The Challenge of Immature Respiratory Control in a Developing Lung

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Professor, Pediatrics, Reproductive Biology,
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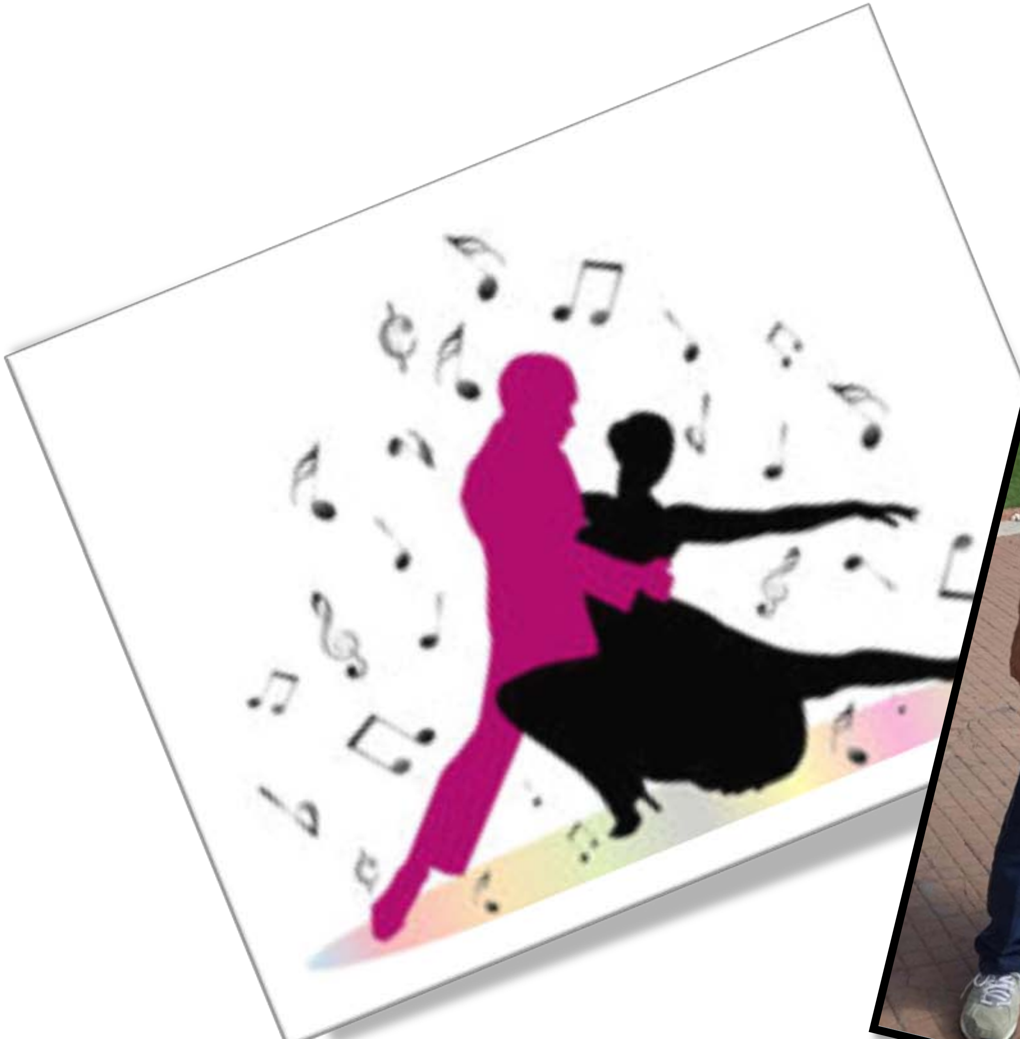
Case Western Reserve University School of Medicine
Drusinsky/Fanaroff Professor
Director, Neonatal Research
Rainbow Babies & Children's Hospital
Cleveland, Ohio

Before 1972

After 1974

Opera House
Sydney, Australia

Rock 'n' Roll Hall of Fame
Cleveland, Ohio, USA



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- ***Where have we been?***
- The challenge of ongoing respiratory morbidity
- Linking immature respiratory control and respiratory morbidity
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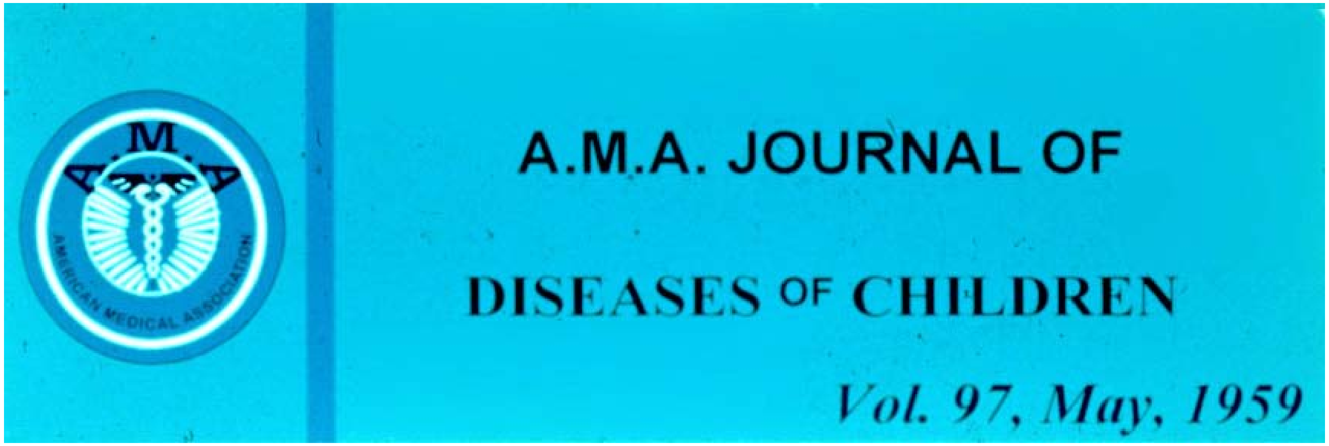
Advice for an Entry Level Neonatologist in the 1970s

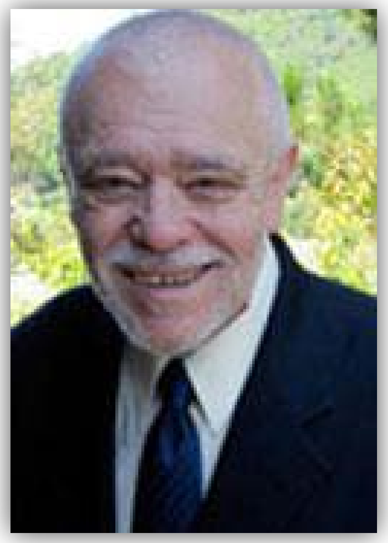
"A solution for prematurity is at hand". *Implication: this is a risky career move*

"All the respiratory problems have been solved". *Implication: avoid respiratory research*



Surface Properties in Relation to Atelectasis and Hyaline Membrane Disease

Mary Ellen Avery, M.D., and Jere Mead, M.D., Boston

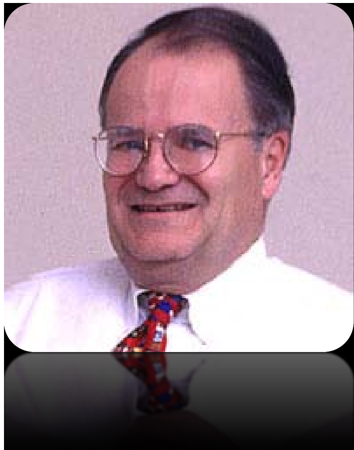


The NEW ENGLAND JOURNAL of MEDICINE

Treatment of the Idiopathic Respiratory-Distress Syndrome with Continuous Positive Airway Pressure

George A. Gregory, M.D., Joseph A. Kitterman, M.D., Roderic H. Phibbs, M.D., William H. Tooley, M.D., and William K. Hamilton, M.D.

N Engl J Med 1971; 284:1333-1340



The New England Journal of Medicine

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Volume 276 | FEBRUARY 16, 1967 | Number

PULMONARY DISEASE FOLLOWING RESPIRATOR THERAPY OF HYALINE-MEMBRANE DISEASE*

Bronchopulmonary Dysplasia

WILLIAM H. NORTHWAY, JR., M.D.,† ROBERT C. ROSAN, M.D.,‡ AND DAVID Y. PORTER, M.D.§

PALO ALTO, CALIFORNIA

March 2012
To my friend
Richard Martin
with Love
Maria

ASSISTED VENTILATION IN TERMINAL HYALINE MEMBRANE DISEASE

BY

MARIA DELIVORIA-PAPADOPOULOS and PAUL R. SWYER

Reprinted from Archives of Disease in Childhood, Vol. 39, No. 207 October 1964

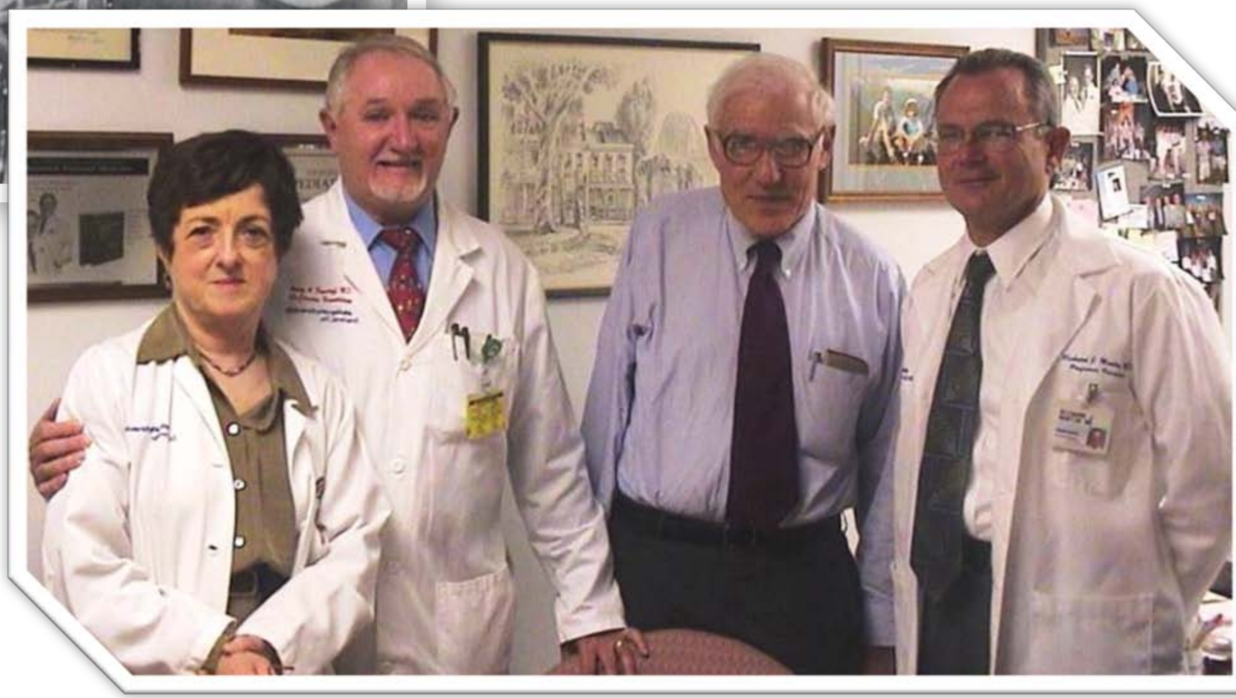
APNEA IN PREMATURE INFANTS: MONITORING, INCIDENCE, HEART RATE CHANGES, AND AN EFFECT OF ENVIRONMENTAL TEMPERATURE

William J. R. Daily, M.A., M.D., Marshall Klaus, M.D., *and*
H. Belton P. Meyer, M.D.

ABSTRACT

"...Continuous monitoring of respiration in small infants is now clinically feasible."

Pediatrics 1969



The Challenge of Immature Respiratory Control in a Developing Lung

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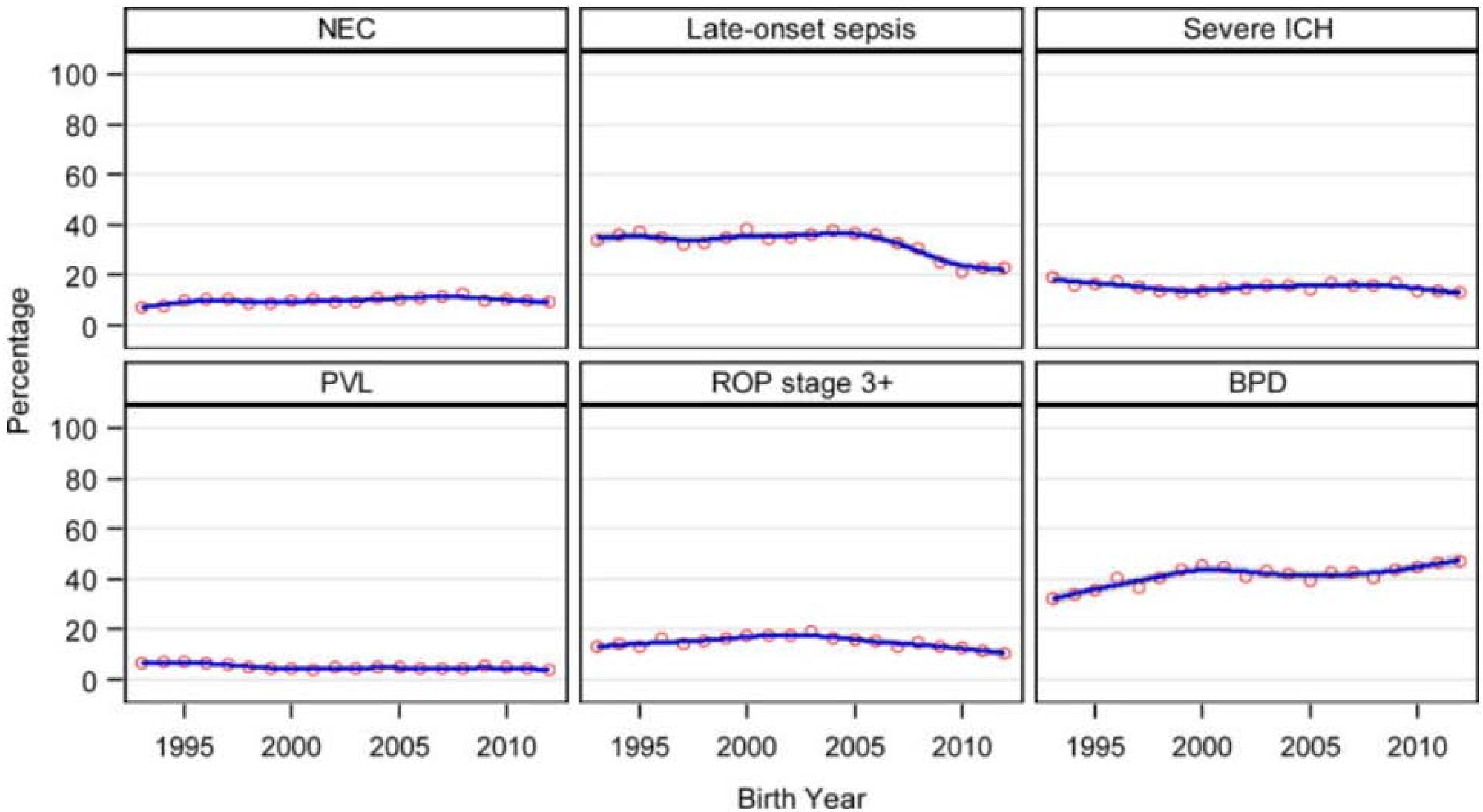
The BPD Challenge

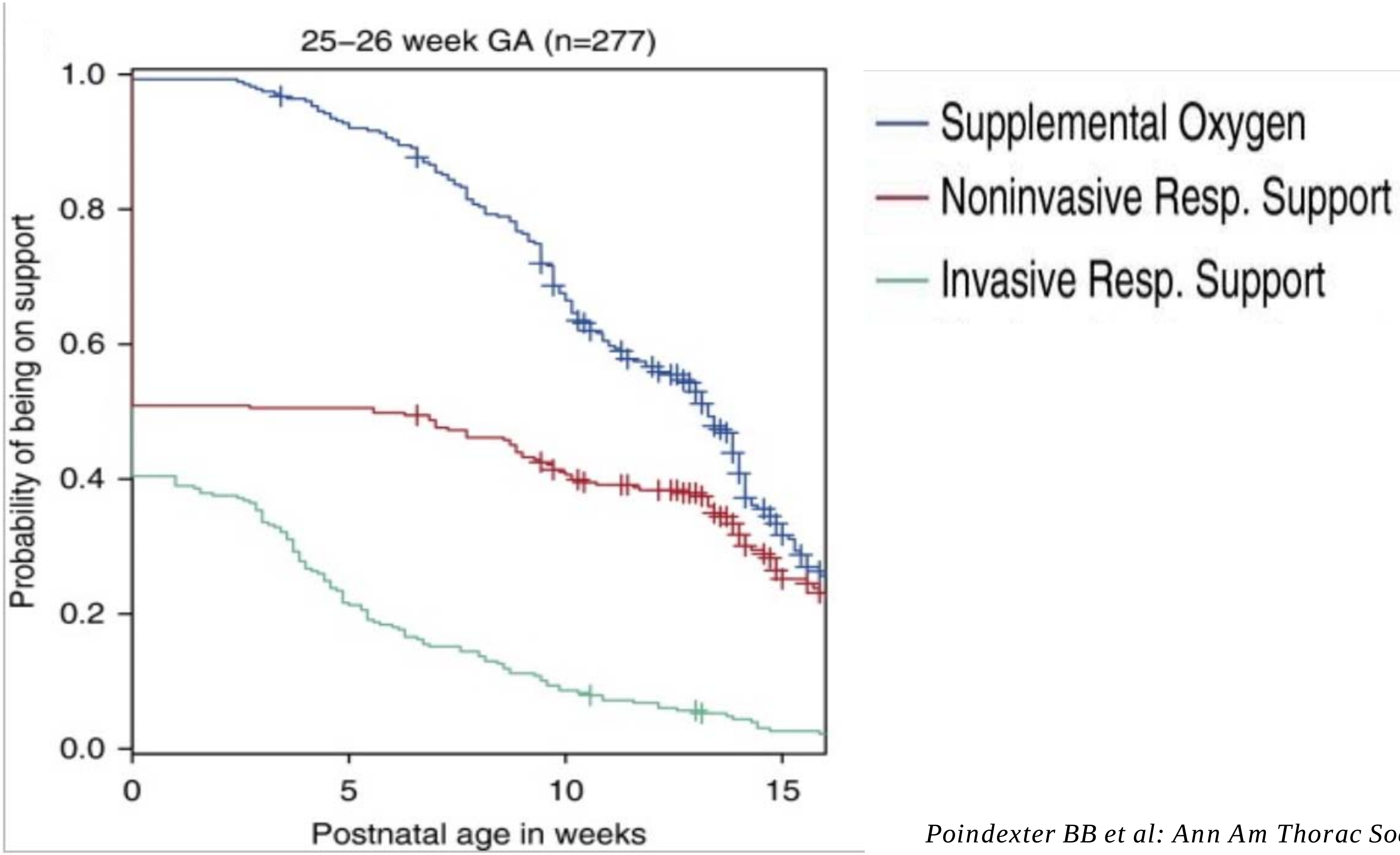
- Incidence in ELBW infants approaches 40%
- No clear definition
- Animal models remain a challenge
- Strong relationship with neurodevelopmental handicap

Neonatal Morbidities at 22-28 Weeks' Gestation [1993-2012]



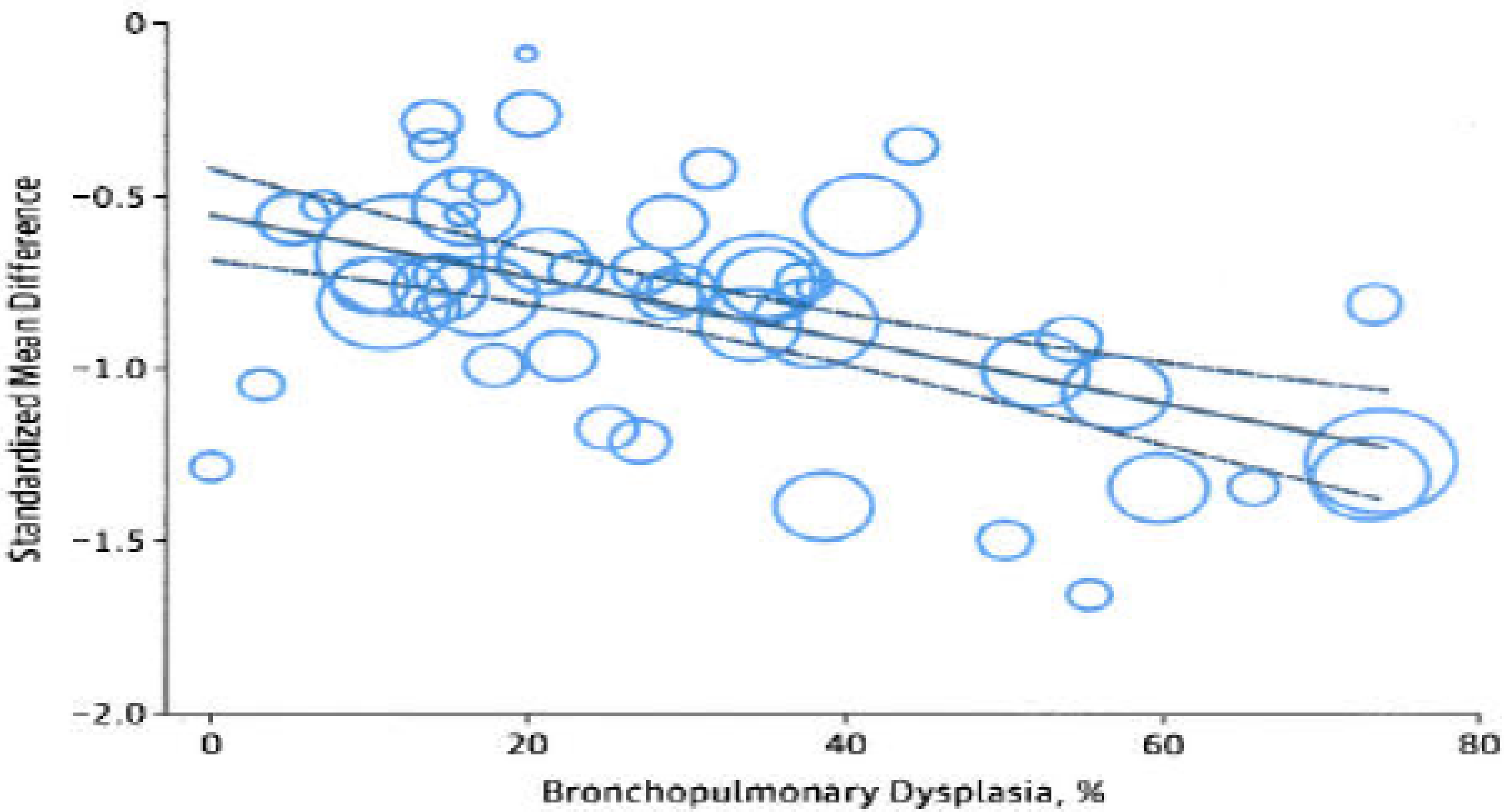
Stoll BJ et al: JAMA 2015

Limitations of Current Definitions of BPD for the Prematurity and Respiratory Outcomes Program

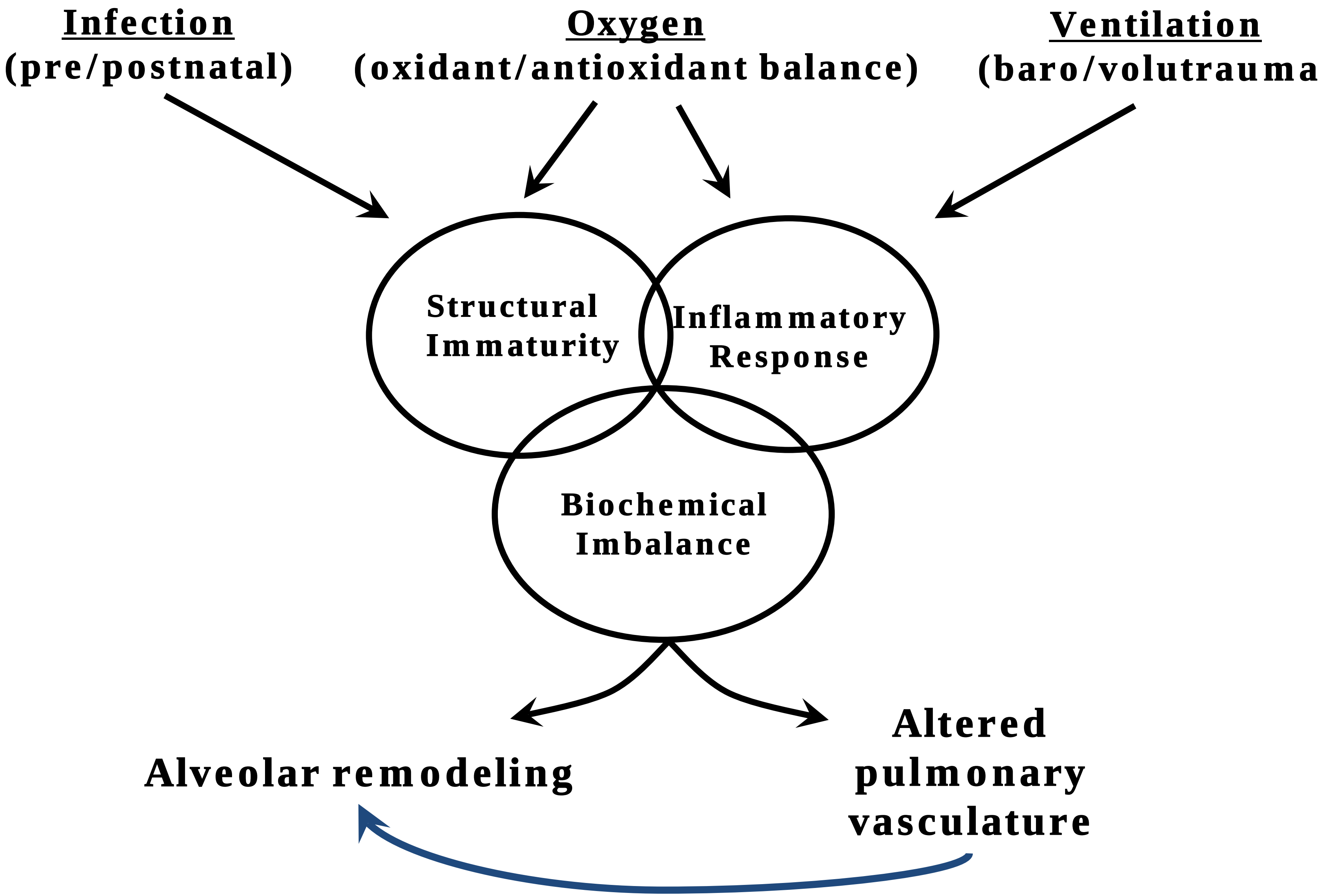


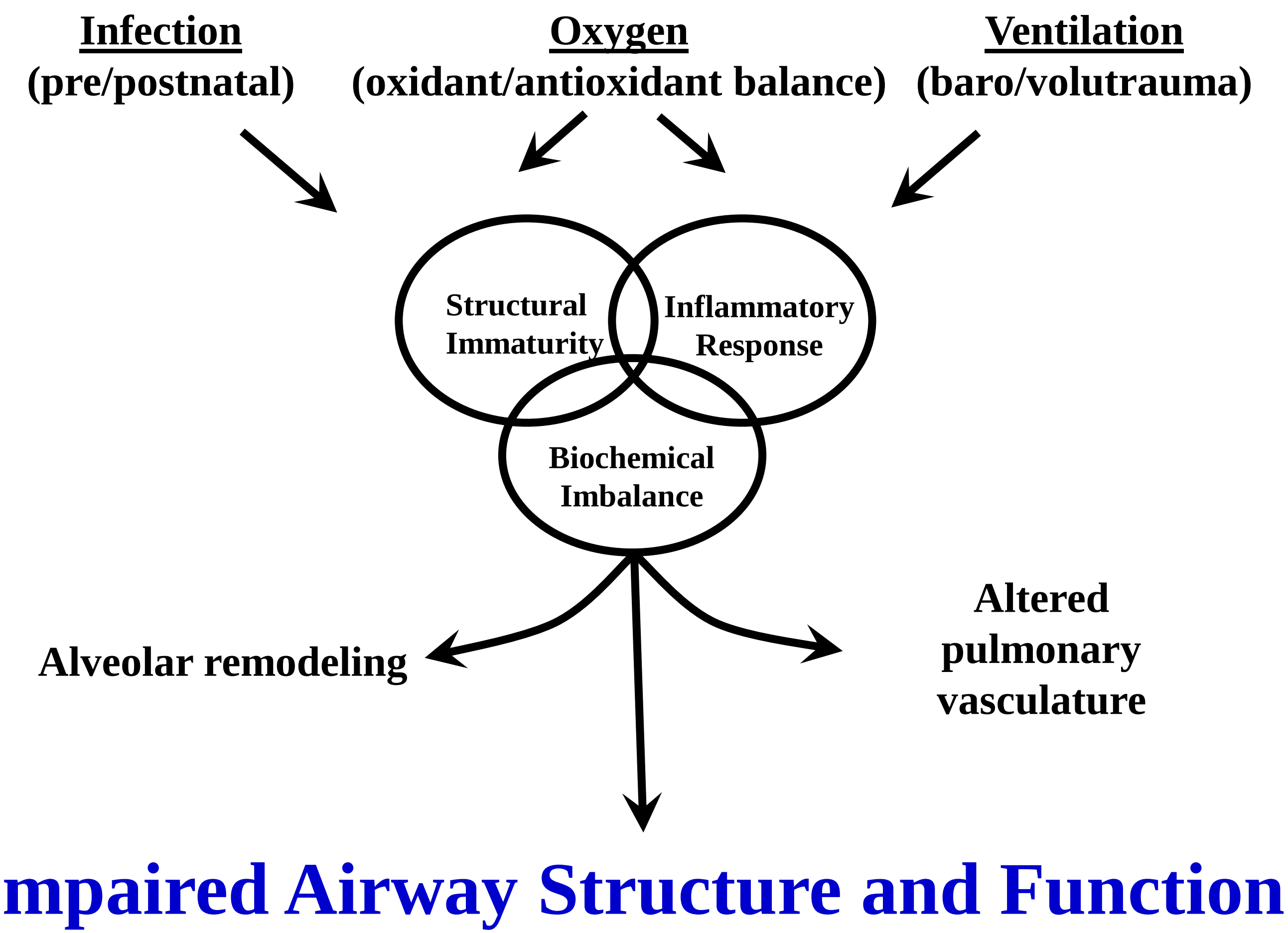
Poindexter BB et al: Ann Am Thorac Soc 2015

Association between BPD Incidence and IQ Deficit



Twilhaar ES et al: JAMA Pediatr 2018


Infection
(pre/postnatal)
Oxygen
(oxidant/antioxidant balance)
Ventilation
(baro/volutrauma)
Structural
Immaturity
Inflammatory
Response
Biochemical
Imbalance
Alveolar remodeling
Altered
pulmonary
vasculature


Infection
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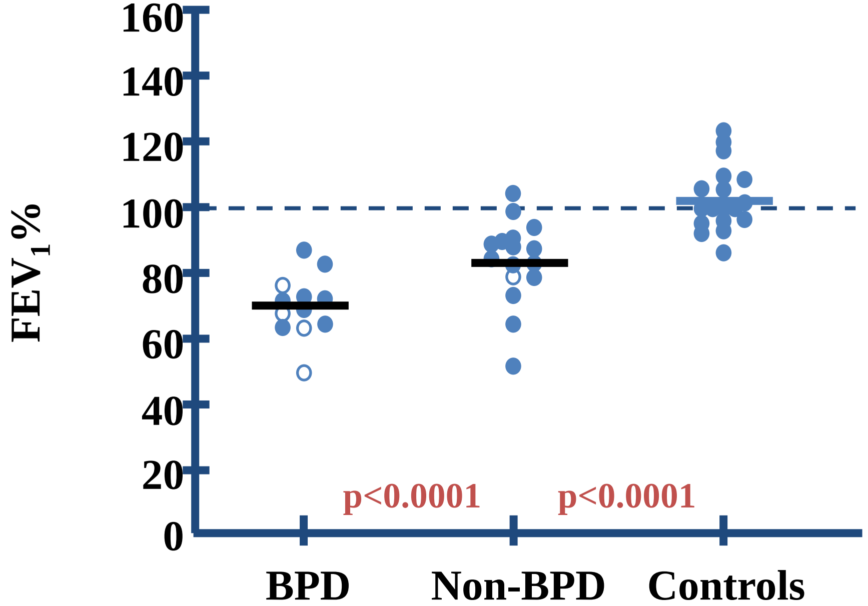
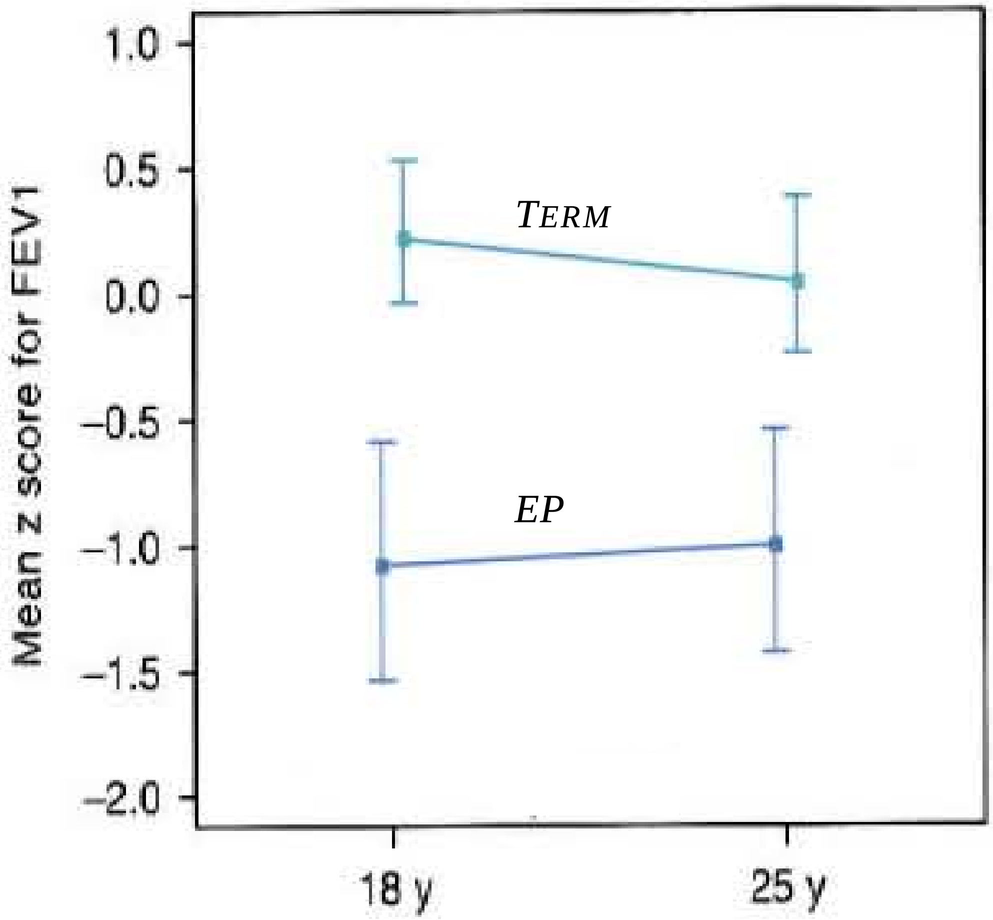
Structural Immaturity
Inflammatory Response
Biochemical Imbalance
Alveolar remodeling
Altered pulmonary vasculature
Impaired Airway Structure and Function

Airway Hyperresponsiveness in School Children Born Very Preterm



Pelkonen AS: Am J Resp Crit Care Med 1997

Adult Progression of Bronchial Responsiveness after Term and Extremely Preterm [EP] Birth



Vollsæter M: Ann Am Thorac Soc, 2015

Ventilation in Extremely Preterm Infants and Respiratory Function at 8 Years

Lex W. Doyle, M.D., Elizabeth Carse, M.D., Anne-Marie Adams, Ph.D., Sarath Ranganathan, Ph.D., Gillian Opie, M.B., B.S., Jeanie L.Y. Cheong, M.D., for the Victorian Infant Collaborative Study Group

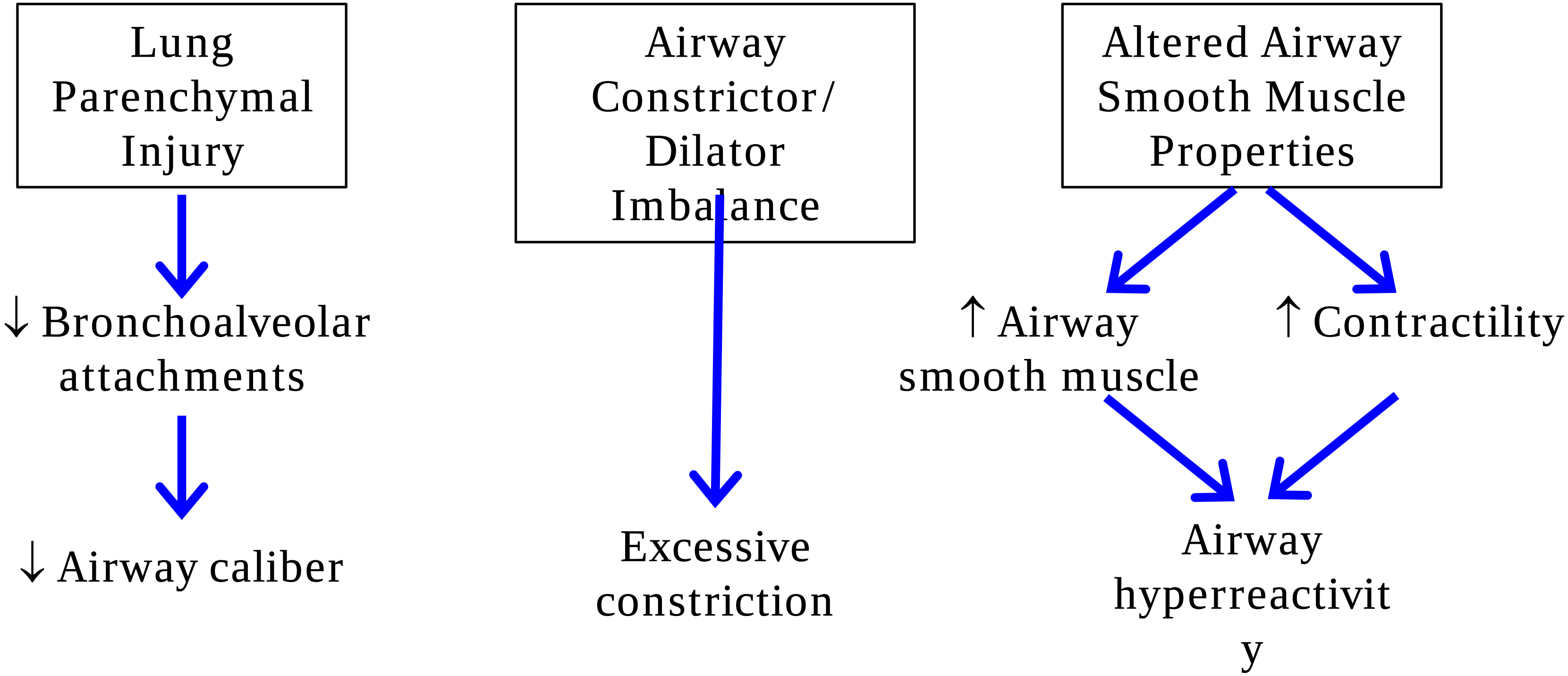
N Engl J Med
Volume 377(4):329-337
July 27, 2017

Days of Respiratory Support in Extremely Preterm Infants [<28 wk]

	1997 [n=151]	2005 [n=170]
Endotracheal ventilation		
Median	19	10
Interquartile range	8–32	2.5–23.5
Mean	23.1±21.0	19.9±28.6
Nasal CPAP		
Median	24	31.5§
Interquartile range	14–36	16.8–42§
Mean	26.0±15.3	33.3±26.0§
Supplemental oxygen		
Median	45	53.5
Interquartile range	10.5–88	9.8–106
Mean	65.1±48.0	75.1±68.0

Expiratory Flows at 8 Years of Age in Each Period

Variable	1997 (N=112)	2005 (N=123)
FEV_1		
Raw value — liters	1.43±0.30	1.25±0.28
z score	−0.65±1.30	−1.19±1.17†
Percent of predicted value	92.0±15.7	85.4±14.4†


Lung Parenchymal Injury
↓ Bronchoalveolar attachments
↓ Airway caliber
Airway Constrictor/ Dilator Imbalance
Excessive constriction
Altered Airway Smooth Muscle Properties
↑ Airway smooth muscle
↑ Contractility
Airway hyperreactivit y

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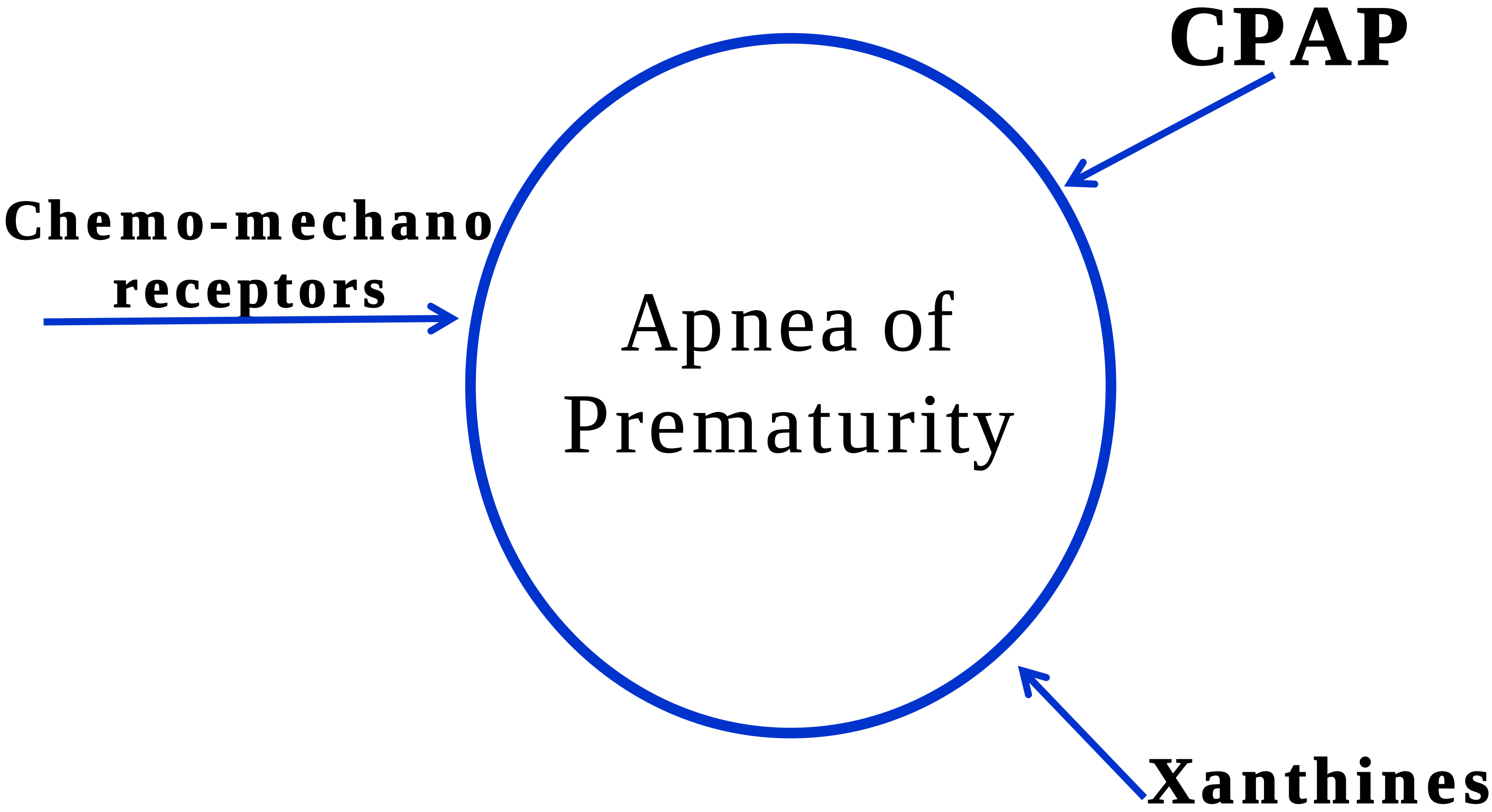
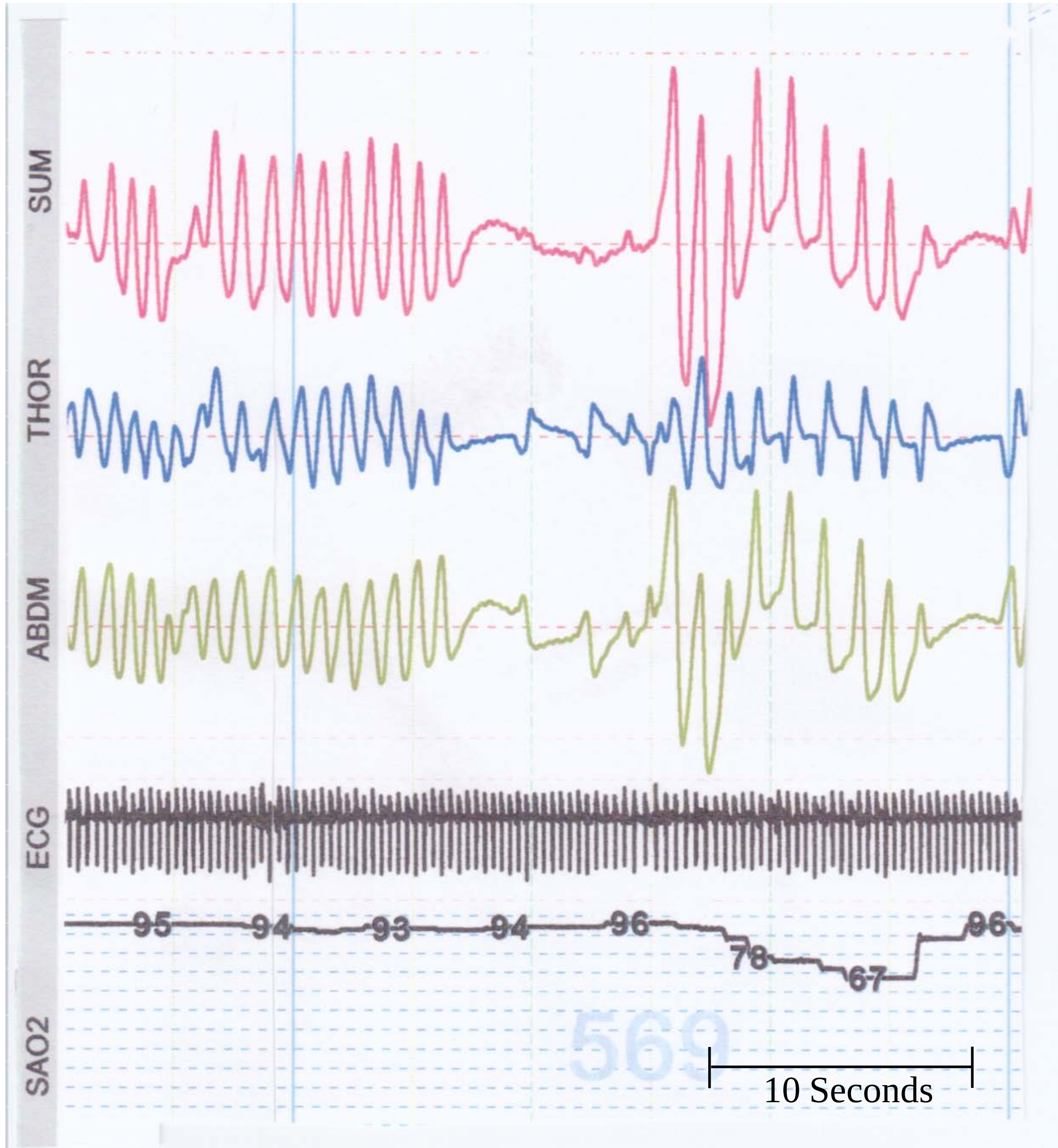
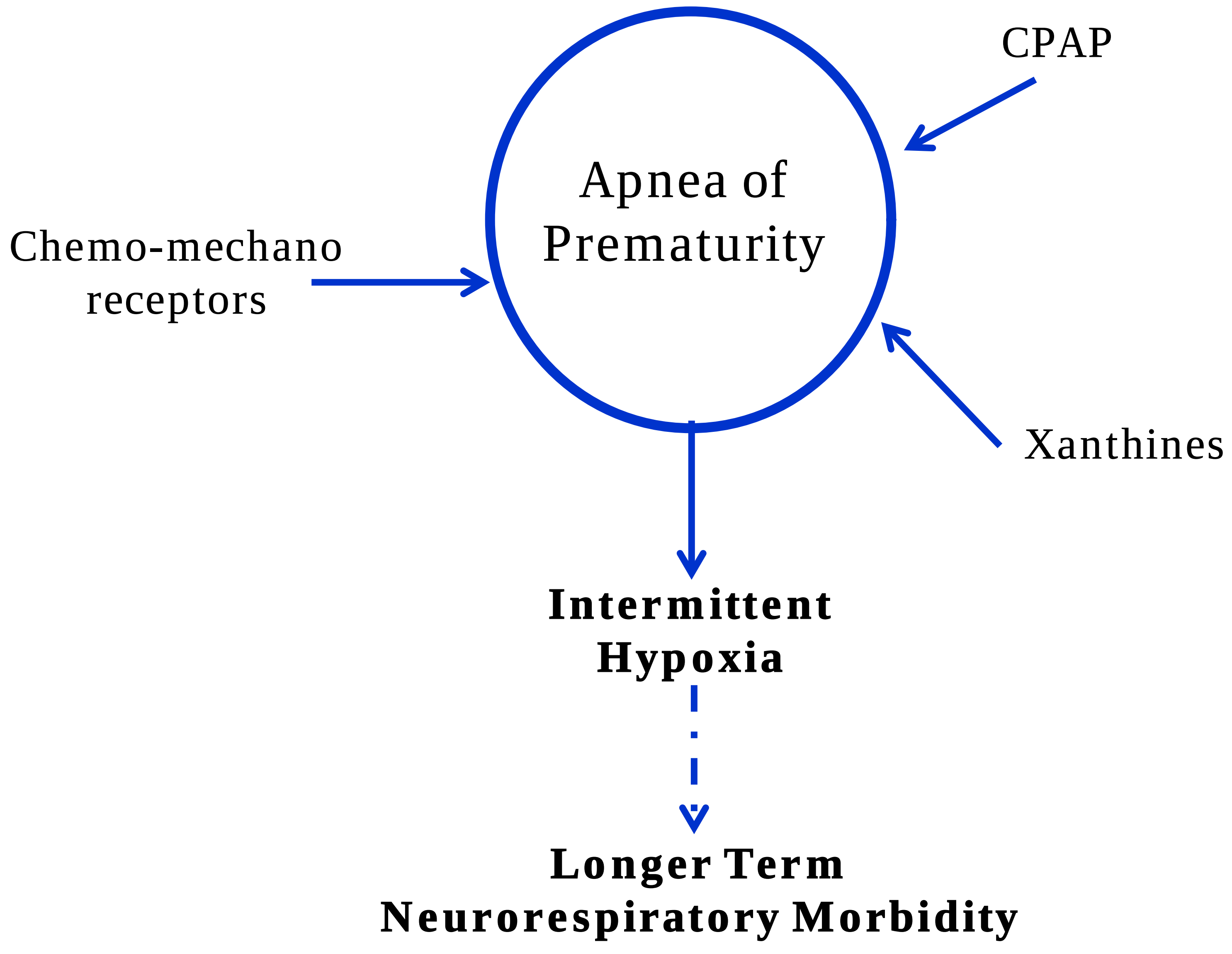
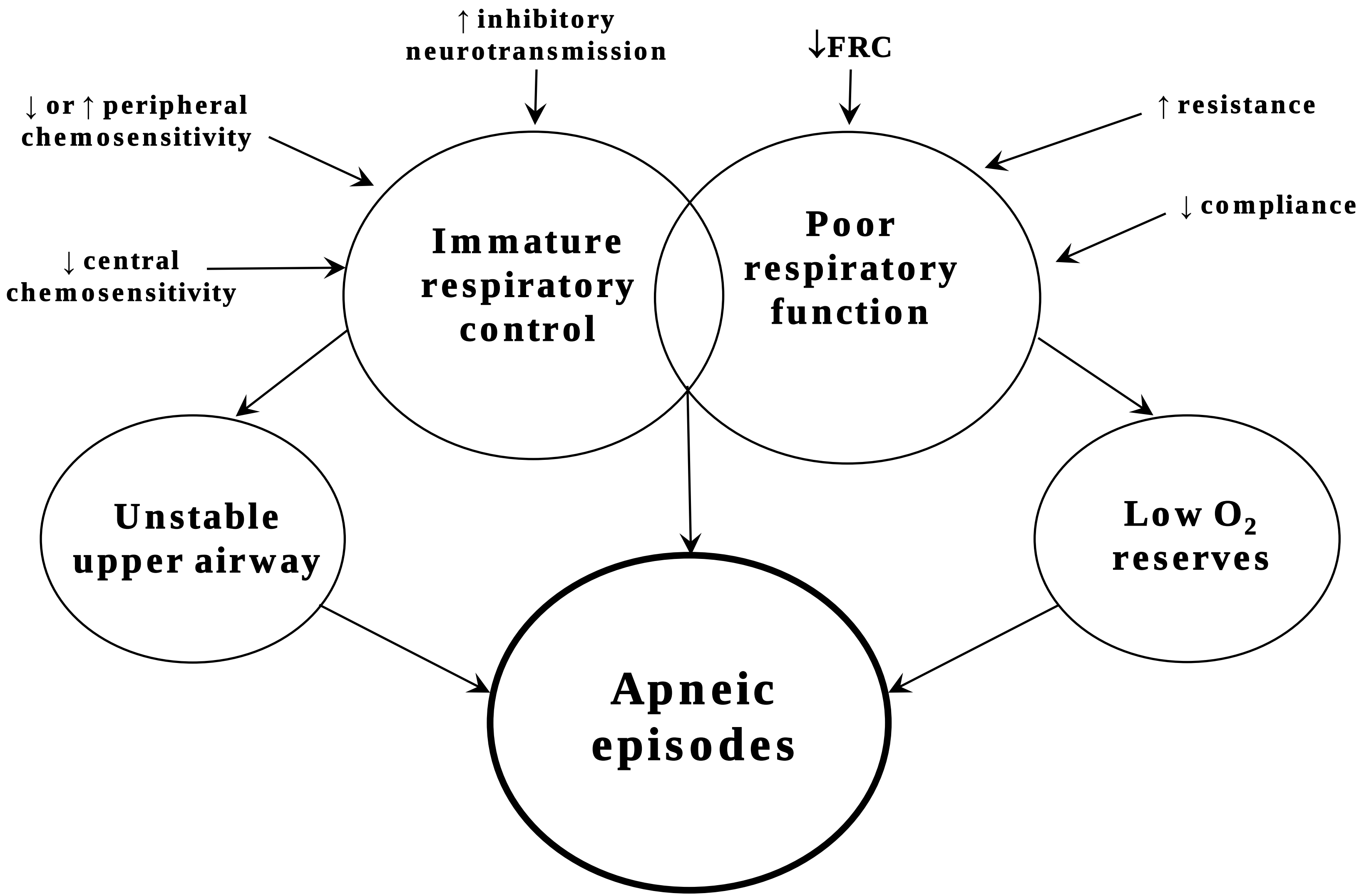
Physiologic Pathways Leading to Mechanisms of Action

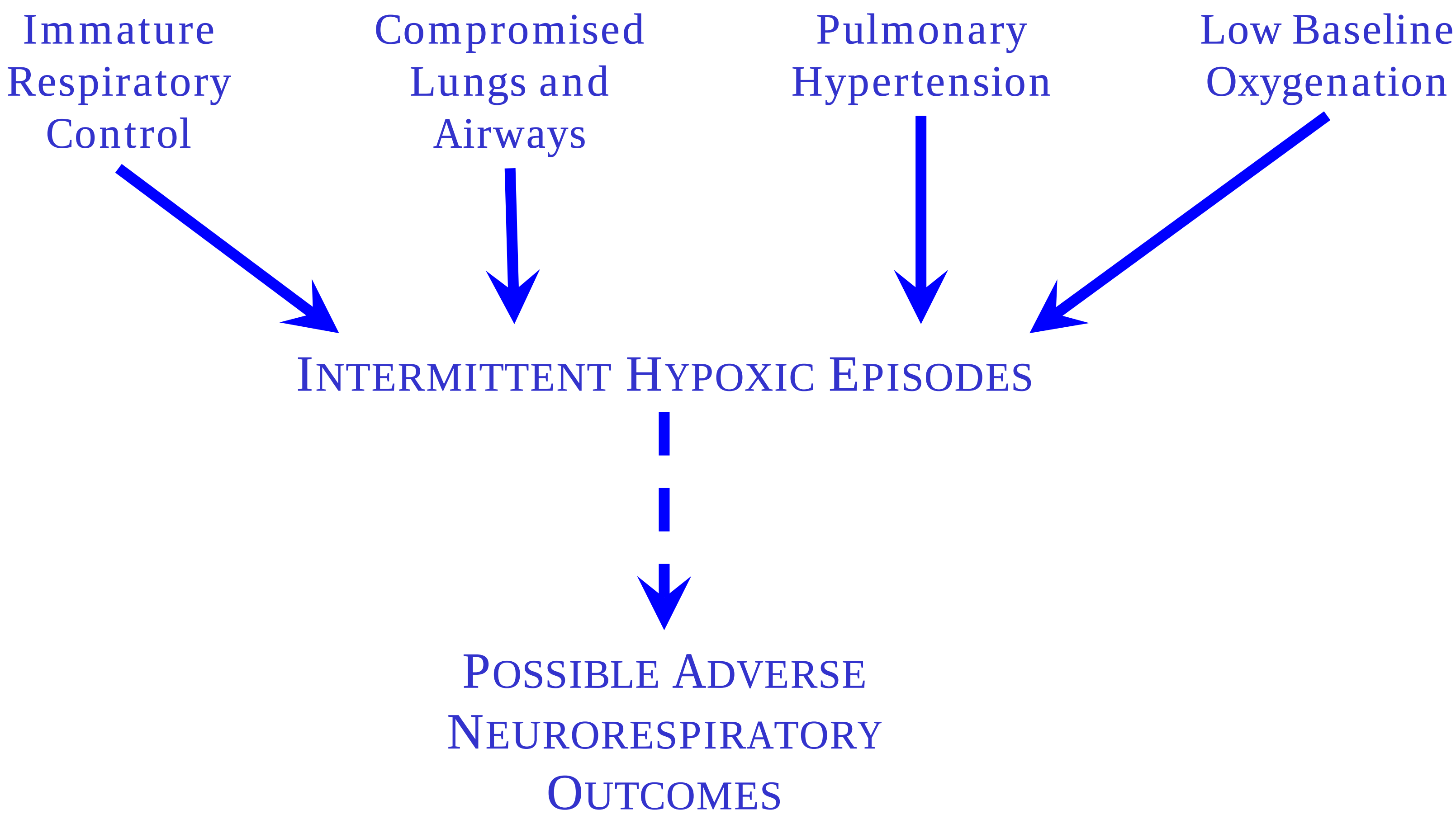



SUM
THOR
ABDM
ECG
SAO2
95
94
93
94
96
78
67
96
569
10 Seconds


Apnea of Prematurity
CPAP
Chemo-mechano receptors
Xanthines
Intermittent Hypoxia
Longer Term Neurorespiratory Morbidity

All Roads Lead to Apnea





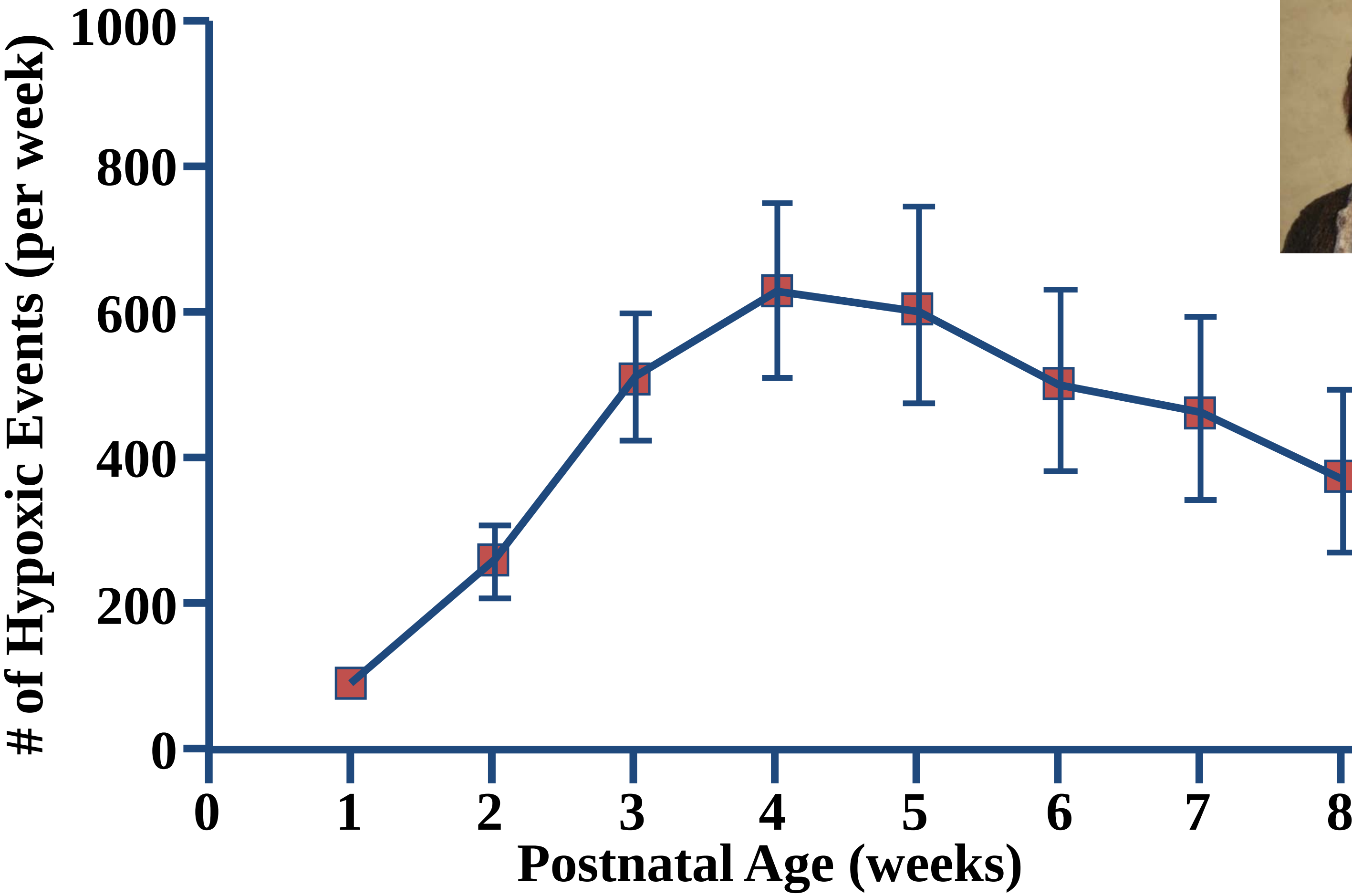
Dylag A: in press 2019

Risk of Bronchopulmonary Dysplasia

“The only treatments that have reduced the incidence of BPD in randomized trials without serious adverse events in premature infants are caffeine and vitamin A”.

Laughon: JAMA Pediatr 2014

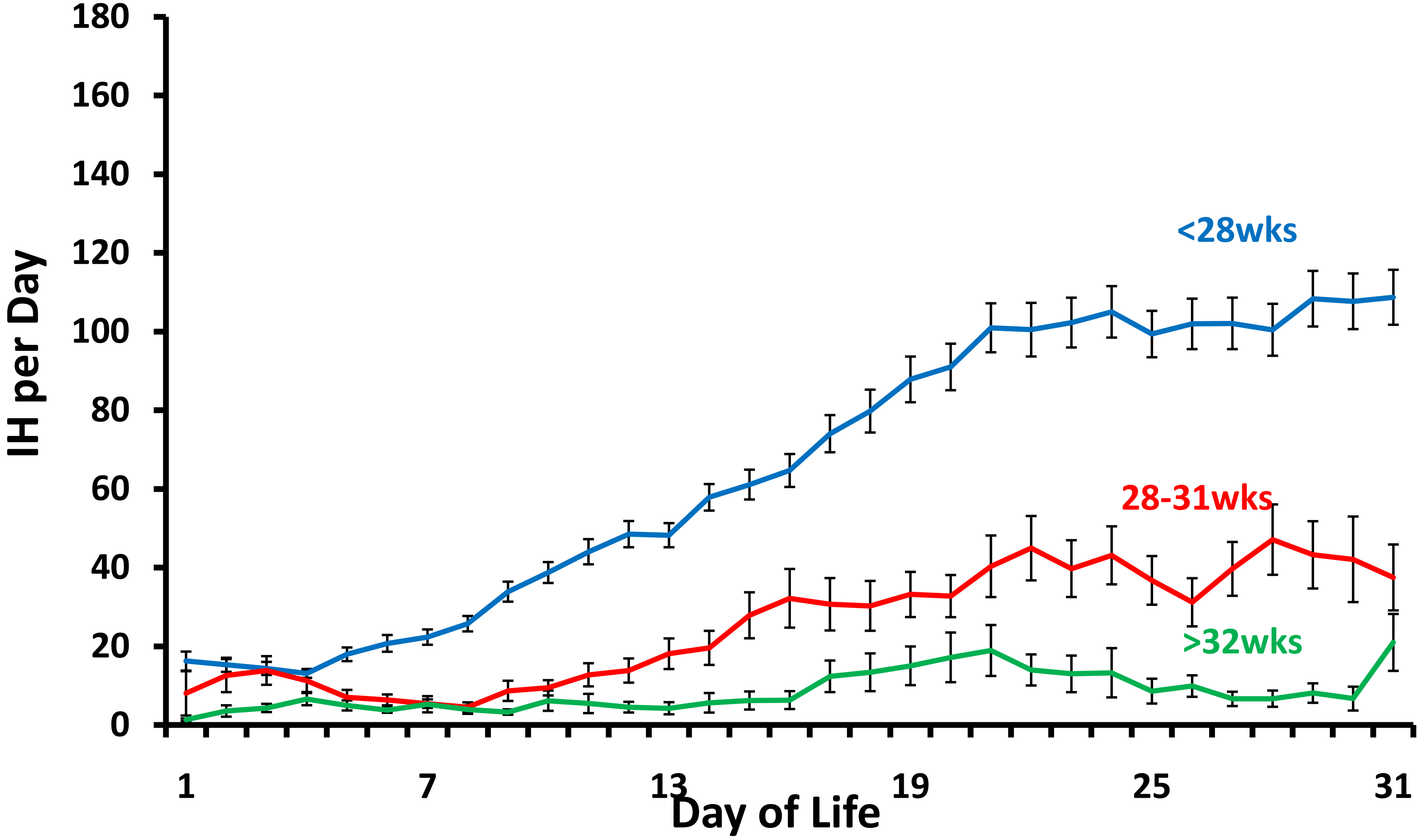
Mean Number of Desaturation Episodes in Infants of 24 to 28 Weeks' Gestation Over the First 8 Weeks



mean±95% confidence interval

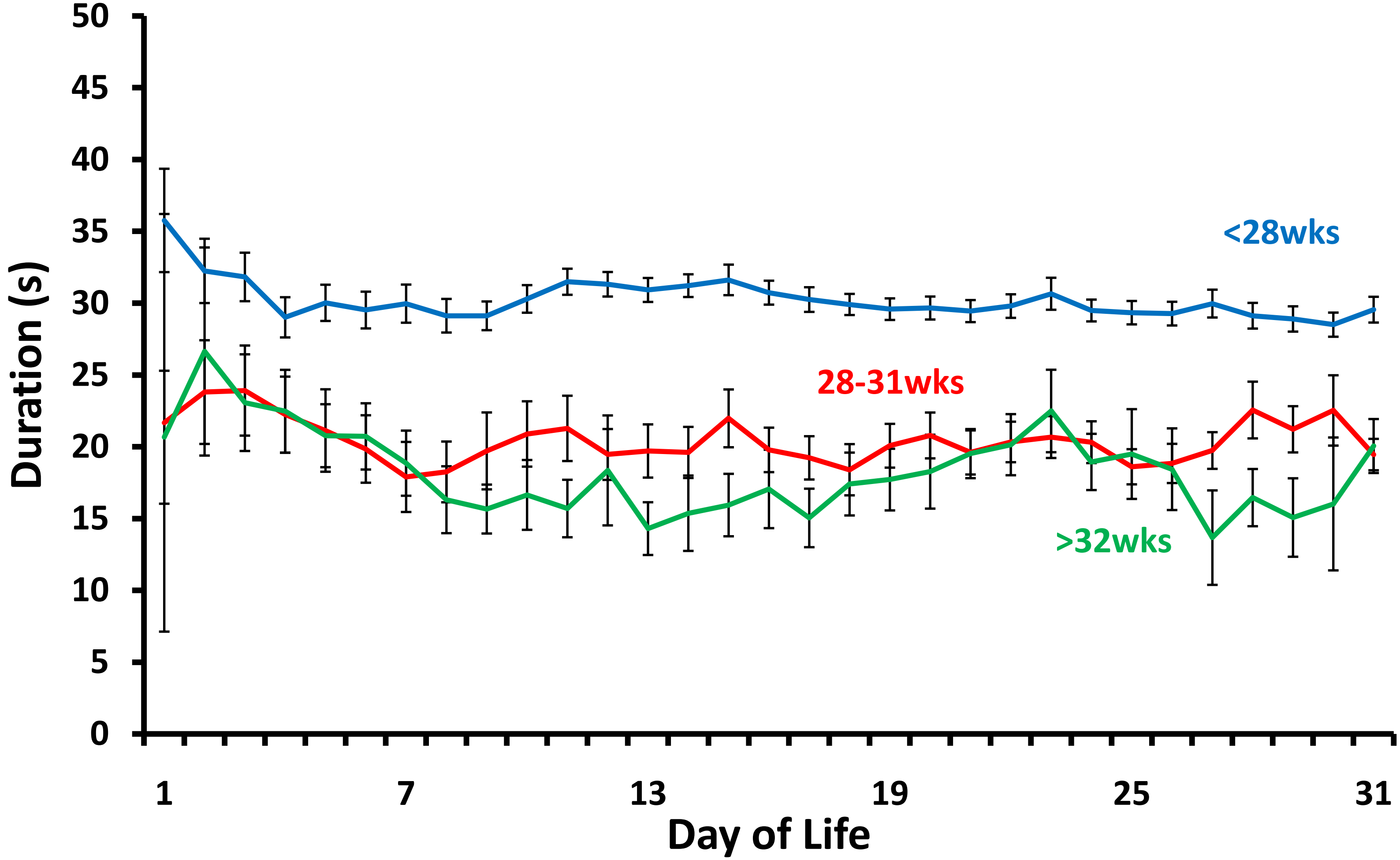
J Di Fiore: J Pediatr 2010

Incidence of Intermittent Hypoxia at Various Gestational Ages



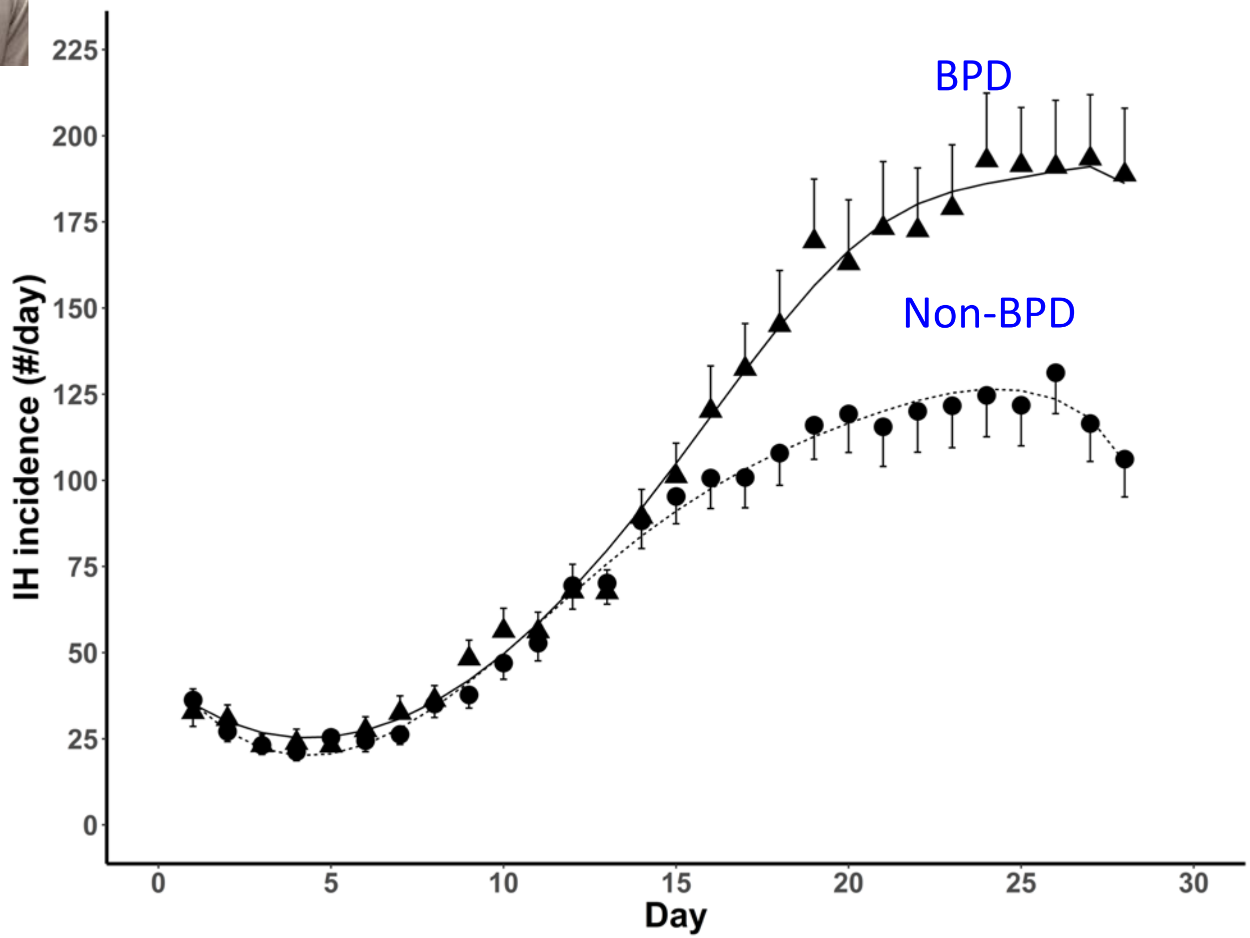
Di Fiore JM: PAS 2019

Duration of Intermittent Hypoxia at Various Gestational Ages



Di Fiore JM: PAS 2019

Neonatal Intermittent Hypoxemia Events are Associated with Diagnosis of Bronchopulmonary Dysplasia at 36 Weeks Postmenstrual Age



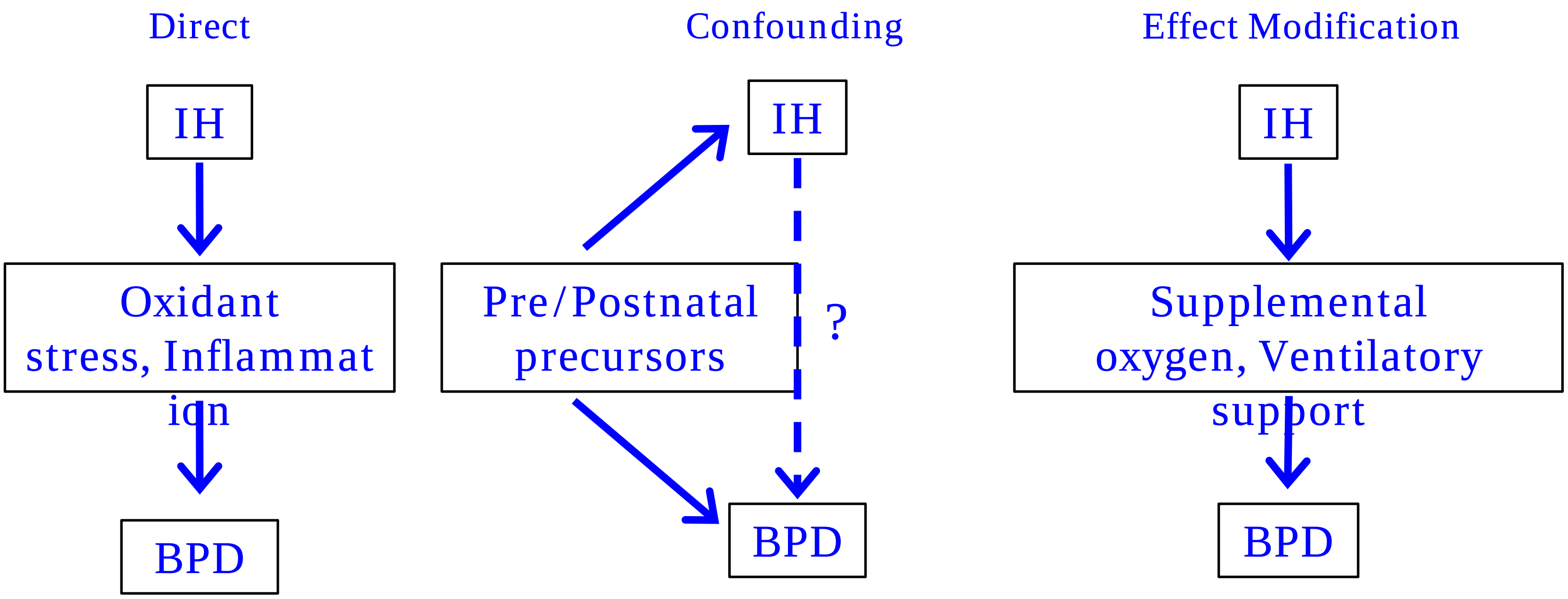
Raffay TM: Pediatr Res, in press, 2019

Oxygen Desaturations in the Early Neonatal Period [1st 4 wks] Predict Development of BPD

"Measures of desaturation, but not bradycardia, significantly added to the predictive model. Desaturation metrics also added to clinical risks for prediction of severe intraventricular hemorrhage, retinopathy of prematurity and prolonged length of stay in the NICU".

Fairchild KD, et al: Pediatr Res 2018

POTENTIAL CAUSAL PATHWAYS BETWEEN INTERMITTENT HYPOXIA AND BRONCHOPULMONARY DYSPLASIA



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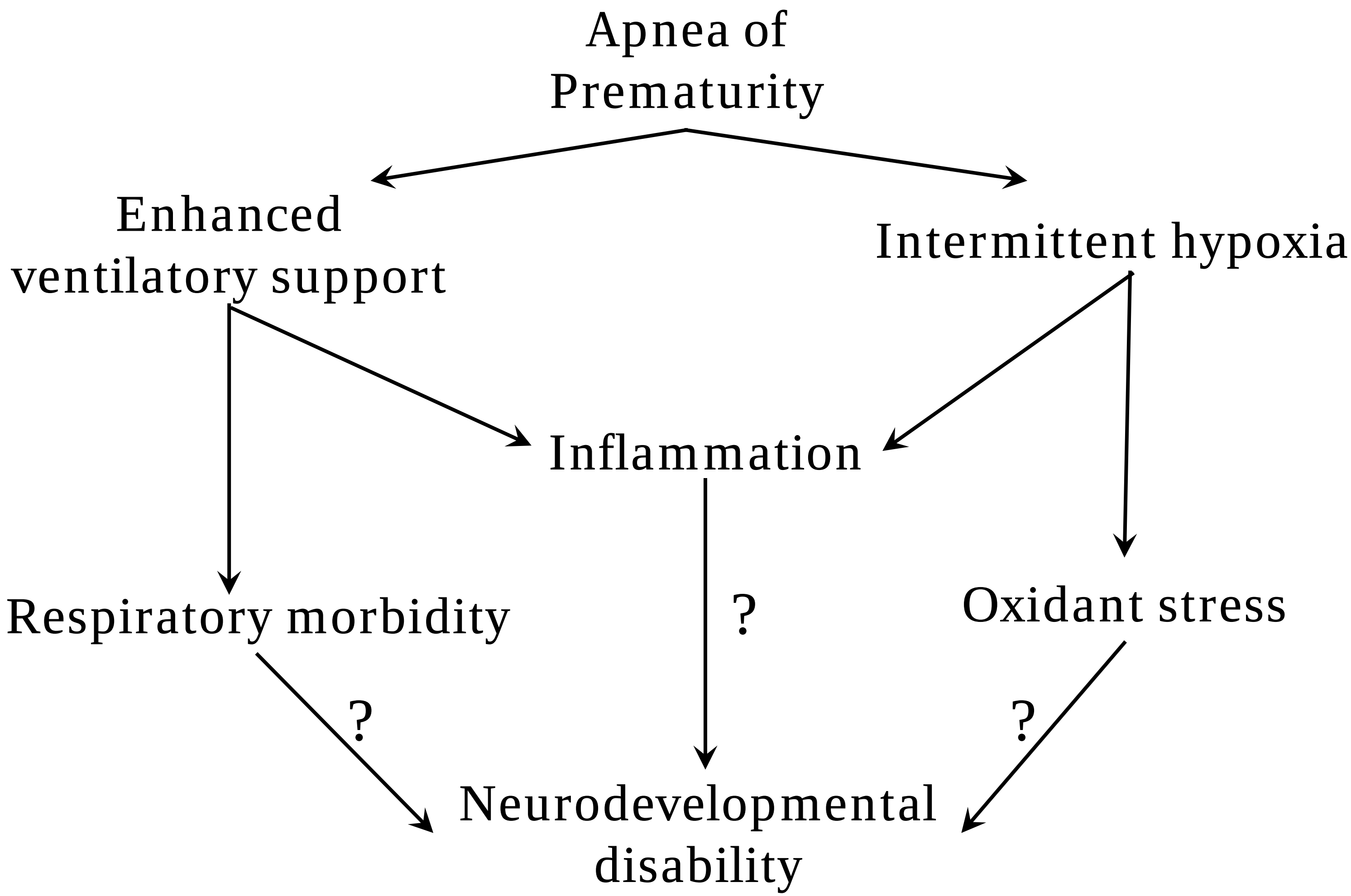
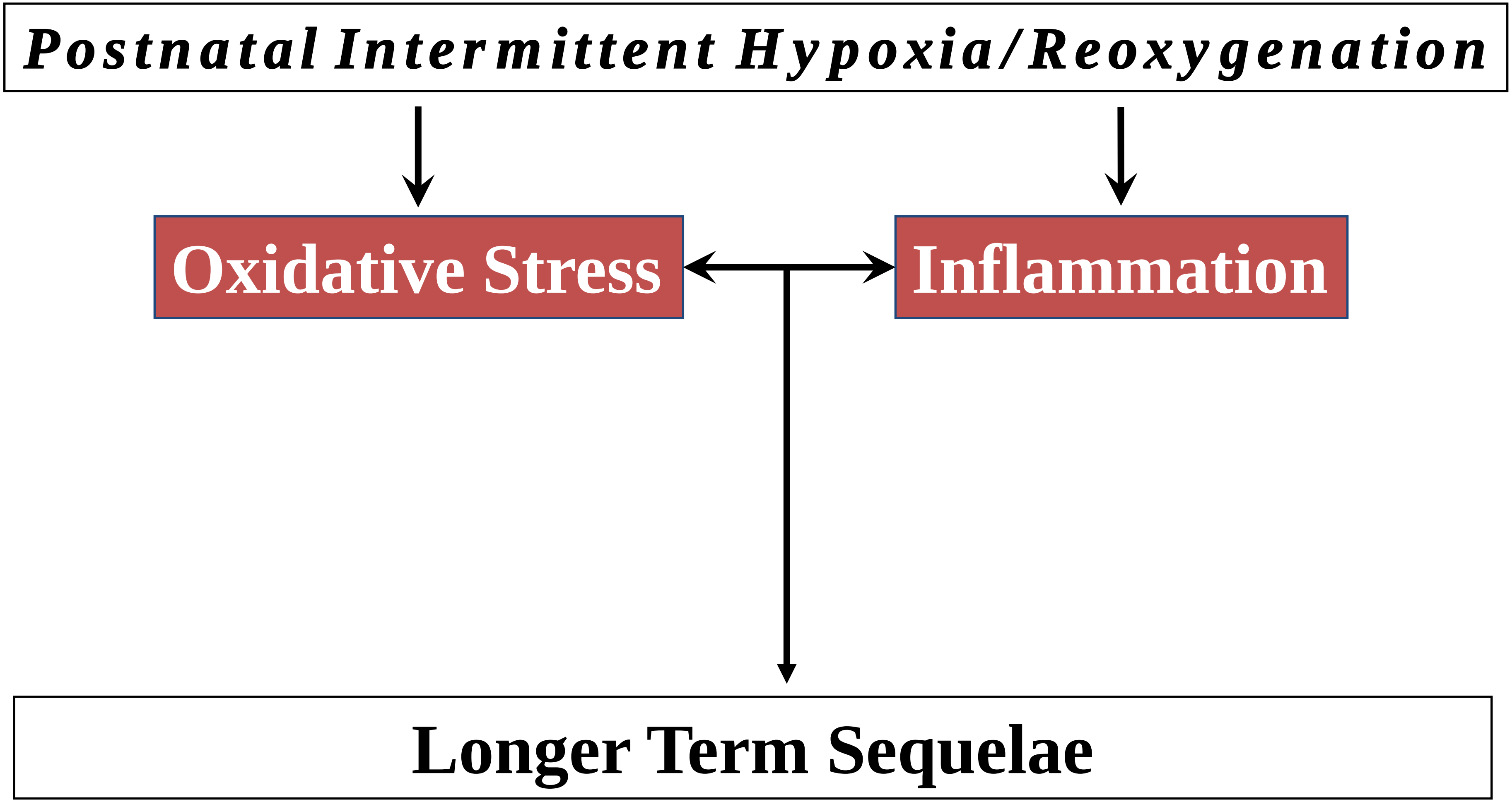
Potential Consequences of Immature Respiratory Control

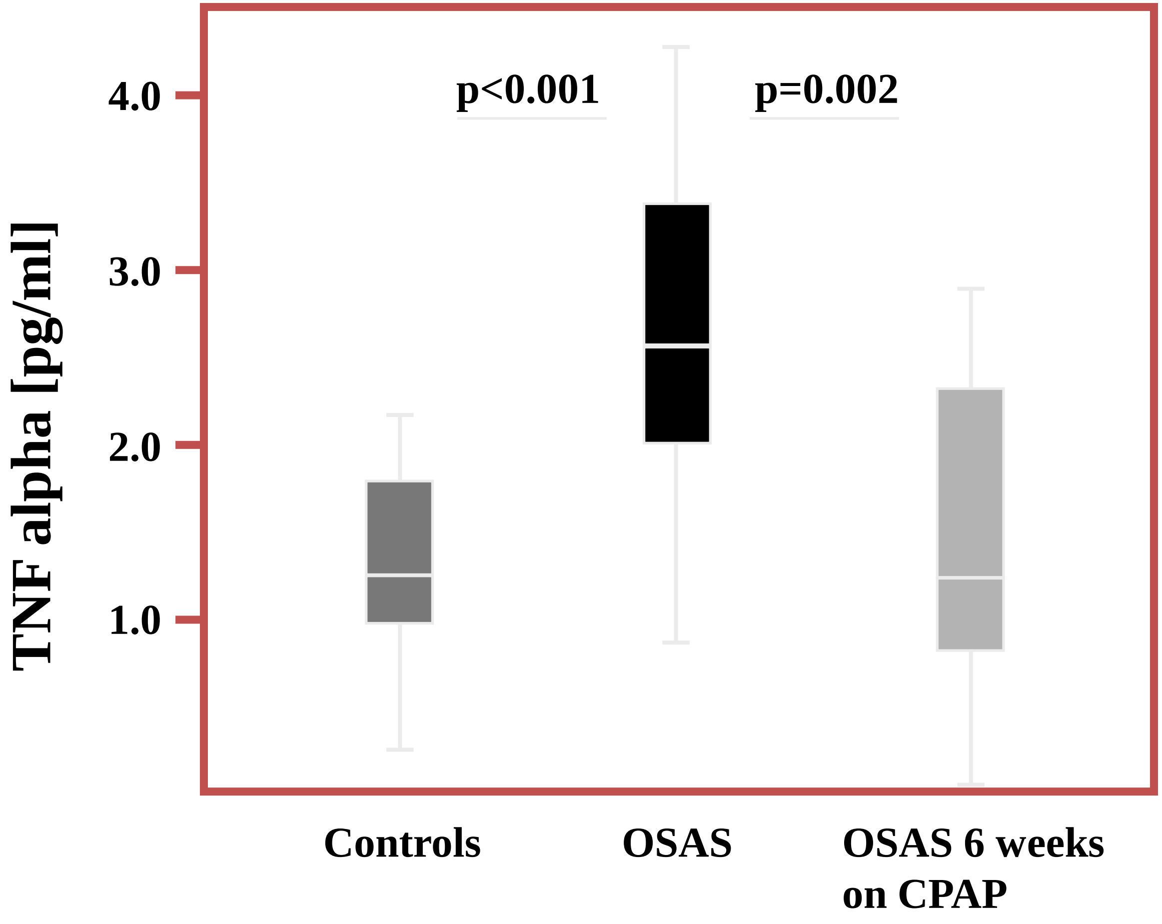


Shah V, Di Fiore JM, Martin RJ: In: Bancalari E, Keszler M, Davis P [eds]: The Newborn Lung, 2019



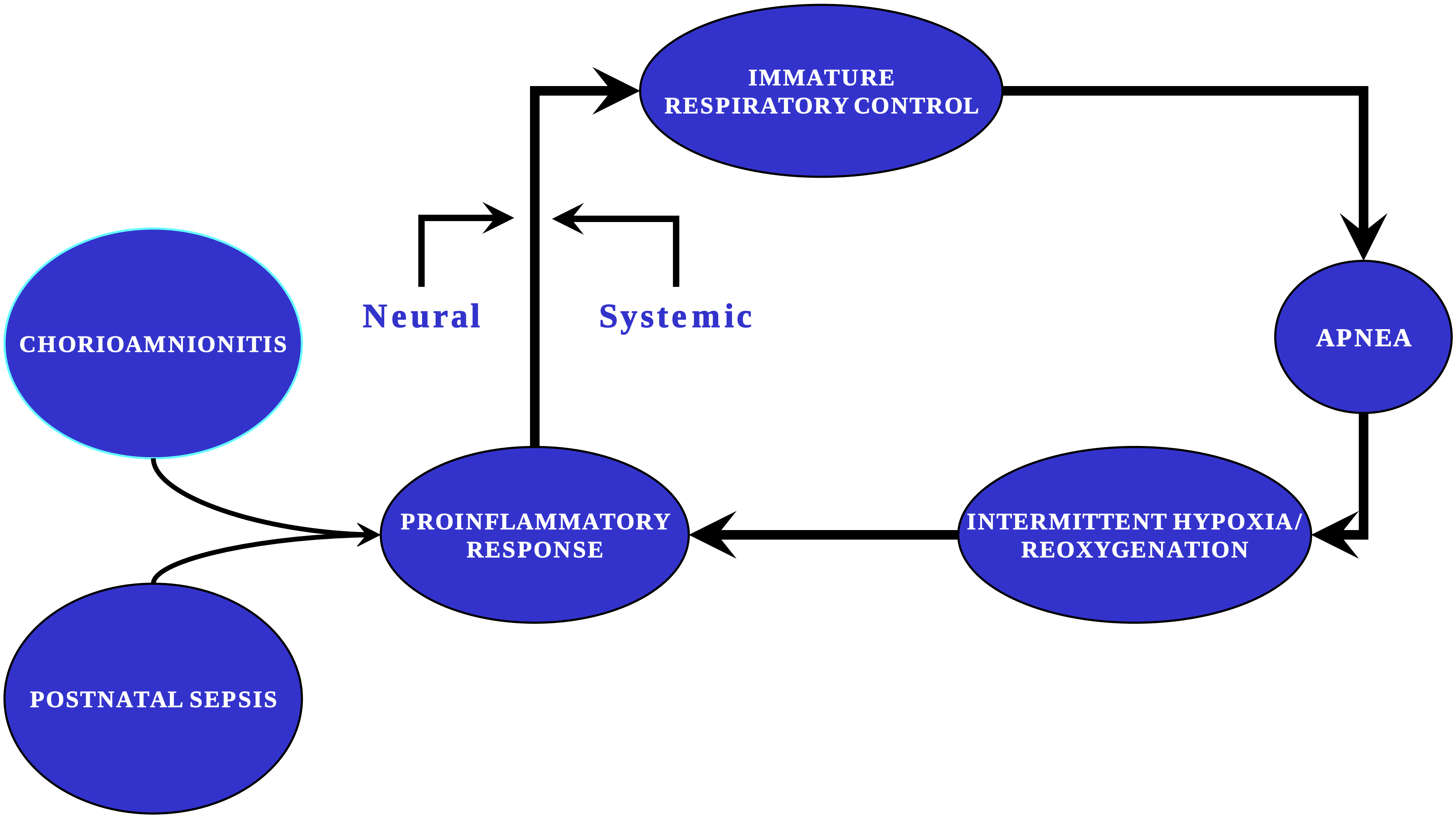
Adapted from Ryan S, et al: Thorax 2009

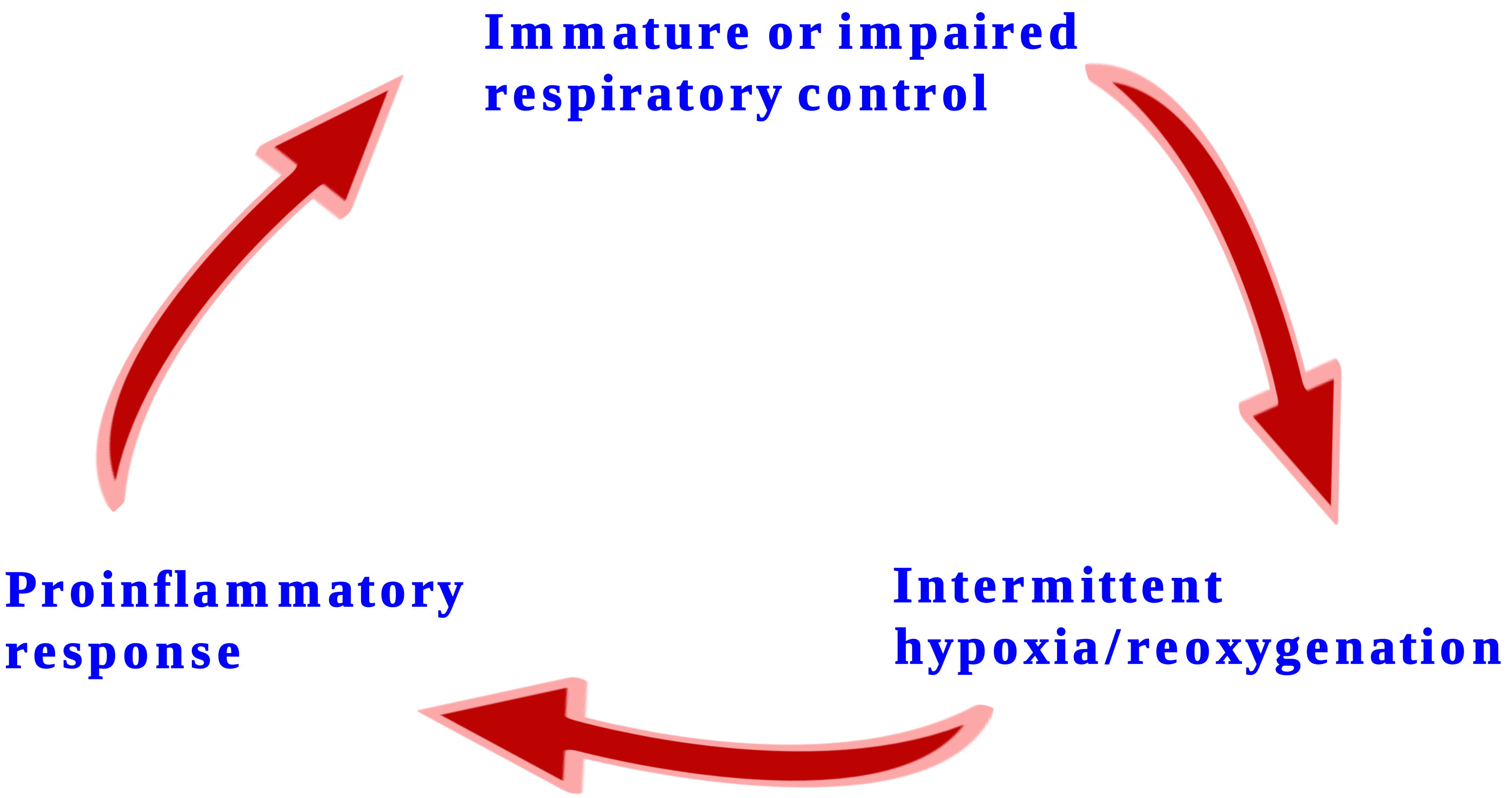
Inflammatory Pathways Associated with Intermittent Hypoxia in Obstructive Sleep Apnea



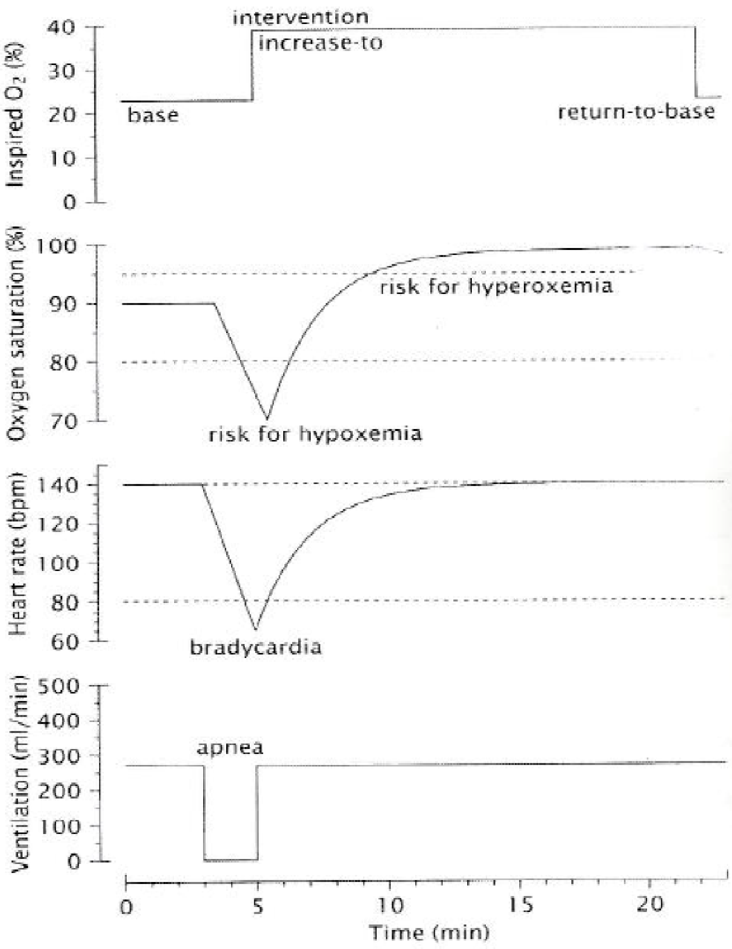
Ryan: Circulation 2005

Proposed Central Role for Respiratory Control in Mediating Inflammatory Responses



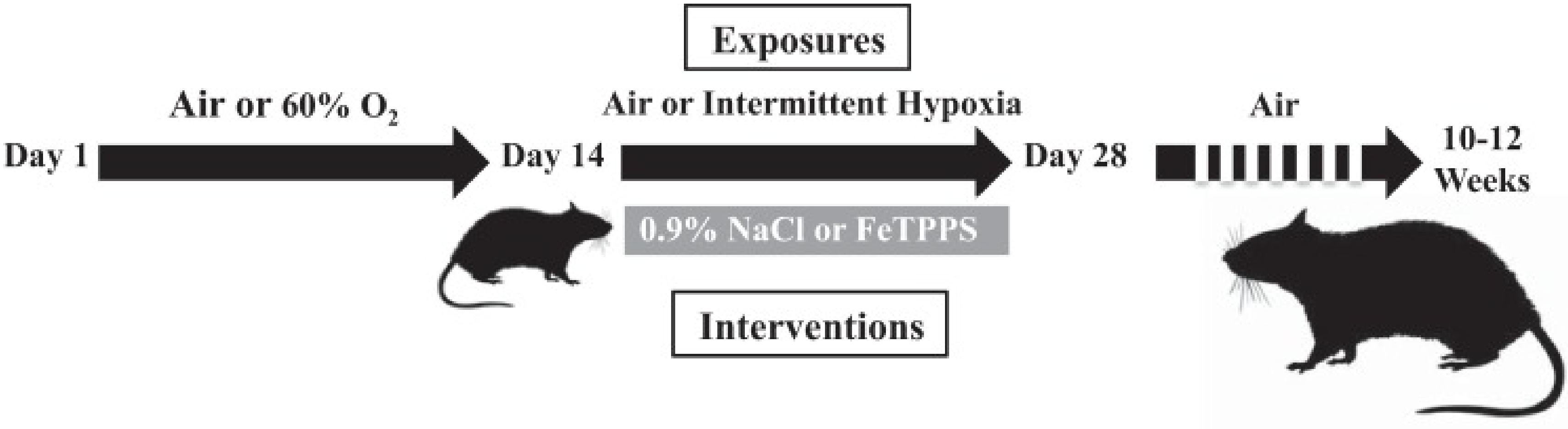

Immature or impaired respiratory control
Intermittent hypoxia/reoxygenation
Proinflammatory response

The Risk for Hyperoxaemia after Apnoea, Bradycardia and Hypoxaemia in CPAP-treated Preterm Infants



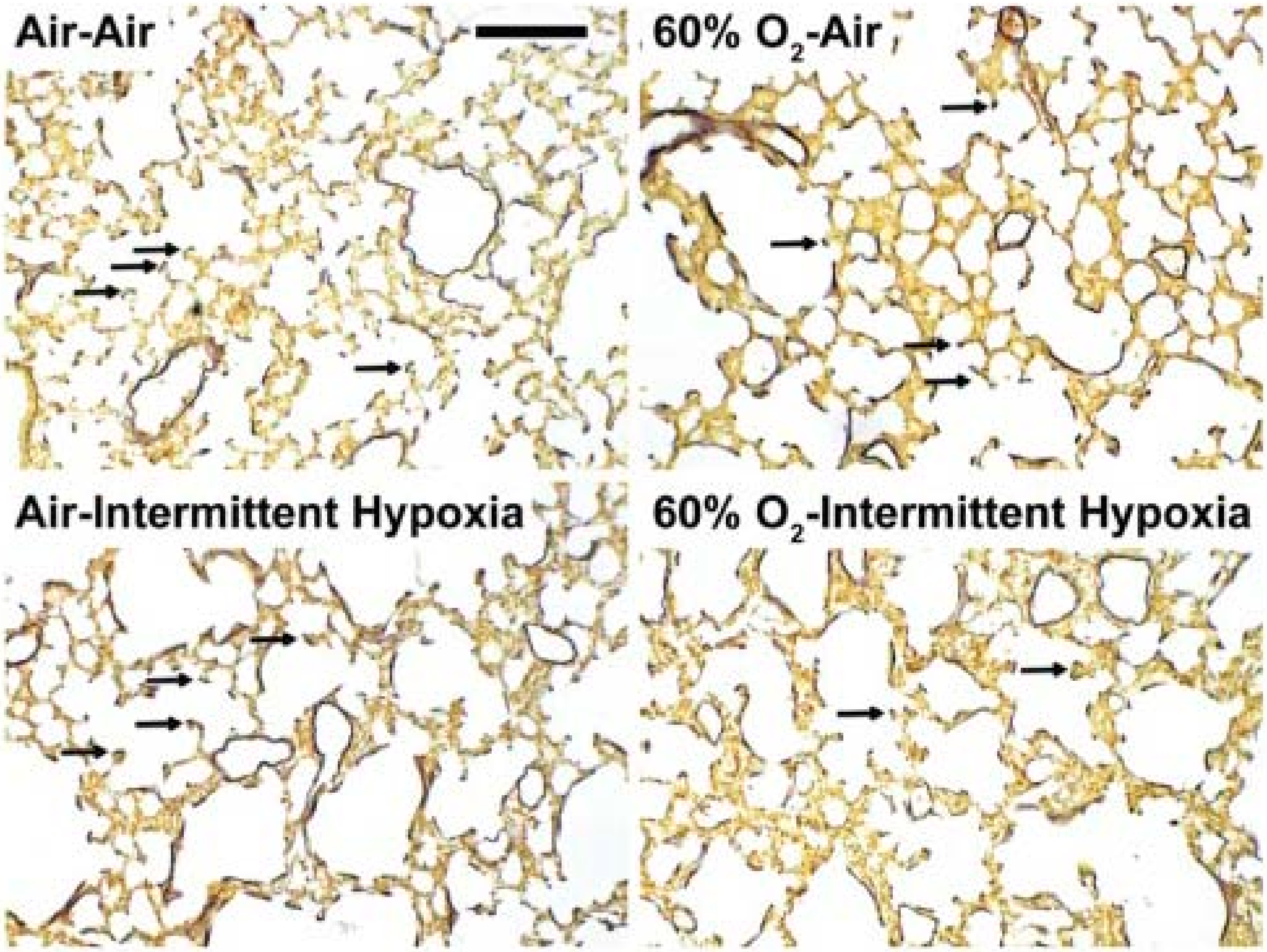
van Zanten HA: Arch Dis Child 2014

Intermittent Hypoxia during Recovery from Neonatal Hyperoxic Lung Injury Causes Long-term Impairment of Alveolar Development: A New Rat Model of BPD



Mankouski A et al: Am J Physiol Lung Cell Mol Physiol 2017

Intermittent Hypoxia during Recovery from Neonatal Hyperoxic Lung Injury Causes Long-term Impairment of Alveolar Development: A New Rat Model of BPD



→ = secondary crests

Mankouski A et al: Am J Physiol Lung Cell Mol Physiol 2017

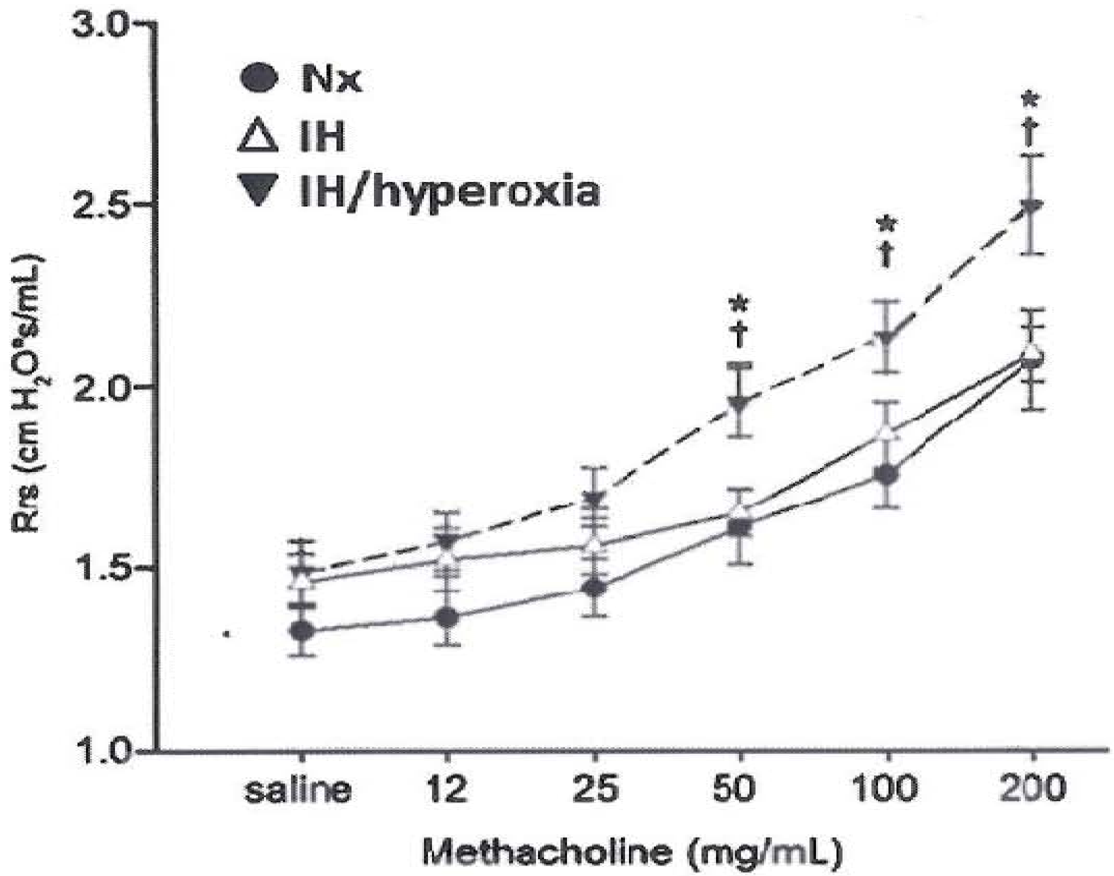
The Contribution of Intermittent Hypoxemia to Late Neurological Handicap in Mice with Hyperoxia-induced Lung Injury

Ratner V, Kishkurno SV, Slinko SK, Sosunov SA, Sosunov AA, Polin RA, Ten VS

"Our results suggest that intermittent hypoxia associated with hyperoxia-induced lung injury, but not lung injury itself, results in significant neurological handicap in neonatal mice with BPD".

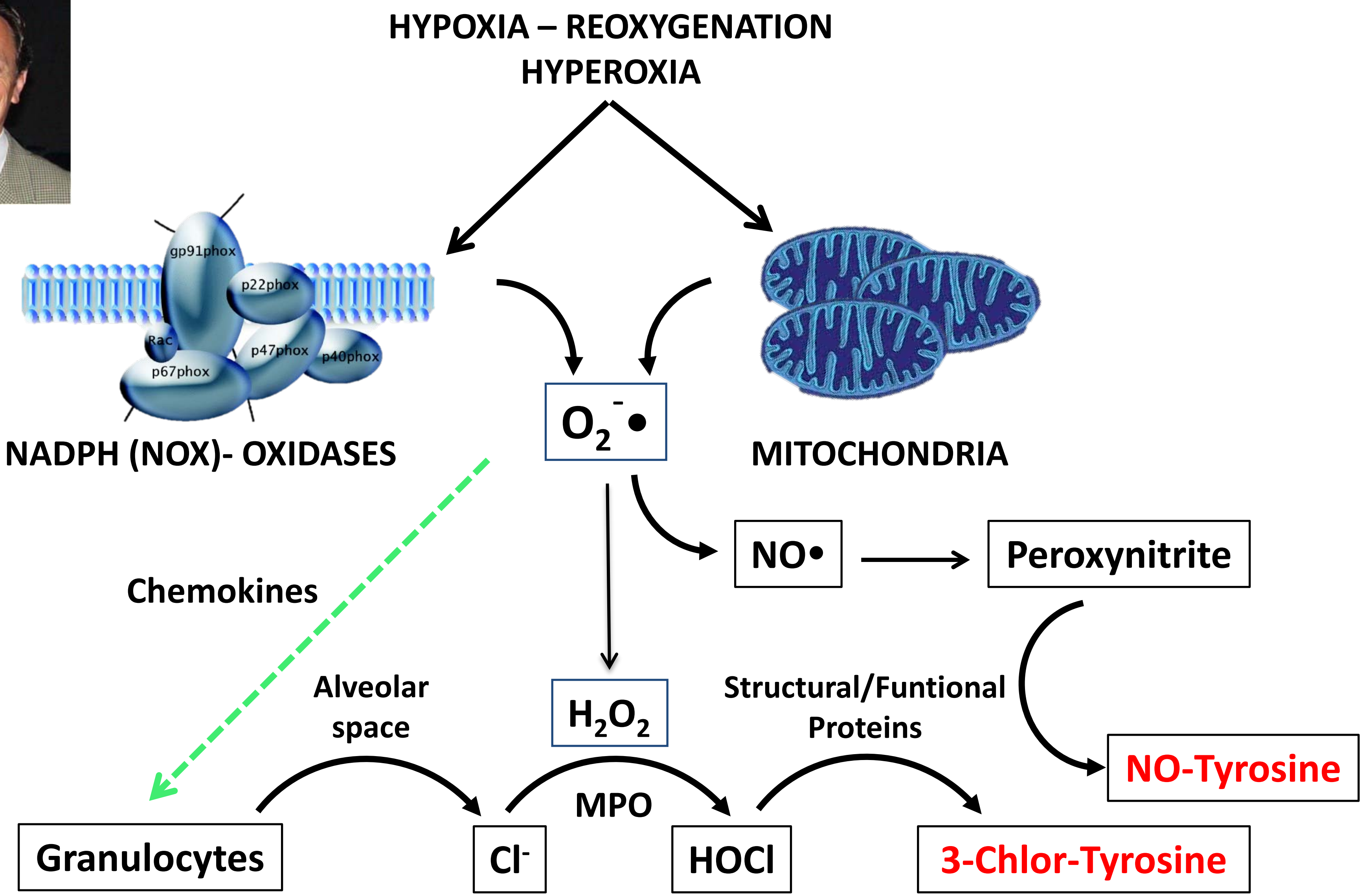
Neonatology 2007; 92(1):50-58

Longer-term Effects of Intermittent Hypoxia [IH]±Hyperoxia on Respiratory System Resistance in Neonatal Mice



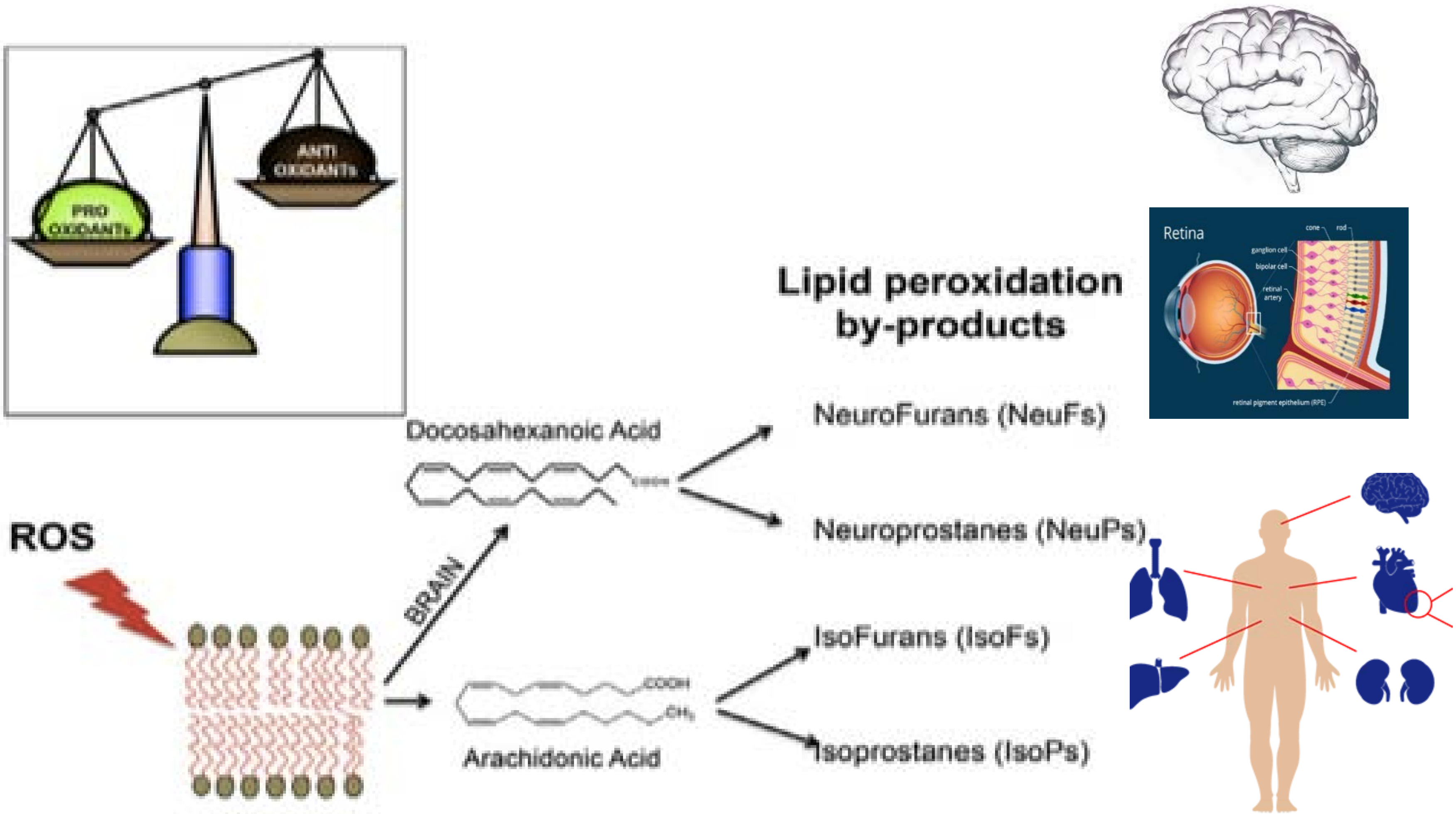
Dylag et al: Pediatr Res 2017

Oxygen & Free Radicals: Protein Inflammation



Vento M et al: Redox Biol 2017

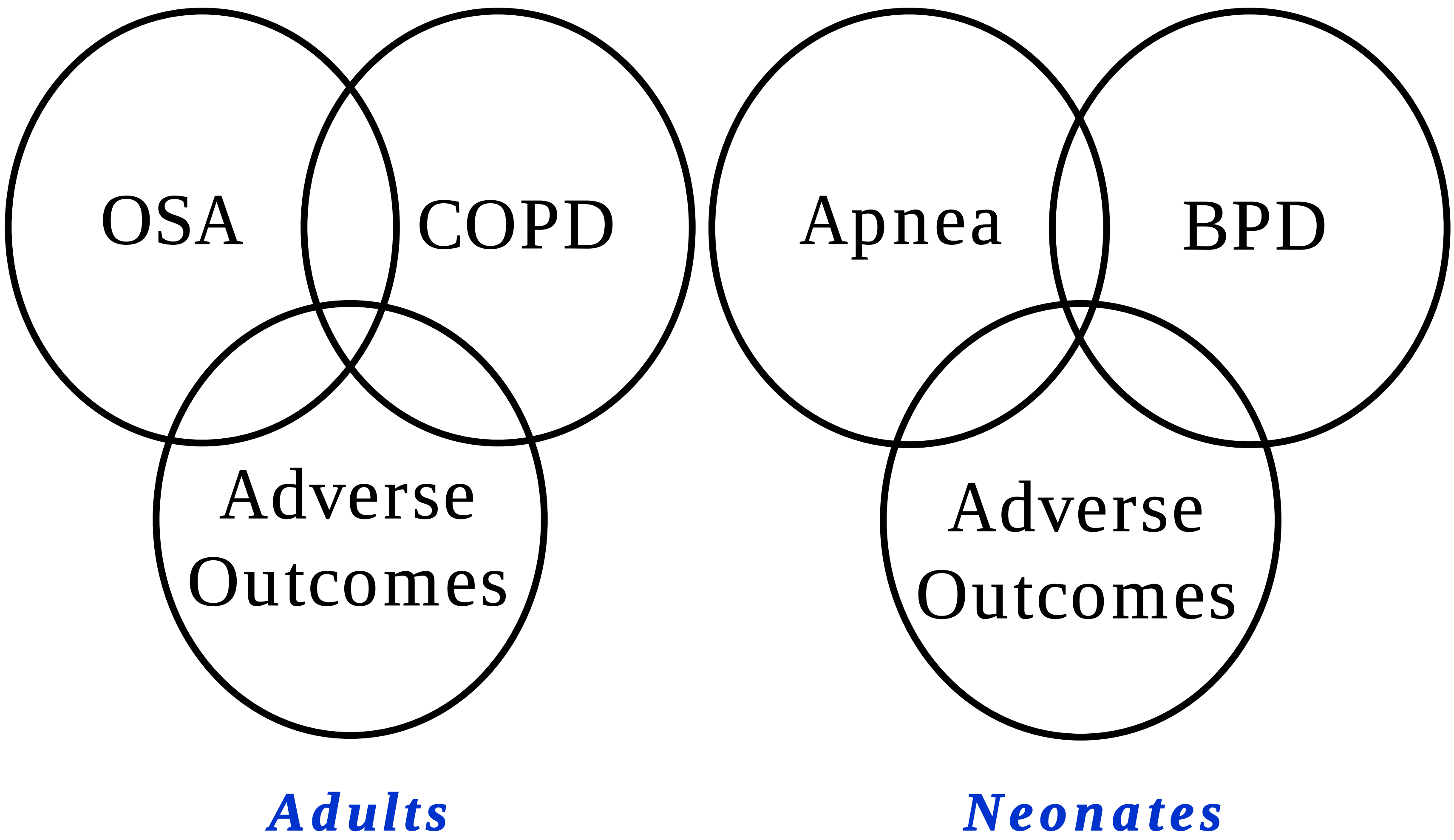
Oxygen & Free Radicals: Lipid Peroxidation Biomarkers



Pericas et al: Analytica Chimica Acta 2015

Rainbow Mouse Pup NICU

Potential Maturational Parallels?



Prematurity-related Ventilatory Control [PreVent] 2016-

An **NHLBI** sponsored multicenter observational study to investigate mechanisms of ventilatory control that contribute to the risk of respiratory morbidity in preterm infants

Case Western • Northwestern • UAB
Univ Miami • Washington Univ • UVA

Thank you to My Research Collaborators

Catherine Mayer

Peter MacFarlane

Thomas Raffay

Juliann Di Fiore

Anna Maria Hibbs

YS Prakash

MAYO CLINIC

NHLBI, NICHD