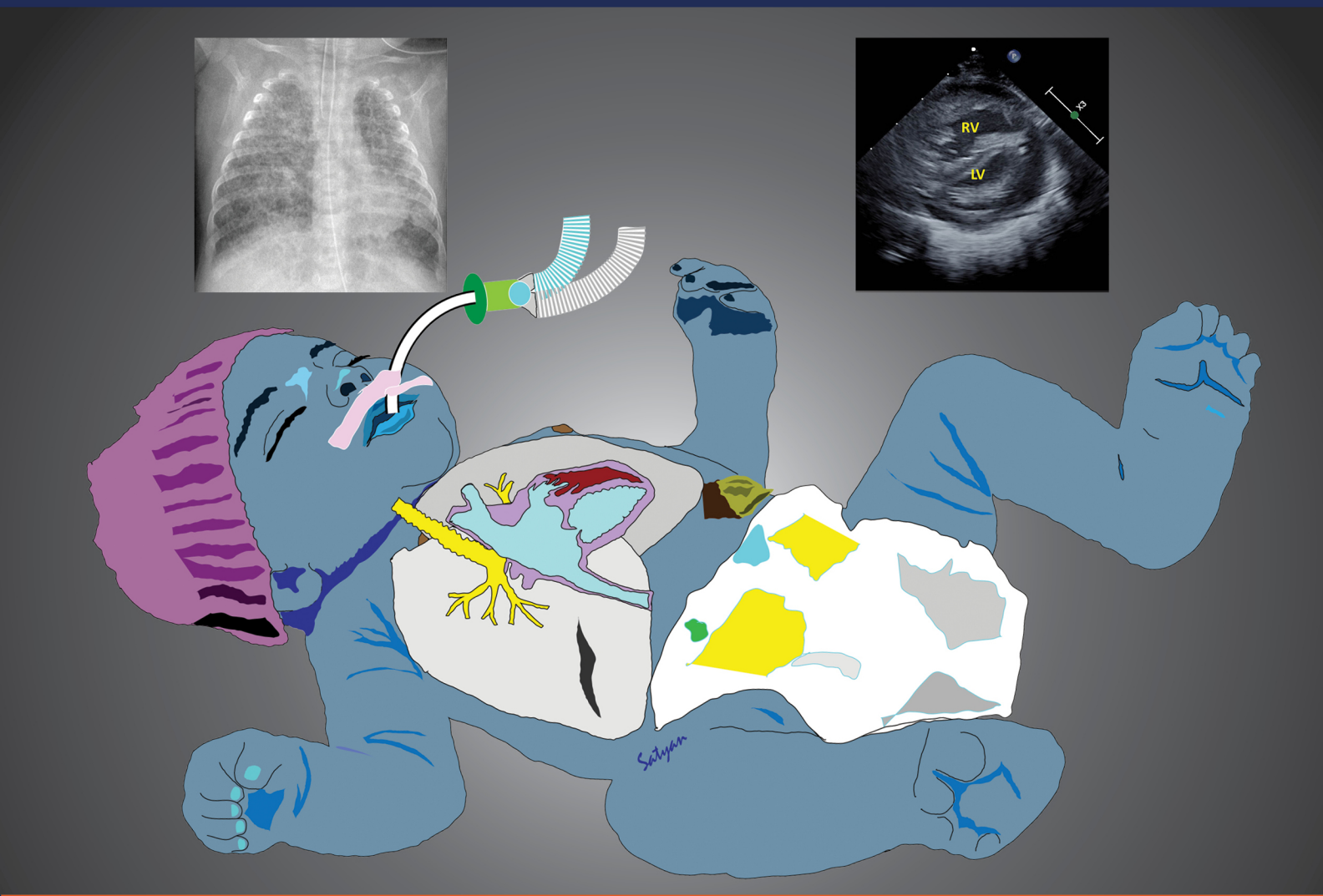
HYPOXIC RESPIRATORY FAILURE IN THE NEWBORN

From Origins to Clinical Management



Edited by

Shyamala Dakshinamurti

Section Editors

Steven H. Abman, Po-Yin Cheung, Satyan Lakshminrusimha, Patrick J. McNamara, and William K. Milsom

CRC Press
Taylor & Francis Group

HYPOXIC RESPIRATORY FAILURE IN THE NEWBORN

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

HYPOXIC RESPIRATORY FAILURE IN THE NEWBORN

From Origins to Clinical Management

Edited by

Shyamala Dakshinamurti

Section Editors

Steven H. Abman
Po-Yin Cheung
Satyan Lakshminrusimha
Patrick J. McNamara
William K. Milsom

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Boca Raton and London
First edition published 2022

by CRC Press
6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742
and by CRC Press

2 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

CRC Press is an imprint of Taylor & Francis Group, LLC

ISBN: 9780367493998 (hbk)
ISBN: 9781032078182 (pbk)
ISBN: 9780367494018 (ebk)

DOI: 10.1201/9780367494018

Typeset in Warnock Pro
by KnowledgeWorks Global Ltd.

CONTENTS

PREFACE

Babies with hypoxic respiratory failure were always the sickest in the newborn ICU. As a neonatology trainee, I would sit at their bedsides on call nights, watching their seesawing oxygen saturations, all our whirring, thumping machines a poor substitute for the safety and sanity of the uterus; willing their fist-sized hearts to pump a little longer, while we figured out a better way to push oxygen into them.

Yet, at these same oxygen levels, a fetus would have thrived. What failed these infants was the elemental transition process from fetus to newborn; the key to be born and to live in this world.

The genesis of this book can be traced back to those roller-coaster call nights. Also to the writings of evo-devo stalwarts Stephen Jay Gould and Sean Carroll; to serendipitous lectures by the inimitable John West on how the elephant lost its pleural space, and Paul Ponganis on the origins of the diving reflex, which felt like bathing one's brain in pure logic; and a chance meeting with Bill Milsom on a mountain in Mongolia. Clear connections can be made from human evolution to the process of our emergence as creatures capable of independent life. The poet Mary Oliver urged, *Pay attention / Be astonished / Tell about it.* This applies to scientists and clinicians too. There is a compelling poetry to physiology that lurks beneath the myriad details.

Gathered here is a collection of reviews by masters in their fields, highlighting the pathways of hypoxia and pulmonary hypertension from the population to the organism and the cell and drawing together international expertise in diagnosis and treatment. I am grateful to my august co-editors for their tremendous insights and enthusiasm in bringing this collection of knowledge together. And as always, delighted and illuminated by Satyan Lakshminrusimha's illustrations.

It must be acknowledged that this book was conceived before, but written during the COVID-19 pandemic. There has been no scientific connection established between COVID and neonatal pulmonary hypertension. But there is an affective connection, in writing about hypoxic respiratory failure at a crystalline moment when the world is struggling with the toll of hypoxic respiratory failure. I thank all the contributing authors for their commitment to this project despite this pressure.

Every book requires a village; in particular, the organizational skills of project managers Nathalie Buissé and Sophia Mbabaali from the George & Fay Yee Centre for Healthcare Innovation, and the Medical Sciences editorial desk at Taylor & Francis/CRC Press.

I thank my family for their support during the compilation of this volume, including eagle-eyed proofreading, and for their gifts of science, mountains and words.

Half a century ago, my cousin Sanjay died of hypoxic respiratory failure soon after birth. How much we have learned since then. To him and every blue baby since, this effort is in memory.

Shyamala Dakshinamurti

EDITOR

Dr Shyamala Dakshinamurti is a neonatologist and biomedical researcher, Professor of Pediatrics and Physiology at the University of Manitoba, Canada, and member of the Biology of Breathing theme, Children's Hospital Research Institute of Manitoba. She is research director for the University of Manitoba's Neonatology fellowship program, and a scientific organizer of the annual Canadian National Perinatal Research Meeting. Dr Dakshinamurti's research is on the hemodynamics of the neonatal pulmonary circuit and the physiology of hypoxia during circulatory transition. She is also a writer interested in science communication.

SECTION EDITORS

Dr Steven H. Abman is Professor of Pediatrics and Director of the Pediatric Heart Lung Center at the University of Colorado Anschutz School of Medicine and the Children's Hospital Colorado, USA. Having trained in Pediatric Pulmonary and Critical Care Medicine, Dr. Abman has had a long-standing interest in the developing lung circulation and pulmonary hypertension in diverse settings, as reflected by his clinical and laboratory-oriented research. He is currently Director of the Pediatric Pulmonary Hypertension Network (PPHNet), Executive Vice-Chairman for the BPD Collaborative and President of the American Pediatric Society.

Dr Po-Yin Cheung is a neonatologist of the Northern Alberta Neonatal Program of Alberta Health Services and a full Professor in the Departments of Pediatrics, Pharmacology and Surgery at the University of Alberta, Canada. He is also an Honorary Clinical Professor of the Department of Paediatrics and Adolescent Medicine at the University of Hong Kong and Honorary Consultant at the NICU of the HKU-Shenzhen Hospital. Dr. Cheung is a clinician-scientist and conducts both clinical and basic science research in neonatal hypoxia-reoxygenation injury and neonatal transition.

Dr Satyan Lakshminrusimha is a neonatologist and the Dennis and Nancy Marks Chair and Professor of Pediatrics at the University of California at Davis, Sacramento, USA. His areas of research interest include optimal oxygenation in neonatal lung injury, neonatal resuscitation, and pulmonary hypertension. Dr Lakshminrusimha enjoys drawing medical illustrations, for which he has developed an international reputation, and has developed mobile apps of neonatal illustrations and infographics.

Dr Patrick J. McNamara is a staff neonatologist and Director of the Division of Neonatology at the University of Iowa Stead Family Children's Hospital and Professor of Pediatrics and Internal Medicine, University of Iowa, USA. He is the current chair of the PanAmerican Hemodynamic Collaborative, Pediatric Academic Society Neonatal Hemodynamics Advisory and Neonatal Hemodynamics (TnECHO) Special Interest Group at the American Society of Echocardiography. His clinical and research interests include myocardial performance in the settings of a hemodynamically significant ductus arteriosus, pulmonary hypertension, and targeted neonatal echocardiography.

Dr William K. Milsom is a comparative physiologist and Emeritus Professor of Zoology at the University of British Columbia, Canada, best known as an authority on the evolution of respiratory processes in vertebrates. He has received the highest awards presented by the Canadian Society of Zoologists (the Fry Medal), the Comparative and Evolutionary Physiology Section of the American Physiological Society (the August Krogh Distinguished Lecture), and the Society for Experimental Biology (UK) (the Bidder Lecture), the three major societies in his discipline. He has also served as the President of the Canadian Society of Zoologists and as President of the International Congress of Comparative Physiology and Biochemistry. In 2012, Dr Milsom received the Distinguished Service Award from the Canadian Society of Zoologists in recognition of contributions to the well-being of zoology in Canada beyond the call of duty.

CONTRIBUTORS

Steven H. Abman
Division of Pulmonary Medicine
Department of Pediatrics
University of Colorado and Children's Hospital Colorado
Aurora, CO

Kurt H. Albertine
Division of Neonatology and Pulmonary
Department of Internal Medicine
University of Utah
Salt Lake City, UT

Karel Allegaert
Department of Development and Regeneration, Department of Pharmaceutical and Pharmacological Sciences
KU Leuven
Leuven, Belgium
and
Department of Clinical Pharmacy, Erasmus MC
Rotterdam, The Netherlands

Gabriel Altit
Division of Neonatology
Department of Pediatrics
McGill University and Montreal Children's Hospital
Montreal, QC, Canada

Pieter Annaert
Department of Pharmaceutical and Pharmacological Sciences
KU Leuven
Leuven, Belgium
and
Department of Clinical Pharmacy
Erasmus MC
Rotterdam, The Netherlands

Judy L. Aschner
Department of Pediatrics
Hackensack Meridian School of Medicine
Nutley, NJ
and
Department of Pediatrics
Albert Einstein College of Medicine
Bronx, NY
and
Joseph M. Sanzari Children's Hospital
Hackensack University Medical Center
Hackensack, NJ

Michelle Baczynski
Department of Respiratory Therapy
Mount Sinai Hospital
Toronto, ON, Canada

Anjali Y. Bhagirath
Children's Hospital Research Institute of Manitoba
Winnipeg, MB, Canada

Adrianne Rahde Bischoff
Department of Pediatrics
University of Iowa Stead Family Children's Hospital
Iowa City, IA

Jason Boehme
Department of Pediatrics
University of California, San Francisco
San Francisco, CA

R. Dale Brown
Departments of Pediatrics and Medicine
Cardiovascular Pulmonary Research Laboratories
University of Colorado
Anschutz Medical Campus
Aurora, CO

Emily Callan
Department of Pediatrics
Children's Hospital of Wisconsin
Milwaukee, WI

Nicholas R. Carr
Division of Neonatology
University of Utah School of Medicine
Salt Lake City, UT

Aravanan Anbu Chakkarapani
Neonatology and Clinical Pediatrics
Sidra Medicine and Weill Cornell Medicine
Doha, Qatar

Po-Yin Cheung
Division of Neonatal-Perinatal Care
Department of Pediatrics
University of Alberta
Edmonton, AB, Canada

Shyamala Dakshinamurti
Section of Neonatology, Department of Pediatrics
Department of Physiology
University of Manitoba
Children's Hospital Research Institute of Manitoba
Winnipeg, MB, Canada

Cassidy Delaney
Department of Pediatrics
School of Medicine
University of Colorado
Anschutz Medical Campus
Aurora, CO

Nolan DeLeon
Children's Hospital Research Institute of Manitoba
Winnipeg, MB, Canada

Yvonne A. Dzal
Department of Biology and Centre for Forest Interdisciplinary Research
University of Winnipeg
Winnipeg, MB, Canada

Germán Ebensperger
Programa de Fisiopatología
Instituto de Ciencias Biomédicas (ICBM)
Facultad de Medicina
International Center for Andean Studies (INCAS)
Universidad de Chile
Putre, Chile

Yasser Elsayed
Section of Neonatology
Department of Pediatrics
University of Manitoba
Winnipeg, MB, Canada

Candice D. Fike
Department of Pediatrics
University of Utah Health
Salt Lake City, UT

Mark K. Friedberg
Cardiology
The Hospital for Sick Children
Toronto, ON, Canada

Csaba Galambos
Pathology
Anschutz Medical Campus
Aurora and Children's Hospital Colorado
Aurora, CO

Harry Gee
Obstetrics and Gynaecology
Birmingham Women's Hospital
Birmingham, United Kingdom

Jason Gien
Neonatal/Perinatal Medicine
University of Colorado
Anschutz Medical Campus
Aurora, CO

Regan E. Giesinger
Department of Pediatrics
University of Iowa
Iowa City, IA

Andrew W. Gill
Department of Paediatrics
University of Western Australia
Perth, Australia

M. Ruth Graham
Department of Anesthesiology, Perioperative and Pain Medicine
University of Manitoba
Winnipeg, MB, Canada

Emilio A. Herrera
Programa de Fisiopatología
Instituto de Ciencias Biomédicas (ICBM)
Facultad de Medicina
International Center for Andean Studies (INCAS)
Universidad de Chile
Putre, Chile

Allyson Hindle
Integrative Physiology
University of Nevada
Las Vegas, NV
and
Anesthesia Center for Critical Care Research
Massachusetts General Hospital
Boston, MA

Stuart B. Hooper
Obstetrics and Gynaecology Monash Health
Monash University
Melbourne, Australia

Amish Jain
Department of Pediatrics
University of Toronto
Toronto, ON, Canada
Mount Sinai Hospital
Toronto, ON, Canada

Robert P. Jankov
Departments of Pediatrics and Cellular and Molecular Medicine
University of Ottawa and Children's Hospital of Eastern Ontario Research Institute
Ottawa, ON, Canada

Richard Keijzer
Division of Pediatric Surgery
Department of Surgery
University of Manitoba and Children's Hospital Research Institute of Manitoba
Winnipeg, MB, Canada

Roberta L. Keller
Department of Pediatrics
University of California
San Francisco, CA

Stephen T. Kempley
Royal London Hospital and Barts and the London School of Medicine
London, United Kingdom

Martin Keszler
Department of Pediatrics
Women and Infants Hospital of Rhode Island
Providence, RI

Afif El Khuffash
Department of Neonatology
The Rotunda Hospital and School of Medicine
Royal College of Surgeons in Ireland
Dublin, Ireland

John P. Kinsella
Division Pediatrics–Neonatology
Children's Hospital Colorado
Colorado Fetal Care Center
USC Health–Neonatal Intensive Care Unit
Anschutz and Children's Hospital
Aurora, CO

Martin Kluckow
Neonatology, Department of Pediatrics
University of Sydney and Royal North Shore Hospital
Sydney, Australia

Girija Ganesh Konduri
Division of Neonatology
Department of Pediatrics
Medical College of Wisconsin and
Children's Research Institute
Milwaukee, WI

Satyan Lakshminrusimha
Department of Pediatrics
UC Davis Children's Hospital
Sacramento, CA

W.L. Amelia Lee
Barts and the London School of Medicine
London, United Kingdom

Philip T. Levy
Division of Newborn Medicine
Boston Children's Hospital
and
Department of Pediatrics
Harvard Medical School
Boston, MA

Aníbal J. Llanos
Programa de Fisiopatología
Instituto de Ciencias Biomédicas (ICBM)
Facultad de Medicina
International Center for Andean Studies (INCAS)
Universidad de Chile
Putre, Chile

Peter M. MacFarlane
Department of Pediatrics
Case Western Reserve University
Cleveland, OH

Emin Maltepe
Department of Pediatrics
University of California, San Francisco
San Francisco, CA

Patrick J. McNamara
Department of Pediatrics and Internal Medicine
University of Iowa Stead Family Children's Hospital
Iowa City, IA

William K. Milsom
Department of Zoology
The University of British Columbia
Vancouver, BC, Canada

Souvik Mitra
Department of Pediatrics
Dalhousie University and IWK Health Center
Halifax, NS, Canada

Catherine Morgan
Division of Pediatric Nephrology
Department of Pediatrics
University of Alberta
Edmonton, AB, Canada

Josef Neu
Division of Neonatology
Department of Pediatrics
University of Florida
Gainesville, FL

Eric B. Ortigoza
Division of Neonatal-Perinatal Medicine
Department of Pediatrics
UT Southwestern Medical Center
Dallas, TX

Allison S. Osborne
Department of Pediatrics
Rainbow Babies & Children's Hospital and Case Western Reserve University
Cleveland, OH

Christina M. Pabelick
Departments of Anesthesiology and Perioperative Medicine and Physiology and Biomedical Engineering
Mayo Clinic, Rochester
Rochester, MN

Graeme R. Polglase
Perinatal Transition Group
The Ritchie Centre
Department of Obstetrics and Gynaecology
Monash University and Hudson Institute of Medical Research
Victoria, Australia

Fabiana Postolow
Section of Neonatology
Department of Pediatrics
University of Manitoba
Winnipeg, MB, Canada

Y.S. Prakash
Departments of Anesthesiology and Perioperative Medicine and Physiology and Biomedical Engineering
Mayo Clinic
Rochester, MN

Roberto V. Reyes
Programa de Fisiopatología
Instituto de Ciencias Biomédicas (ICBM)
Facultad de Medicina
International Center for Andean Studies (INCAS)
Universidad de Chile
Putre, Chile

Danielle R. Rios
Clinical Associate Professor
University of Iowa
Iowa City, IA

Nicola J. Robertson
Perinatal Neuroscience and Neonatology
EGA Institute for Women's Health
University College London
London, England

Ola D. Saugstad
Department of Pediatrics
University of Oslo
Oslo, Norway
and
Ann and Robert H. Lurie Children's Hospital of Chicago and
Northwestern University Feinberg School of Medicine
Chicago, IL

Arvind Sehgal
Monash Newborn
Monash Children's Hospital
Melbourne, Australia
and
Department of Pediatrics
Monash University

María Serón-Ferré
Programa de Fisiopatología
Instituto de Ciencias Biomédicas (ICBM)
Facultad de Medicina
International Center for Andean Studies (INCAS)
Universidad de Chile
Putre, Chile

Divyen K. Shah
Royal London Hospital
Barts and the London School of Medicine
London, United Kingdom

Prakesh S. Shah
Division of Neonatology, Department of Pediatrics
Mount Sinai Hospital
Toronto, ON, Canada

Tatum Simonson
Division of Pulmonary, Critical Care, & Sleep Medicine
Department of Medicine
University of California San Diego School of Medicine
San Diego, CA

Dominique Singer
Division of Neonatology and Pediatric Critical Care Medicine
University Medical Center Eppendorf
Hamburg, Germany

Anne Smits
Department of Development and Regeneration
KU Leuven
Leuven, Belgium
Neonatal Intensive Care Unit
University Hospital Leuven
Leuven, Belgium

Robin H. Steinhorn
Rady Children's Hospital
UC San Diego
San Diego, CA

Kurt R. Stenmark
Departments of Pediatrics and Medicine
Cardiovascular Pulmonary Research Laboratories
University of Colorado
Anschutz Medical Campus
Aurora, CO

Edwin W. Taylor
School of Biosciences
University of Birmingham
Birmingham, United Kingdom

Payam Vali
Department of Pediatrics
UC Davis Children's Hospital
Sacramento, CA

Maximo Vento
Department of Pediatrics
Health Research Institute La Fe
Valencia, Spain

Stephen Wedgwood
Department of Pediatrics
UC Davis School of Medicine
Sacramento, CA

Dany E. Weisz
Department of Pediatrics
University of Toronto
Sunnybrook Health Sciences Centre
Toronto, ON, Canada

David F. Wertheim
Department of Networks and Digital Media
Kingston University
London, United Kingdom

Jason Williams
Department of Biochemistry and Molecular Genetics
University of Colorado Anschutz Medical Campus, Aurora
Aurora, CO

Michelle J. Yang
Division of Neonatology
University of Utah School of Medicine
Salt Lake City, UT

Bradley A. Yoder
Division of Neonatology – Department of Pediatrics
University of Utah
Salt Lake City, UT

Hui Zhang
Departments of Pediatrics and Medicine
Cardiovascular Pulmonary Research Laboratories
University of Colorado Anschutz Medical Campus
Aurora, CO

Faith Zhu
Department of Pediatrics
University of Toronto
Toronto, ON, Canada

INTRODUCTION

Shyamala Dakshinamurti, William K. Milsom, Satyan Lakshminrusimha, Steven H. Abman, Po-Yin Cheung and Patrick J. McNamara

Contents

We have all been hypoxic.

We have craved oxygen since the day one of our eukaryotic ancestors first swallowed an aerobic mitochondrial bacterium and then, seduced by the prospect of multicellularity, began feeding its hungry cytochromes oxygen.

Nearly a century ago, Sir Joseph Barcroft postulated "the Everest *in utero*," a fetal environment in the womb comparable to the most hostile environmental conditions faced by adventurous mankind. Subsequently, expeditions reaching the summit of Everest mapped out the limits of human tolerance for hypoxemia. Fetal tolerance for intrauterine hypoxia arises from evolutionarily conserved physiological mechanisms, the antecedents of which can be learned from diving mammals or species at high altitudes. In whimsy we say, the fetus remembers when it was a turtle or a diving seal; then it is born and forgets. It's not merely whimsy; several chapters in this book recast Just So Stories in the form of stringently tested comparative physiology. The response to hypoxia in animals living in extreme environments illuminates how the human fetus handles its hypoxemic state, and why the human newborn suddenly cannot. The physiological changes seen during the transition from intrauterine to extrauterine life can be read as retracing the evolution and development of hypoxia tolerance, critical to biological study and clinical practice alike; while postnatal hypoxia creates a multisystem cliffhanger.

The conventional terminology "persistent pulmonary hypertension of the newborn," as with the term it once replaced, "persistent fetal circulation," is currently under siege. It is not necessarily persistent; it is not only in the newly born; it has bounced from one WHO classification category to another while remaining among the most rapidly progressive vasculopathies. The term "acute pulmonary hypertension" is more accurate, but it fails to capture the arrest of pulmonary circuit adaptation as a uniquely neonatal circumstance, triggered by hypoxia, inflammation, or pressure phenomena at a profoundly vulnerable moment of development. We, therefore, group these closely related pathophysiologies under the umbrella definition "hypoxic respiratory failure of the newborn," examine common pathways of disease, distinguish distinct natural histories and then differentiate PPHN (if that's what we should still call it) from other pulmonary hypertensions presenting during infancy.

This book covers the broad ground: The origins of hypoxia adaptation, the impact of oxygen on the circulatory transition at birth, the biochemistry of hypoxia in the pulmonary circulation, and the diagnosis and clinical management of hypoxic respiratory failure. In other words: What we once were; why we have been protected; what happens when that protection is lifted; how to diagnose when we have entered the maelstrom; what to do next, and what we still don't know. The impact of hypoxia is not limited to the lung; the "collateral damage" of hypoxia on other systems is reviewed, in addition to cardiovascular effects. Common threads run the length of the volume; you may want to read with multiple bookmarks in hand. The diving reflex appears in various forms in every section, as do cardiorespiratory coupling and reactive oxygen species. The introductions to each section of the book are gathered below, to highlight their internal connectivity.

The past decades have brought substantial advances in the care of pulmonary hypertension in the newborn. For the sake of our patients and their families, we must learn more, to do better.

Part 1: The origins of hypoxia tolerance

William K. Milsom

The inverse relationship between mass-specific metabolic rate and body size is well established across all animal taxa. Thus, mammals are born with a high demand for oxygen that increases progressively with the development of thermoregulatory capacity. In the human infant, this is accompanied by a loss (or resetting) of tolerance to hypoxia. The primary responsibility of the newborn to hypoxia is a reduction in metabolic rate, and this ability also decreases progressively with the development of thermoregulatory capacity. Prolonged hypoxia has proinflammatory properties potentially underlying neurologic vulnerability, particularly with respect to the respiratory control system. Human populations that reside at altitude in the Himalayas, Andean altiplano, and Ethiopian highlands, however, exhibit a distinct composite of phenotypes, with similarities and differences in various physiological processes leading to increased hypoxia tolerance. The mechanisms that underlie enhanced tolerance can represent instances of acclimatization (phenotypic plasticity), or genetic adaptation (genetic assimilation of positive traits, or genetic compensation to mitigate maladaptive plastic responses to hypoxia). These phenomena are well described in the opening chapters of this section. What follows are chapters describing species in which the fetus, newborn, and/or adult are extremely hypoxia tolerant. These are species that thrive in hypoxic environments at altitude, in underground burrows, or while breath-hold diving. These studies, and our growing knowledge of the phylogeny and ontogeny of differences in hypoxia tolerance, inform our understanding of the huge physiological shifts of the human neonatal transition and the dangers of perinatal hypoxia.

Part 2: Fetal hypoxia and neonatal transition

Satyan Lakshminrusimha

The current COVID-19 pandemic has highlighted the importance of maternal oxygenation during pregnancy. The morbidity and mortality of pregnant women with COVID-19 are

DOI: 10.1201/9780367494018-1

significantly higher than nonpregnant women. Several pregnant women with COVID-19 and hypoxemic respiratory failure have required extracorporeal membrane oxygenation (ECMO). While the placenta and fetal circulation protect the fetus from deleterious effects of mild maternal hypoxia, profound hypoxemia results in hypoxic fetoplacental vasoconstriction and deleterious effects on the fetus. Timely respiratory and cardiovascular support to correct maternal hypoxia is crucial to optimize fetal well-being.

Pulmonary transition at birth is truly a miracle! During fetal period, the placenta serves as the organ of gas exchange. All fetal organ systems are functional except the lungs. The fetal lungs are dormant and filled with liquid and has low blood flow, partly due to hypoxic pulmonary vasoconstriction. The fetus is relatively hypoxemic (compared to postnatal standards) but not hypoxic, as it efficiently delivers oxygen to its tissues with abundant cardiac output and high levels of fetal hemoglobin to compensate for low PaO_2. At birth, with the first cry, air enters the alveoli increasing PaO_2 resulting in a drop in pulmonary vascular resistance, switch in ductal shunt from right-to-left to left-to-right, and an 8–10-fold increase in pulmonary blood flow. Expiratory braking during crying and active absorption of lung liquid enables air to replace lung liquid in the alveoli.

As gas exchange shifts from placenta to the lungs at birth, the source of left ventricular preload changes from umbilical venous return shunting across the oval foramen to pulmonary venous return. This switch is gradual (with some much-needed overlap) while physiological cord clamping is "delayed" until respirations are established. Abrupt or immediate cord clamping soon after birth, prior to establishing neonatal respiration, can potentially lead to hypoxia and bradycardia as the newly born infant is deprived of both sources of oxygen from placenta and lungs. Physiological cord clamping is associated with better short-term and long-term outcomes.

Birth asphyxia, defined as failure to establish breathing at birth, accounts for 900,000 deaths every year, based on World Health Organization estimates, and is one of the leading causes of neonatal mortality. Ventilation of the lungs during resuscitation with the right concentration of oxygen is the key to minimizing morbidity and mortality from birth asphyxia. While 21% oxygen is adequate for most term infants for initial resuscitation, the optimal initial oxygen concentration in preterm infants is still an enigma. Chapters by eminent scientists covering these important topics are included in Part 2.

Part 3: Biology of hypoxic respiratory failure in the neonate

Steven H. Abman

Part 3 of this book addresses biologic mechanisms that contribute to hypoxic respiratory failure in sick newborns. At birth, the lung circulation rapidly responds to birth-related stimuli, including the sudden rise in alveolar PO_2 that leads to the fall in pulmonary vascular resistance and rise in pulmonary blood flow, which is essential for postnatal survival. PPHN, a key component of neonatal hypoxic respiratory failure, represents the failure of the lung circulation to undergo sufficient vasodilation, leading to profound hypoxemia due to marked right-to-left extrapulmonary shunting across the ductus arteriosus and foramen ovale. Past laboratory studies identified the critical role of the enhanced production of vital endothelium-derived vasodilators, such as nitric oxide (NO) and prostacyclin (PgI_2), and reduced production of potent vasoconstrictors, especially endothelin-1 (ET-1) in mediating this dramatic transition of the pulmonary circulation. This past work led to the development of current pharmacologic interventions that are commonly used to treat neonatal pulmonary hypertension, including inhaled NO, phosphodiesterase type 5 inhibitors, diverse forms of synthetic PgI_2 analogs and ET-1 receptor inhibitors. Despite remarkable success in many settings, PPHN remains associated with substantial morbidity and mortality. In addition, growing recognition of the contribution of PPHN physiology to hypoxic respiratory failure in preterm infants has led to further challenges in how to best understand the underlying pathophysiology and optimal therapies in this fragile population. As a result, more work to better understand fundamental mechanisms through which prematurity, antenatal stress and postnatal injury impair pulmonary vascular, cardiac and respiratory function during the first weeks of life remains an important target for basic research.

In this section, chapters from outstanding investigators in the field of developmental lung biology, lung vascular disease and cardiac development, key signaling pathways that are altered in endothelial and smooth muscle cells by hypoxia, molecular biology of oxygen sensing and injury as related to the generation of reactive oxygen species, metabolic adaptations from fetal to neonatal life and novel epigenetic mechanisms of hypoxia-induced tissue injury are explored in great detail. Overall, this section provides exciting new leads that will yield important translational insights linking the science of vascular and cardiac function and disease with developmental biology, and ultimately, clinical care.

Part 4: Hypoxia and collateral damage

Po-Yin Cheung

Hypoxia is systemic and affects all organs and systems in the neonate with hypoxic respiratory failure.

"Oxygen Radical Disease of Neonatology", a term originally coined by Professor Ola Saugstad in 1988, remains one of the key concepts in the management of neonates with hypoxic respiratory failure. Reperfusion or reoxygenation injury remains the cornerstone of organ injury and complications. Indeed, oxygen may not be the silver bullet for hypoxia. Coming out of the *in utero* hypoxic environment, the relative postnatal hyperoxia and the interplay between oxygen and pathophysiological conditions of the neonate affect the developing respiratory system. As a defensive mechanism in the redistribution of blood flow during hypoxia, there are differential regional perfusion responses resulting in neuroprotection, intestinal and renal compromise. Tools for assessing organ perfusion and injury have been increasingly used in the clinical arena. The use of these tools improves the monitoring and management of perfusion deficits. Hypoxic-ischemic encephalopathy receives the most attention because of its significant acute and long-term neurodevelopmental consequences. While therapeutic hypothermia is the standard care for moderate or severe hypoxic-ischemic encephalopathy of term and near-term neonates, recent reports have fueled the discussion of its use in other populations. Further, adjunctive therapies are emerging to alleviate the cerebral injury. Understanding the pathogenetic course of cerebral injury including biochemical cascades and disruption of the blood-brain barrier helps develop therapeutic agents. The kidney is the first important organ that is

affected by hypoxia. However, similar to the therapeutic agents for cerebral injury, clinical treatments cannot reverse, but are merely limited to the prevention of reno-tubular injury. While the renal injury may heal, the long-term sequelae in neonatal kidneys after hypoxia need further research. Systemic hypoxia causes a unique injury to the intestine with ischemia and necrosis. Hypoxic-ischemic intestinal injury has no clear association with inflammation or the dysbiosis that is typical for necrotizing enterocolitis, although the two diseases have similar clinical and histopathological presentations. An individualized therapeutic approach is the key in precision medicine. It is important to better understand clinical pharmacology in hypoxic neonates such that we can predict drug-related effects based on drug- and population-specific pharmacokinetics and pharmacodynamics. Little information is available regarding the interactions between drugs and therapeutic hypothermia. Some neonates with hypoxic respiratory failure will require surgeries and need special anesthetic considerations. The risk and management of intraoperative pulmonary hypertensive crisis require the evaluation of perioperative risk, evidence-based approaches to respiratory support and rationalized pathophysiology-driven anesthetic and hemodynamic management in these neonates. Taken together, collateral effects of hypoxia on the brain, intestine, kidneys and other systems are inter-related in the acute pathophysiology, intercurrent therapeutic states and long-term outcomes.

Part 5: Diagnosis and management of neonatal hypoxic respiratory failure

Patrick J. McNamara

Part 5 focuses on the approach to diagnosis and management of neonatal hypoxemic respiratory failure, which remains a major cause of both morbidity and mortality in many parts of the world. As highlighted in prior sections, the biology of the neonate, during the transitional period birth, is at higher risk of impairment in the normal postnatal fall in pulmonary vascular resistance – which may lead to impaired efficacy of oxygenation, suboptimal right ventricular function and poor systemic blood flow. One of the major challenges for clinicians relates to the fact that many forms of major congenital heart disease may have a similar presentation, which may lead to incorrect treatment choices and adverse patient outcomes. Therefore, immediate access to timely and comprehensive echocardiography is imperative to enable accurate diagnostic ascertainment and disease/physiology-specific interventions. Recent advances in echocardiography evaluation, and in particular the growth of neonatologist-led hemodynamic programs, have led to improvements in understanding of the relationship of pulmonary vascular resistance/pressure to right ventricular function, the interdependence between both ventricles and the downstream effects on both pulmonary and end-organ perfusion. The art of clinical care, and its relevance to management, is further emphasized through increased appreciation of the importance of mechanical ventilation strategies, optimization of functional residual capacity and the interaction between intrathoracic pressure, ventilation and hemodynamics. It is imperative that clinicians consider heart-lung interaction as a biological continuum that is an essential determinant of effective tissue oxygenation and carbon dioxide clearance. Traditionally, the terms “persistent fetal circulation” and “persistent pulmonary hypertension of the newborn” have been used to characterize this clinical syndrome where impaired efficacy of oxygenation is the dominant clinical feature. Several chapters in this section suggest that clinicians should classify the nature of pulmonary hypertension as “acute” or “chronic”, which has both diagnostic and therapeutic relevance. In addition, both acute and chronic forms of pulmonary hypertension are distinguished by unique clinical phenotypes that influence the approach to monitoring and treatment choices. The importance of phenotypic characterization is best demonstrated in patients with congenital diaphragmatic hernia, where impaired oxygenation may relate to classic pulmonary arterial hypertension with impaired right heart performance or may relate to pulmonary venous hypertension secondary to a left ventricular phenotype. Timely access to comprehensive echocardiography facilitates enhanced diagnostic precision and the implementation of a disease-specific approach to treatment. Finally, acute pulmonary hypertension is an important consideration of hypoxemic respiratory failure in premature infants and adverse neonatal outcomes; however, timely diagnosis and early intervention with targeted pulmonary vasodilator therapy and heart function support may lead to improved outcomes.


THE ORIGINS
OF HYPOXIA
TOLERANCE

Part 1
The Origins of Hypoxia Tolerance

Edited by William K. Milsom

THE HUMAN FETUS AND METABOLIC ADAPTATIONS TO HYPOXIA

Dominique Singer

Contents

Introduction

Perinatal hypoxia is one of the greatest, if not *the* greatest threat to human fetuses and newborns. Hypoxic-ischemic encephalopathy (HIE) can result in cerebral palsy and other life-long disabilities. Attempts to treat asphyxiated babies by induced hypothermia have proven to be fairly effective, yet complementary therapies to further mitigate or even repair HIE are still under investigation (1–3).

However, HIE would probably occur even more frequently if human fetuses and newborns were not able to protect themselves by a number of physiological mechanisms that show striking similarities with natural adaptation strategies to oxygen deficiency and food scarcity in the animal kingdom. A comparative physiological analysis of these adaptations may help to better understand both the progression of perinatal hypoxia and the diagnostic and therapeutic challenges of HIE.

Being born as a small endotherm – A delicate challenge

When looking for particularly hypoxia-tolerant creatures, one would actually expect anything but small endotherms. There are two main reasons for this.

Size relationship of metabolic rate

According to a common biological law, also known as Kleiber's rule (4), the specific basal metabolic rate (in watts per kilogram) is higher in small than in large animals (Figure 2.1a). The "allometric" (nonproportional) size relationship of metabolic rate is usually explained by the fact that small mammals (or birds) need a stronger "internal heater" to compensate for the higher heat losses caused by their relatively larger body surface area. However, a similar relationship applies to all living beings whether they keep their body temperature constant or not. Hence, there must be a more fundamental explanation that probably involves the self-adjustment of energy requirements to supply conditions. Whatever may be the ultimate cause, the overall metabolic rule implies that small animals need more food and more oxygen per unit of body weight and should thus exhibit a worse tolerance to starvation and hypoxia than larger species. For mammalian neonates that also fall under this rule (the basal metabolic rate of a human term baby amounts to 2.0–2.5 Watts per kg compared to roughly 1 Watt per kg for adults), this would mean that they are inherently maladapted to the risks of undersupply and hypoxia simply because of their small body size (5–8).

Metabolic cost of temperature regulation

Mammals and birds are endothermic (warm-blooded) animals that maintain a higher gradient between body and ambient temperature than ectothermic (cold-blooded) organisms due to an elevated metabolic rate. The specific basal metabolic rate of mammals is 4(–10) times higher than the resting metabolic rate of reptiles of comparable body size. Endotherms are thus not only dependent on a continuous food supply, but they also exhibit a lower hypoxia tolerance than ectotherms that can often survive for long periods without any O_2 (and food) supply (9–11).

Furthermore, unlike ectotherms that usually tolerate larger thermal variations (poikilothermy), endothermic animals keep their body temperature constant (homeothermy). The cold defense reaction includes an increase in metabolic rate with decreasing ambient temperatures, which is steeper the smaller the body size and the larger the surface-to-volume ratio. In newborn mammals, heat is produced by nonshivering thermogenesis (NST) in the brown adipose tissue (BAT), which is based on an uncoupling of oxidative phosphorylation and thus accompanied by a high O_2 consumption rate. Thus, newborn babies experience

DOI: 10.1201/9780367494018-2

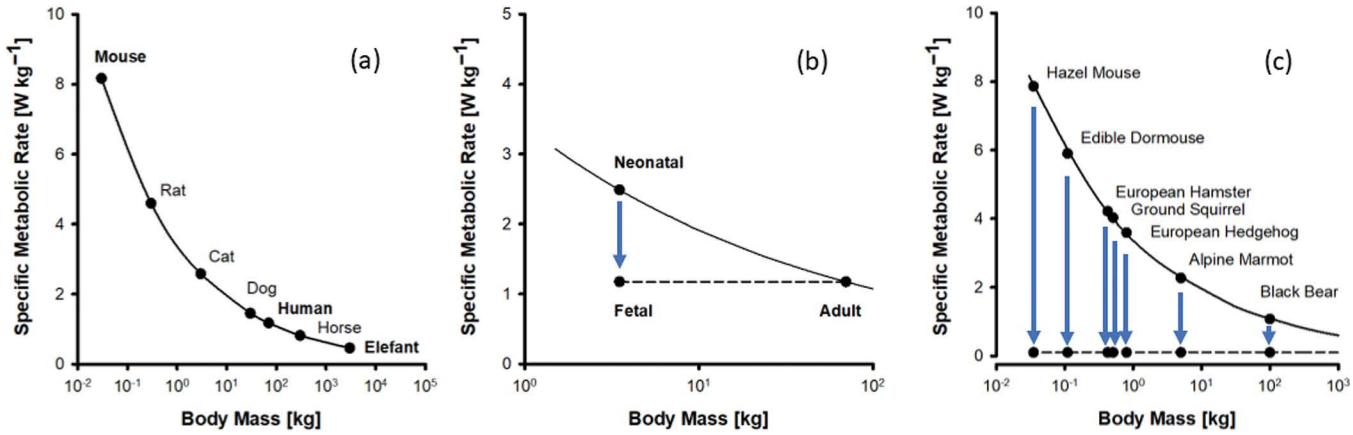


FIGURE 2.1 Metabolic size relationship as a target of perinatal and seasonal metabolic adaptations. (a) Following an overall biological rule ("mouse-to-elephant curve"), the specific metabolic rate increases with decreasing body mass. (b) The mammalian fetus, however, behaves more like an organ of its mother. The "disproportionately" low metabolic rate favors tissue oxygenation in spite of low intrauterine O_2 tensions. (c) A similar metabolic adaptation is found in hibernating mammals that exhibit a uniform minimal metabolic rate that equals the basal metabolic rate achieved by the largest mammals based on body size alone.

a higher thermometabolic stress than adults and are known to be at higher risk of hypothermia, due to the limits of thermoregulation being reached earlier (12–14).

All in all, small mammals have particularly high energy requirements both due to their small body size and thermoregulatory properties, making them particularly susceptible to conditions of undersupply. From this point of view, it is not surprising that over the some 150 million years of mammalian evolution, both the intrauterine development and – above all – the process of being born have been optimized by a number of self-protective mechanisms (15–17).

Being satisfied with little – The fetus as a euthermic hibernator

The intrauterine environment might be imagined as a Garden of Eden where everything is available in abundance. However, this is not the case. In particular with respect to O_2, the fetus has to cope with scarcity even under normal developmental conditions. The mean O_2 partial pressure in the fetal circulation amounts to 25–30 mmHg and thus corresponds to the arterial blood gas values that have been measured in extreme mountaineers climbing on the top of the world without additional oxygen ("Everest *in utero*"). The exceptionally low O_2 tension has previously been thought to reflect a worse gas exchange capacity of the placenta as compared to the lung. Meanwhile, it is assumed that (given the immaturity of O_2 free radical detoxification systems) Mother Nature deliberately put the mammalian fetus in a hypoxic compartment to prevent it from O_2 toxicity (18, 19).

Hematological adaptations to the low O_2 environment

Even though these ambient conditions are normal during intrauterine life (and should therefore be referred to as "low-oxygen" rather than as "hypoxic" conditions), the fetus has to compensate for the reduced pO_2 to cover its O_2 needs. As described in many physiological textbooks, this compensation primarily consists of two complementary hematological mechanisms.

Left shift of the O_2 dissociation curve

First, the well-known left shift of the O_2 dissociation curve of fetal hemoglobin (down to a half-saturation pressure of approximately 19 mmHg as opposed to approximately 28 mmHg in human adults). The markedly increased O_2 affinity results in the fact that at a pO_2 between 25 and 30 mmHg, the mean O_2 saturation in the fetal circulation amounts to 65–70% rather than 50% as would be expected, under comparable ambient conditions, in unacclimated adults.

Increase in hemoglobin concentration

Second, the increase in hemoglobin concentration (up to roughly 18–20 g/dl in term neonates as opposed to 13–15 g/dl in adults). This is a kind of high-altitude acclimatization responding to the fact that despite its higher O_2 affinity, the O_2 saturation of the fetal hemoglobin is still well below the almost 100% in oxygenated adult blood.

The two adaptive mechanisms ensure that the total O_2 content of fetal blood is in the order of adult blood which is often misinterpreted as if the low pO_2 in the fetal circulation was fully compensated. However, this is not true, since – independently of the amount of O_2 carried by the red cells – the driving force for the diffusion of gases is partial pressure. Hence, even the aforementioned adaptive responses cannot prevent the O_2 from being "pressed" into the fetal tissues under a much lower tension than in adults. This would inevitably affect tissue oxygenation if there were not another adaptive mechanism.

Metabolic adaptation to the low O_2 environment

The key to understanding this additional adaptation is Warburg's law (20), stating that the "critical depth" (of penetration of O_2 into tissue by diffusion) does not only depend on the partial pressure gradient from outside to inside but also on the rate at which O_2 is consumed by the tissue. The lower the O_2 consumption rate, the higher the penetration depth, or in other words: the adverse effect of a lowered partial pressure can be counteracted by a reduced tissue respiration rate.

This is the background for a widely underestimated self-protective mechanism to be found in mammalian fetuses, namely the suppression of the usual metabolic size relationship. In fact, the general rule that the specific metabolic rate increases with decreasing body mass ("mouse-to-elephant curve") seems to be somehow "switched off" during intrauterine life (Figure 2.1b). From a metabolic point of view, the mammalian fetus behaves more "like an organ of its mother," with the metabolic increase

up to the level expected from body size occurring only after birth (6, 21–23).

The deviation from the usual metabolic size relationship was first described by Hasselbalch (24) in avian embryos and explained by the fact that if their energy turnover was as high as expected from their small body size, the diffusion capacity of the egg shell would not be high enough to cover the resulting O_2 demand (25). Unlike in avian embryos, metabolic measurements in mammalian fetuses are methodologically difficult and accordingly rare, starting from the first observations by Bohr (21, 26–30). Since then, it has been repeatedly shown that mammalian (including human) neonates still have a disproportionately low specific O_2 consumption rate immediately after birth, before rising more or less rapidly to the metabolic level appropriate to their own body size (22, 31–33). As was first observed by Brück (34) in his pivotal studies on the metabolism of human term and preterm neonates, and later confirmed by our own respirometric measurements (35), the earliest postnatal metabolic rates are remarkably independent of gestational age and birth weight and thus reflect the suppression of metabolic size relationship during intrauterine life.

Another indirect and often overlooked sign of intrauterine metabolic reduction in humans is heart rate. After a sharp increase in the first trimester, the fetal heart rate levels off at about 140 beats per minute, where it remains more or less unchanged until the expected date of birth (36). This is significantly lower than would be expected in adult mammals of comparable size, especially in the earlier stages of pregnancy (e.g. a 100 g mammal corresponding in body weight to a human fetus at 16 weeks of gestation would have a heart rate of around 400 beats per minute) (5, 37). Since the heart rate directly parallels the metabolic rate, the "inappropriately" low heart rate clearly reflects the metabolic suppression that adapts the human fetus to its low-oxygen habitat.

The protective effect of the reduced metabolic rate can be illustrated in marsupial mammals that are physiologically born in an extremely immature state and spend most of their fetal development in their mother's abdominal pouch. According to our own studies on *Monodelphis* neonates, tiny creatures of 100 mg weight and 1 cm length, these animals show no postnatal metabolic increase at all and maintain a metabolic level that in their case amounts to only 20% of what would be expected in an adult marsupial of comparable size (35). This has three major implications.

Favored gas exchange

First, it compensates for the scarce O_2 supply, which in their case is not due to an "insufficient" placenta, but to a very immature lung (38). As has been shown by Mortola and coworkers (39) in a slightly different marsupial species, a considerable part of the O_2 uptake in these animals during their first days of life occurs via skin respiration – which would be unimaginable without a unique combination of small size and disproportionately low metabolic rates (6).

Favored growth rate

Second, the low maintenance metabolism allows for a high growth efficiency despite a necessarily limited substrate supply. In the aforementioned marsupial species, an increase to 500% of birth weight within the first 10 days of life was observed, although neither their milk intake nor the caloric content of the milk was exceptionally high.

Favored temperature control

Third, both marsupial neonates and mammalian fetuses can "afford" the suppression of metabolic size relationship because they are passively thermostated, be it in the maternal abdominal pouch or in the womb, and therefore do not need a stronger "internal heater" to compensate for higher heat losses over their relatively larger body surface area. In the case of the mammalian fetus in particular, it could even be that with an appropriately high metabolic rate, the heat transport capacity of the placenta might not be sufficient to remove the excess heat from the amniotic cavity (28).

Remarkably, the intrauterine metabolic reduction is the only exception to the general metabolic size relationship apart from hibernating mammals that fall to a uniform minimum specific metabolic rate that corresponds to the specific basal metabolic rate of the very largest mammals and might thus reflect a common limit to metabolic reduction (Figure 2.1c) (40–42). This also applies to black bears that give birth to their offspring while in hibernation and thus provide a "missing link" between intrauterine and seasonal adaptations (43). Similar to fetuses, at least some hibernating mammals exhibit a decreased (venous) blood pO_2 (44, 45), suggesting that a low-oxygen atmosphere could be a common permissive factor of metabolic reduction both in the natural overwintering strategies and in the "euthermic hibernation" of mammalian fetuses.

Staying alive with even less – Oxyconforming responses of the feto-placental unit

Even though the fetus is already adapted to the low-oxygen atmosphere through hematological and metabolic adaptations, there is still a substantial adaptive reserve, in that a number of exogenous and endogenous conditions are tolerated without jeopardizing the pregnancy as a whole (46). This applies to high-altitude pregnancies, to food scarcity and famines, to pregnancy disorders with impaired placental perfusion, and to cases of severe fetal anemia. In terms of O_2 supply, a further reduction by approximately 50% (e.g. in highland pregnancies up to 4000–4500 m of altitude; or in fetal anemias down to 9–8 g/dl of serum hemoglobin) is usually tolerable without major adverse effects, except for a mild-to-moderate Intra-Uterine Growth Restriction (IUGR). This adaptive reserve is due to a coordinated response of the feto-placental unit that consists of two main factors.

Metabolic gatekeeper role of the placenta

Recent findings indicate that the placenta plays an important gatekeeper role in the allocation of energy flows. The basic premise here is that only 60% of the oxygen supplied to the feto-placental unit is passed on to the fetus, while 40% is consumed by the placental tissue itself. With reduced O_2 delivery, the placenta appears to reduce its own O_2 consumption in order to maintain fetal O_2 supply (Figure 2.2a). The metabolic reduction that is accompanied by a decrease in mitochondrial density impairs active transport and synthetic processes (thus resulting in a more or less pronounced IUGR), yet prevents the fetus from a critical O_2 deficit. It seems that maintaining adequate oxygenation has priority over unrestricted growth in intrauterine life (29, 30, 47, 48).

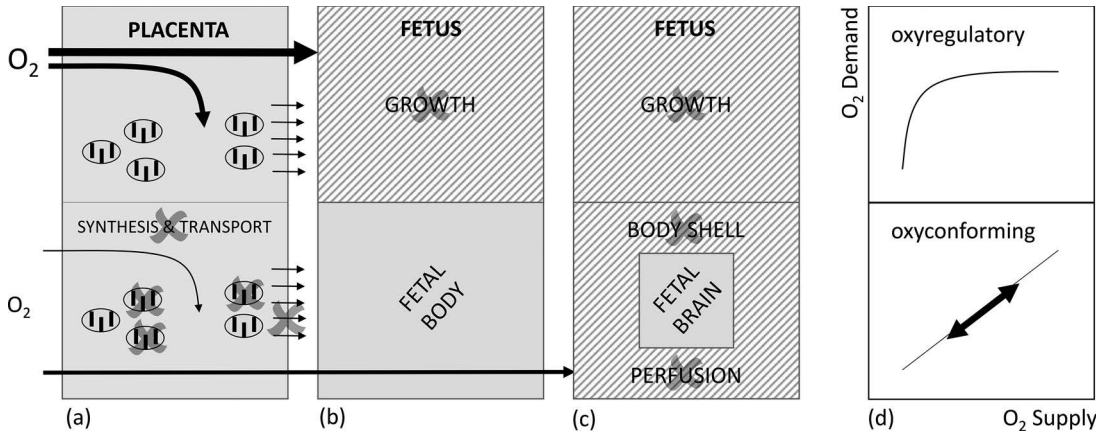


FIGURE 2.2 Self-protective responses of the feto-placental unit in mammals. (a) Since the placenta itself consumes up to 40% of the total O_2 supplied to the feto-placental unit, it can prevent the fetus from hypoxia by reducing its own metabolic rate. (b) The fetus is able to compensate for the resulting lack of substrate supply by "refraining" from growth in favor of maintenance metabolism. (c) A critical O_2 deficiency leads to a redistribution of blood flow from the body shell to the central organs (brain-sparing effect, diving reflex). (d) The gradual adjustment of metabolic demand to energy supply reflects an oxyconforming response that differs from the usual oxyregulatory behavior of mammalian tissues.

Metabolic programming of the fetus

The fact that the metabolic rate in mammalian fetuses is lower than expected from body size also means that the growth metabolism accounts for a relatively high proportion of the total energy turnover. This in turn offers the fetus the opportunity to adapt to an inadequate supply by "refraining" from growth (Figure 2.2b). Accordingly, IUGR that from a clinical perspective is usually considered as a pathological symptom of impaired supply, can be interpreted as a physiological adaptation that enables the fetus to survive a further shortage despite an already limited O_2, and substrate availability. The earlier the underlying metabolic changes start and the longer they last, the more the fetal organism is programmed to "low flame," meaning that even a normal supply of substrate acts as a surplus and thus promotes a metabolic syndrome later in life (49–51).

The placental decrease in O_2 consumption in response to decreasing O_2 supply, also referred to as hypoxic hypometabolism (52, 53), is an "oxyconforming" response that differs from the usual "oxyregulatory" behavior of mammalian tissues that tend to maintain their metabolic rate until final breakdown (Figure 2.2d). It has long been assumed that oxyconformism is confined to lower vertebrates (frogs) or even invertebrates (intertidal worms) that are able to adapt to changing supply conditions by adjusting their metabolic rate more flexibly (54, 55). Recent studies suggest that not only the placenta but also the fetus itself shows an oxyconforming behavior in that its own metabolic rate underlies some variations depending on the fluctuating O_2 tensions in the fetal circulation (30). This may reflect, among other things, the varying contribution of growth metabolism to the overall metabolic rate. However, it is also related to a redistribution of blood flow that the fetus exhibits in response to deteriorating O_2 supply conditions (brain-sparing effect), and that may be regarded as a precursor of the birth-related diving response (Figure 2.2c) (56, 57).

Surviving with a minimum – A deep dive through the birth canal

Whenever the fetus is at risk of suffering a severe O_2 deficiency during the birth process (58), a reaction occurs that is very well-known to the entire delivery room staff as a red flag: the so-called dips or decelerations in the cardiotocographic (CTG) monitoring. They differ from the stress response an adult would show in the case of suffocation, namely an acceleration in heart rate and an increase in cardiac output to maintain an adequate O_2 supply to the tissues. Since this typical oxyregulatory response enables the organism to escape or fight a threatening situation, it has proven to be an obviously successful adult survival strategy in the course of evolution. Its major disadvantage, however, is that under the conditions of an already limited O_2 supply, the O_2 demand will increase even further. As the fetus completely relies on energy supply via the umbilical cord, any attempt to fight against the O_2 lack would be futile and would only lead to a reduced hypoxia tolerance due to the increased O_2 consumption rate. It is therefore reasonable from an evolutionary perspective that the fetus responds to an acute (perinatal) hypoxia with a different physiological reaction that is called the "diving response", by analogy to aquatic mammals (seals) that exhibit a similar pattern during longer periods of submersion (59–61). This comprises three main components.

Lowering heart rate

A cornerstone of the diving response in both aquatic mammals and mammalian fetuses is the gradual decrease in heart rate. Given that the myocardium, together with the brain, accounts for a significant proportion of total O_2 consumption in the fetal life, bradycardia per se makes a significant contribution to reducing energy requirements.

Redirecting blood flow

Since the slowed heart rate results in a reduced cardiac output, an adequate supply of the organism would no longer be possible if there were no redistribution of blood flow. That's why the diving reflex involves a centralization of the circulation in favor of the vital organs (heart, brain). The temporary reduction of peripheral perfusion leads to an accumulation of lactate in peripheral tissues and a subsequent washout after re-emergence. As pointed out by Scholander in a landmark paper (62), the post-diving lactate peak in seals is similar to the transient lactate increase that is observed in human neonates immediately after birth, and that, incidentally, makes it difficult to draw a clear line between a beneficial self-protective response and an actual perinatal asphyxia.

Holding breath

Not unlike at deep rest, all spontaneous fetal motor activity is also suppressed under stress, so as to avoid any unnecessary energy expenditure. This includes the intermittent respiratory movements the fetus is known to exhibit, just to prepare the diaphragm for its life-long activity. Only when a critical degree of hypoxia is reached, the apnea is interrupted by serial gasps that, if occurring in the birth canal, can lead to a meconium aspiration syndrome. Once the baby is born, the gasps provide the blood with a minimum of O_2, just enough to maintain the greatly slowed heart rate for a while ("autoresuscitation") (63–65).

As a whole, the diving response results in a slower consumption of the remaining O_2 reserves (that, both in fetuses and diving mammals, are elevated by a high hematocrit). The clinical appearance of a "depressed" neonate with apnea, bradycardia, and reduced peripheral perfusion actually corresponds to the full picture of the diving reflex. Just as in a seal taking a deep breath after re-emergence at the water surface, a rapid increase in the baby's APGAR values from the first to the fifth minute of life reflects a rapid recovery from a self-protective response (66, 67). In case of persisting hypoxia of any cause, the diving reflex will be maintained and completed by a suppression of thermogenesis in the O_2- and pH-sensitive BAT which, while preventing an adverse thermoregulatory increase in metabolic rate, increases the risk of inadvertent hypothermia (28, 52, 68, 69).

Summary and conclusions – The mammalian fetus as a paragon of coping with the lack

In summary, mammalian, including human, fetuses and newborns are equipped with a number of self-protective mechanisms that prevent them from the risks of intrauterine and perinatal life. Since the most important of these risks is a temporary lack of O_2 and nutrient supply, being in contrast to the particularly high metabolic demands of small endotherms, it is not surprising that these mechanisms are mainly based on a reduction in metabolic rate. Most of them are known from adaptations to a predictable (e.g. seasonal) undersupply in the animal kingdom (53, 60, 70) suggesting that, vice versa, the perinatal period might even act as a common ontogenetic source of adaptive responses among mammals.

With regard to perinatal adaptation, it should be emphasized that the self-protective mechanisms are arranged in a cascade-like manner and exhaust themselves gradually (Figure 2.3). This means that the more of them have already been activated *in utero* (e.g., in a growth-restricted fetus), the fewer are left at birth. The cumulative protective benefit is only effective as long as the gap between supply and demand can be narrowed by reducing demand to an indispensable minimum. This also means that neonatal hypoxia tolerance is more a "resistance" than a "tolerance" in its strict sense, delaying the onset of critical hypoxia rather than attenuating the harmful effects of O_2 lack. In fact, there is little, if any, evidence that neonatal tissues really "tolerate" hypoxia better than adult ones do. Although lactate acidosis plays an important role in the assessment of perinatal asphyxia, an overall (enzymatic) increase in the anaerobic capacity, i.e. the ability to extract energy from lactic acid fermentation, has never been proven in neonatal tissues (71).

What is unique about placental, fetal, and neonatal tissues is their ability to "deliberately" reduce their metabolic rate in response to decreased energy supply – a capability often misinterpreted as a low metabolic trait. In adult mammals experiencing a gap between energy demand and supply, counter-regulatory responses (tachycardia) are initiated to compensate for the reduced supply (oxyregulatory behavior). If these are not successful, a "passive" breakdown in metabolic rate occurs – as if a light bulb goes out as soon as the battery is exhausted. An alternative way to respond to shortened supply is to "actively" reduce demand (oxyconforming behavior) – as if a light bulb is provisionally dimmed in view of the imminent exhaustion of the battery. The phenomenological similarity between active and passive reduction in energy consumption (the light bulb becomes darker) partly explains the clinical problems in determining the

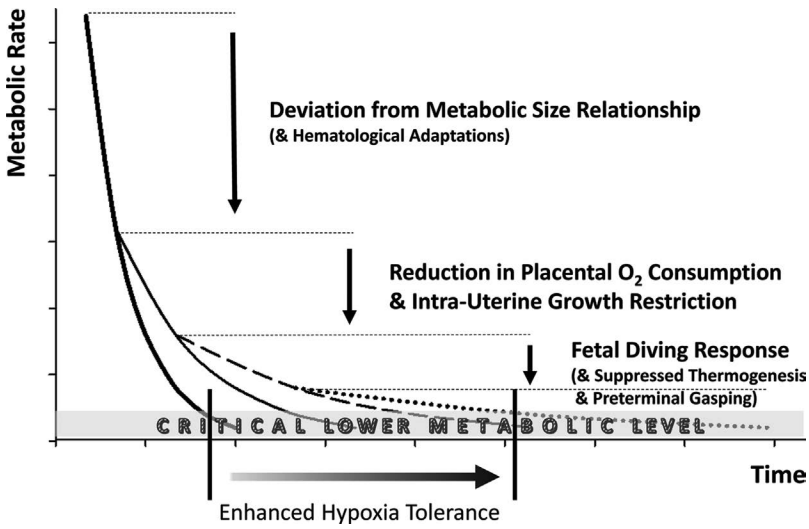


FIGURE 2.3 Cascade-like arrangement of self-protective mechanisms in mammalian fetuses and neonates. The declining curves represent the "passive" metabolic breakdown resulting from an imbalance between O_2 demand and supply. Whenever the metabolic rate falls below a critical lower limit, this results in irreversible damage. However, any "active" reduction in metabolic rate leads to a gradually slowed metabolic breakdown and an accordingly enhanced hypoxia tolerance (schematic view, arbitrary units).

boundaries between protective reactions and signs of damage in perinatal asphyxia.

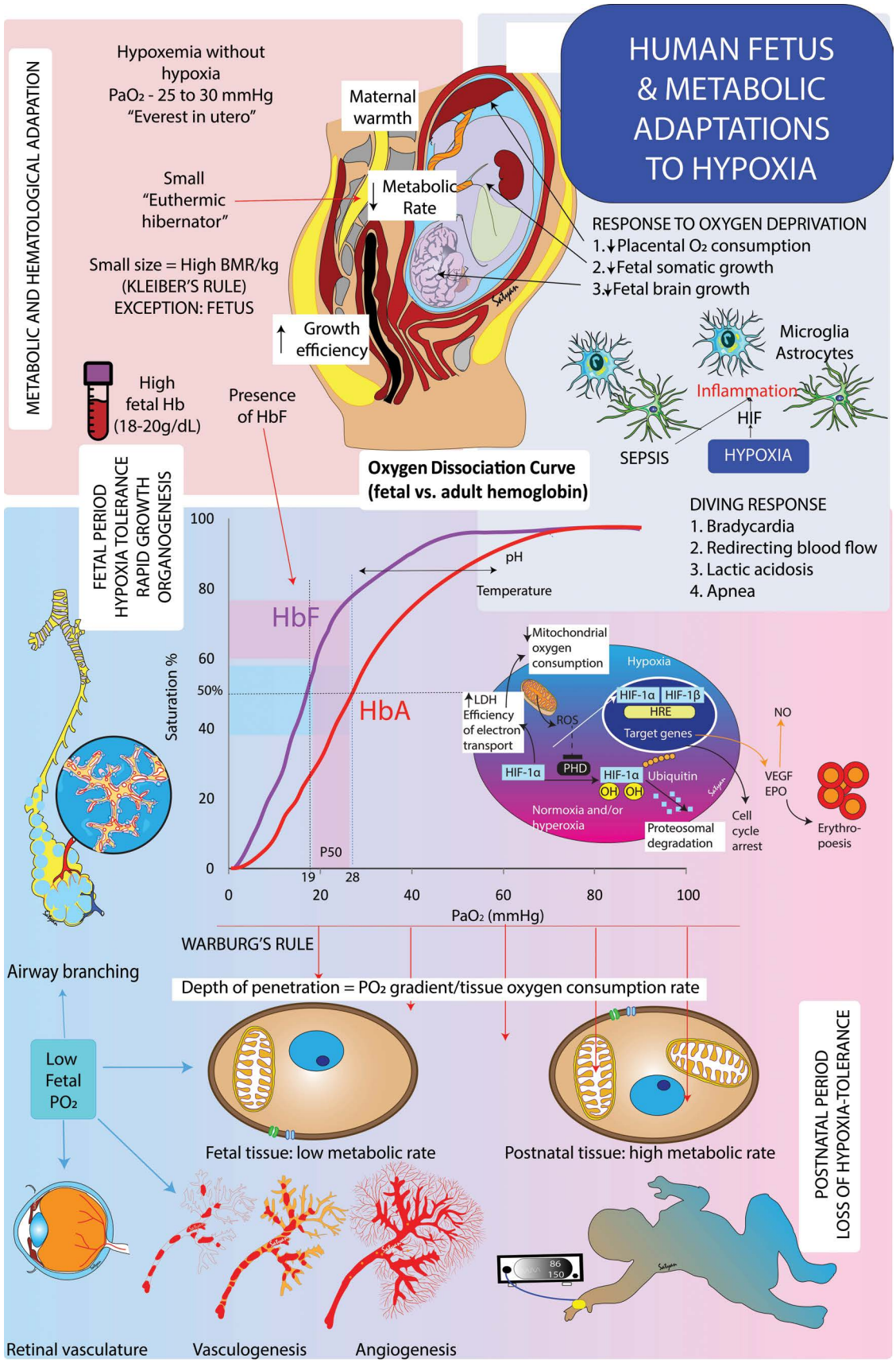
Animal experiments on newborn mammals have revealed that their extra hypoxia tolerance is the more pronounced the smaller and more immature they are at birth (72, 73). In addition to a suppression of thermogenesis, a reduction of the metabolic rate at normal body temperature and thus a hypoxic hypometabolism was identified as the essential mechanism (15, 52, 74). Interestingly, however, this ability (obviously some kind of transient return to the fetal metabolic level) is lost more or less quickly, much in parallel with the postnatal increase in metabolic rate and its link to body size (23, 75). It may be that some of the natural adaptation strategies (e.g., hibernation) imply a temporary disabling of this link in a low-oxygen environment.

Finally, the optimization of the birth process over millions of years of mammalian evolution may explain the difficulties of finding effective treatments for HIE. It must be assumed that nature has left out nothing that could have contributed to reducing vulnerability. External cooling as an attempt to reduce the newborn's metabolic rate differs from the endogenous metabolic suppression occurring in natural adaptations. However, the latter is only effective as long as the hypoxic state persists. Should it eventually be possible to activate the "fetal hibernation gene" even after a hypoxic-ischemic event, this might be of huge benefit not only for asphyxiated neonates and adult stroke or cardiac arrest patients.

In the meantime, it is essential to make use of the time margins built into the birth process through a cascade of self-protective mechanisms. This offers the opportunity to identify perinatal risks in time and to avert them by taking appropriate obstetric and/or neonatological measures.

References

1. Shankaran S. Curr Opin Pediatr. 2015; 27:152–157.
2. Davidson JO, et al. Front Biosci. 2018; 23:2204–2226.
3. Gunn AJ, et al. Handb Clin Neurol. 2019; 162:217–237.
4. Kleiber M. *The fire of life: an introduction to animal energetics*. New York: Wiley; 1961.
5. Schmidt-Nielsen KC. Cambridge: Cambridge University Press; 1984.
6. Singer D. Respir Physiol Neurobiol. 2004; 141:215–228.
7. Singer D. Thermochim Acta. 2006; 446:20–28.
8. Bejan A, et al. *Design in nature*. New York: Anchor Books; 2012.
9. Belkin DA. Science. 1963; 139(3554):492–493.
10. Suarez RK, et al. Am J Physiol. 1989; 257:R1083–R1088.
11. Else PL, et al. Physiol Biochem Zool. 2004; 77:950–958.
12. Okken A, Koch J, eds. *Thermoregulation of sick and low birth weight neonates*. Berlin: Springer; 1995.
13. Agren J. *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant*, 10th. ed. Martin RJ, Fanaroff AA, Walsh MC, eds. Philadelphia: Elsevier Saunders; 2015. pp. 502–512.
14. Singer D, et al. *Innovations and frontiers in neonatology (Pediatr Adolesc Med, vol. 22)*; Basel: Karger; 2020. pp. 95–111.
15. Mortola JP. Respir Physiol. 1999; 116:95–103.
16. Singer D. Comp Biochem Physiol A. 1999; 123:221–234.
17. Singer D. Anästhesiol Intensivmed Notfallmed Schmerzther. 2002; 37:441–460.
18. Ar A, et al. Israel J Zool. 1994; 40:307–326.
19. Reich B, et al. Dev Neurosci. 2016; 38:311–330.
20. Warburg O. Biochem Z. 1923; 142:317–333.
21. Rahn H. *A companion to animal physiology*. Taylor CR, Johansen K, Bolis L, eds. Cambridge: Cambridge University Press; 1982. pp. 124–137.
22. Wieser W. Respir Physiol. 1984; 55:1–9.
23. Singer D, et al. Comp Biochem Physiol A. 2007; 148:780–784.
24. Hasselbalch AK. Skand Arch Physiol. 1900; 10:353–402.
25. Paganelli CV, et al. In: *Respiration and metabolism of embryonic vertebrates*. Seymour RS, ed. Dordrecht: Dr W Junk Publishers; 1984. pp. 193–204.
26. Bohr C. Skand Arch Physiol. 1900; 10:413–424.
27. Dawes GS, et al. J Physiol. 1959; 146:295–315.
28. Schröder HJ, et al. Exp Physiol. 1997; 82:403–414.
29. Murray AJ. Placenta. 2012; 33:e16–e22.
30. Postigo L, et al. J Physiol. 2009; 587:693–708.
31. Hill JR, et al. J Physiol. 1965; 180:239–265.
32. Bauer K, et al. J Pediatr. 2003; 142:390–396.
33. Bauer J, et al. Am J Clin Nutr. 2009; 90:1517–1524.
34. Brück K. In: *Perinatal physiology*, 2nd. Stave U, ed. New York: Plenum; 1978. pp. 455–498.
35. Singer D. Thermochim Acta. 1998; 309:39–47.
36. DuBose TJ. Fertil Steril. 2009; 92:e57–e58.
37. Lindstedt SL, et al. Quart Rev Biol. 1981; 56:1–16.
38. Szdzuy K, et al. J Anat. 2008; 212:164–179.
39. Mortola JP, et al. Nature. 1999; 397:660.
40. Geiser F. J Comp Physiol. 1988; 158B:25–37.
41. Singer D, et al. In: *Surviving hypoxia: mechanisms of control and adaptation*. Hochachka PW, Lutz PL, Sick T et al., eds. Boca Raton FL: CRC Press; 1993. pp. 447–458.
42. Heldmaier G, et al. Respir Physiol Neurobiol. 2004; 141:317–329.
43. Tøien, et al. Science. 2011; 331:906–909.
44. Musacchia XJ, et al. Am J Physiol. 1971; 221:128–130.
45. Revsbech IG, et al. J Comp Physiol B. 2017; 187:847–856.
46. Bennet L. J Physiol. 2017; 595:1865–1881.
47. Carter AM. Placenta. 2000; 21(Suppl A):S31–S37.
48. Schneider H. Placenta. 2000; 21(Suppl A):S38–S44.
49. Godfrey KM, et al. Public Health Nutr. 2001; 4:611–624.
50. Rinaudo P, et al. Annu Rev Physiol. 2012; 74:107–130.
51. Myers DA, et al. Adv Exp Med Biol. 2014; 814:147–157.
52. Mortola JP. Respir Physiol Neurobiol. 2004; 141:345–356.
53. Gorr TA. Acta Physiol. 2017; 219:409–440.
54. Boutilier RG, et al. J Exp Biol. 1997; 200:387–400.
55. Buchner T, et al. Comp Biochem Physiol B. 2001; 129:109–120.
56. Jensen A, et al. Eur J Obstet Gynecol Reprod Biol. 1999; 84:155–172.
57. Cohen E, et al. Neonatology. 2015; 108:269–276.
58. Turner JM, et al. Am J Obstet Gynecol. 2020; 222:17–26.
59. Elsner R, et al. Monogr Physiol Soc. 1983; 40:1–168.
60. Hill RW, et al. *Animal physiology*. Sunderland (Mass): Sinauer; 2004.
61. Panneton WM. Physiology. 2013; 28:284–297.
62. Scholander PF. Sci Am. 1963; 209:92–106.
63. Sanocka UM, et al. J Appl Physiol. 1992; 73:749–753.
64. Fewell JE. Respir Physiol Neurobiol. 2005; 149:243–255.
65. Manole MD, et al. Pediatr Res. 2006; 60:174–179.
66. Casey BM, et al. N Engl J Med. 2001; 344:467–471.
67. Iliodromiti S, et al. Lancet. 2014; 384:1749–1755.
68. Malan A, et al. J Comp Physiol B. 1988; 158:487–493.
69. Jayasinghe D. Neonatology. 2015; 107:220–223.
70. Larson J, et al. J Exp Biol. 2014; 217:1024–1039.
71. Jones CT, et al. Physiol Rev. 1985; 65:357–430.
72. Himwich HE, et al. Am J Physiol. 1941; 133:327–339.
73. Lutz PL, et al. Comp Biochem Physiol B Biochem Mol Biol. 1996; 113:3–13.
74. Rohlicek CV, et al. J Appl Physiol. 1998; 84:763–768.
75. Mourek J. Physiol Bohemoslov. 1959; 8:106–111.


HUMAN FETUS & METABOLIC ADAPTATIONS TO HYPOXIA
METABOLIC AND HEMATOLOGICAL ADAPATION
Hypoxemia without hypoxia
PaO₂ - 25 to 30 mmHg
"Everest in utero"
Small "Euthermic hibernator"
Small size = High BMR/kg (KLEIBER'S RULE)
EXCEPTION: FETUS
Maternal warmth
Metabolic Rate
Growth efficiency
High fetal Hb (18-20g/dL)
Presence of HbF
RESPONSE TO OXYGEN DEPRIVATION
1.↓Placental O₂ consumption
2.↓Fetal somatic growth
3.↓Fetal brain growth
Microglia
Astrocytes
Inflammation
HIF
SEPSIS
HYPOXIA
DIVING RESPONSE
1. Bradycardia
2. Redirecting blood flow
3. Lactic acidosis
4. Apnea
FETAL PERIOD
HYPOXIA TOLERANCE
RAPID GROWTH
ORGANOGENESIS
Oxygen Dissociation Curve (fetal vs. adult hemoglobin)
HbF
HbA
pH
Temperature
Saturation %
P50
PaO₂ (mmHg)
Mitochondrial oxygen consumption
Hypoxia
HIF-1α
HIF-1β
HRE
Target genes
LDH
Efficiency of electron transport
ROS
PHD
Ubiquitin
OH
Normoxia and/or hyperoxia
Proteosomal degradation
Cell cycle arrest
NO
VEGF
EPO
Erythro-poesis
WARBURG'S RULE
Airway branching
Depth of penetration = PO₂ gradient/tissue oxygen consumption rate
Low Fetal PO₂
Fetal tissue: low metabolic rate
Postnatal tissue: high metabolic rate
POSTNATAL PERIOD
LOSS OF HYPOXIA-TOLERANCE
Retinal vasculature
Vasculogenesis
Angiogenesis