The Challenge of Optimizing Oxygenation: What about Intermittent Hypoxic Episodes?

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Rainbow Babies
& Children's Hospital

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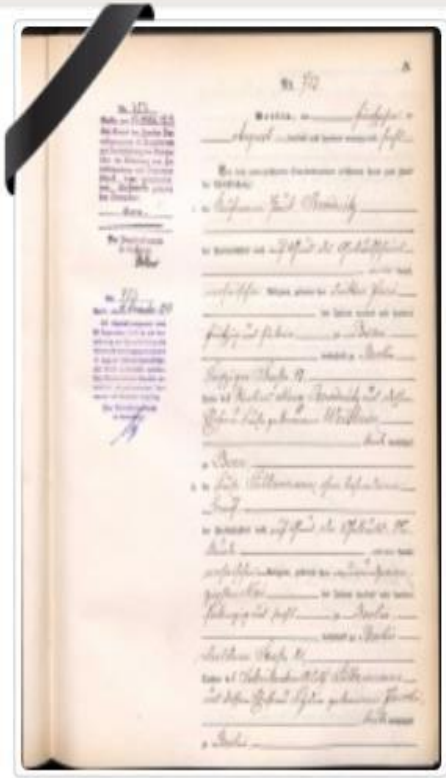


Paul Brodnitz

Born: June 3 1857 In: Posen (Poznań), Posen (Wielkopolskie), Germany (Poland)

Died: Mar 20 1922 (at age 64)

Info | Events

Photos

Immediate family

Luise Brodnitz (born Silbermann)
His wife

Ilse Charlotte Simon (born Brodnitz)
His daughter

Julia Dorothea Brodnitz
His daughter

Margot Birnholz (born Brodnitz)
His daughter

Max Brodnitz
His father

Louise Brodnitz (born Weißbein)
His mother

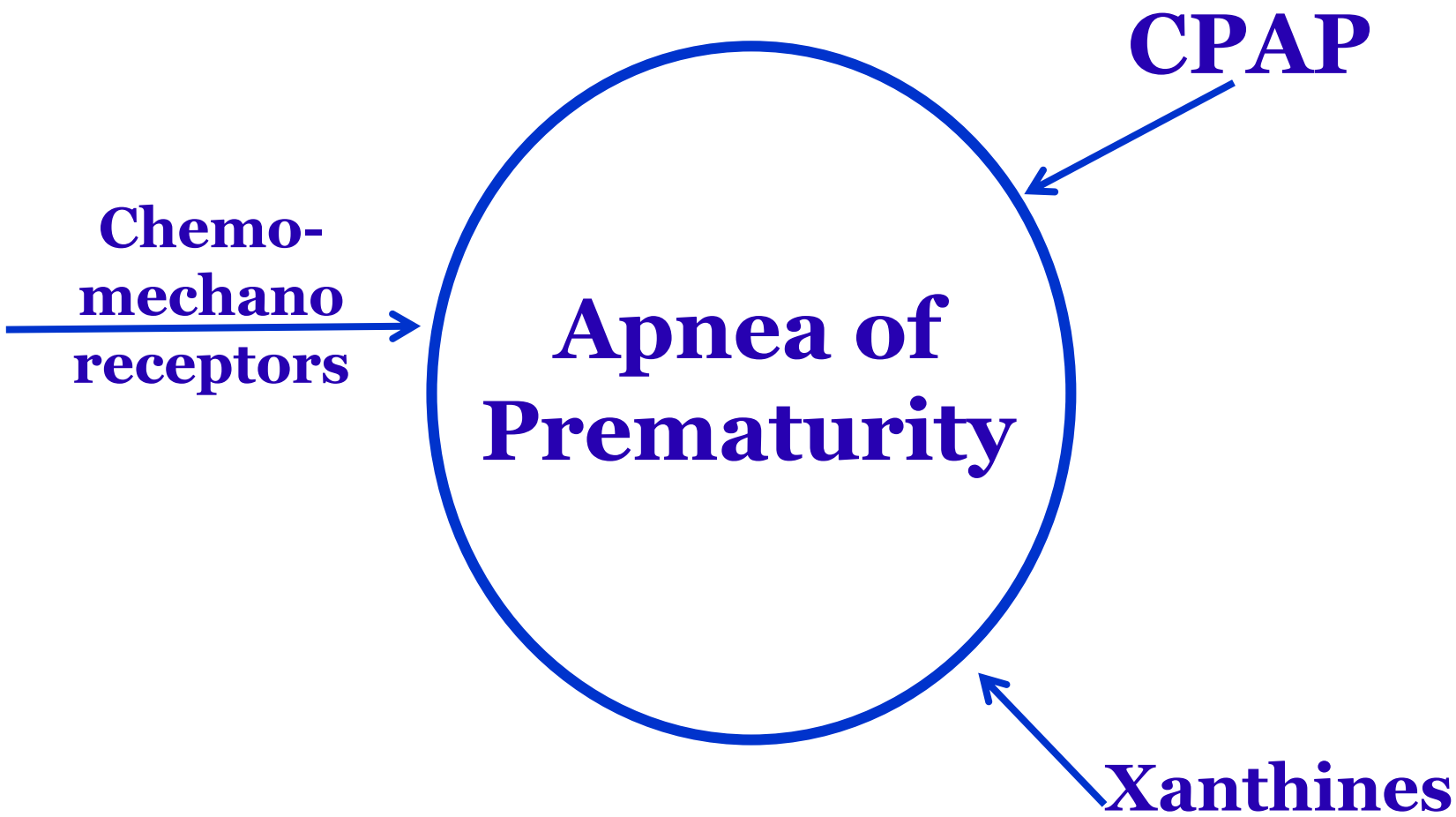
View in tree

View in PedigreeMap™

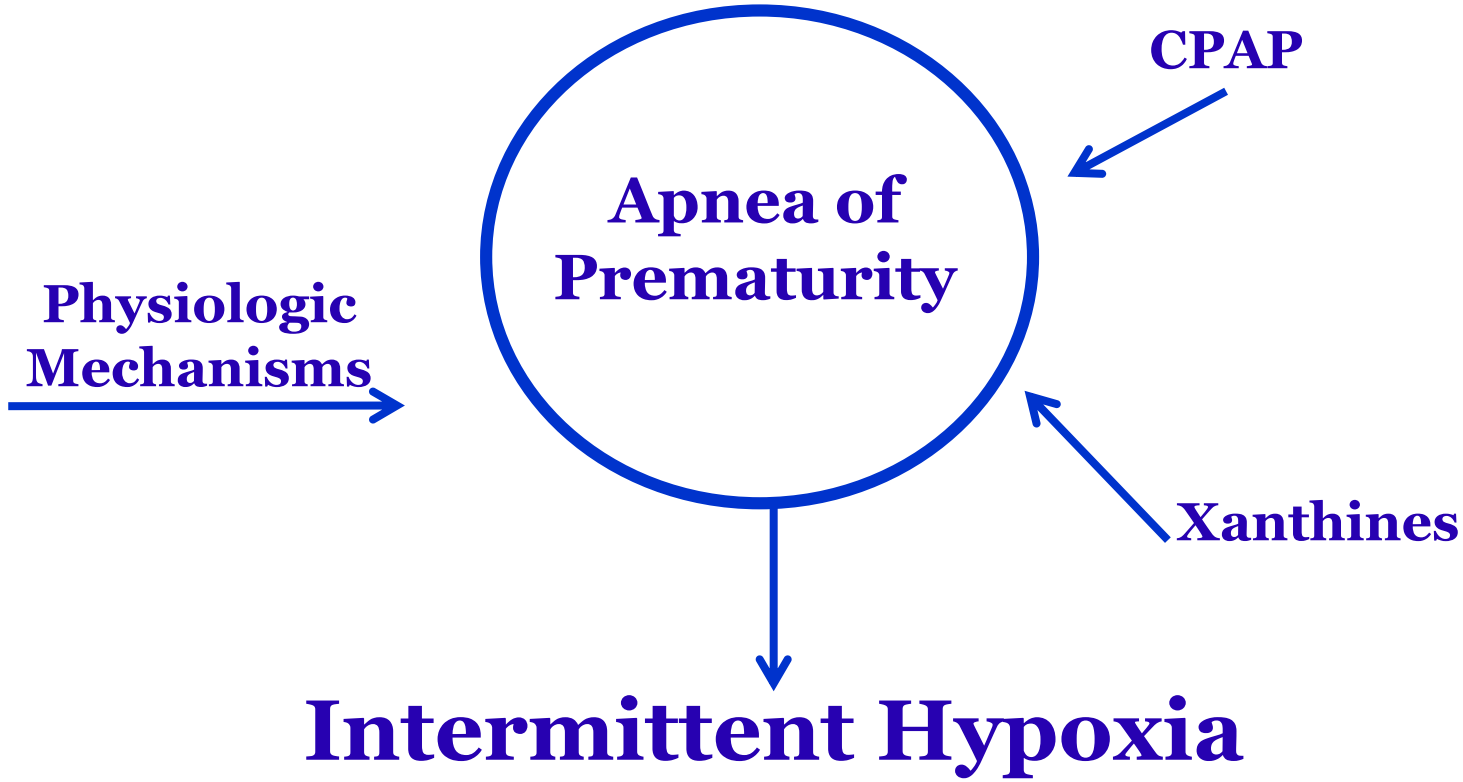
1974 ~ Present
Cleveland, Ohio

Apnea of Prematurity

Physiologic Pathways Leading to Mechanisms of Action



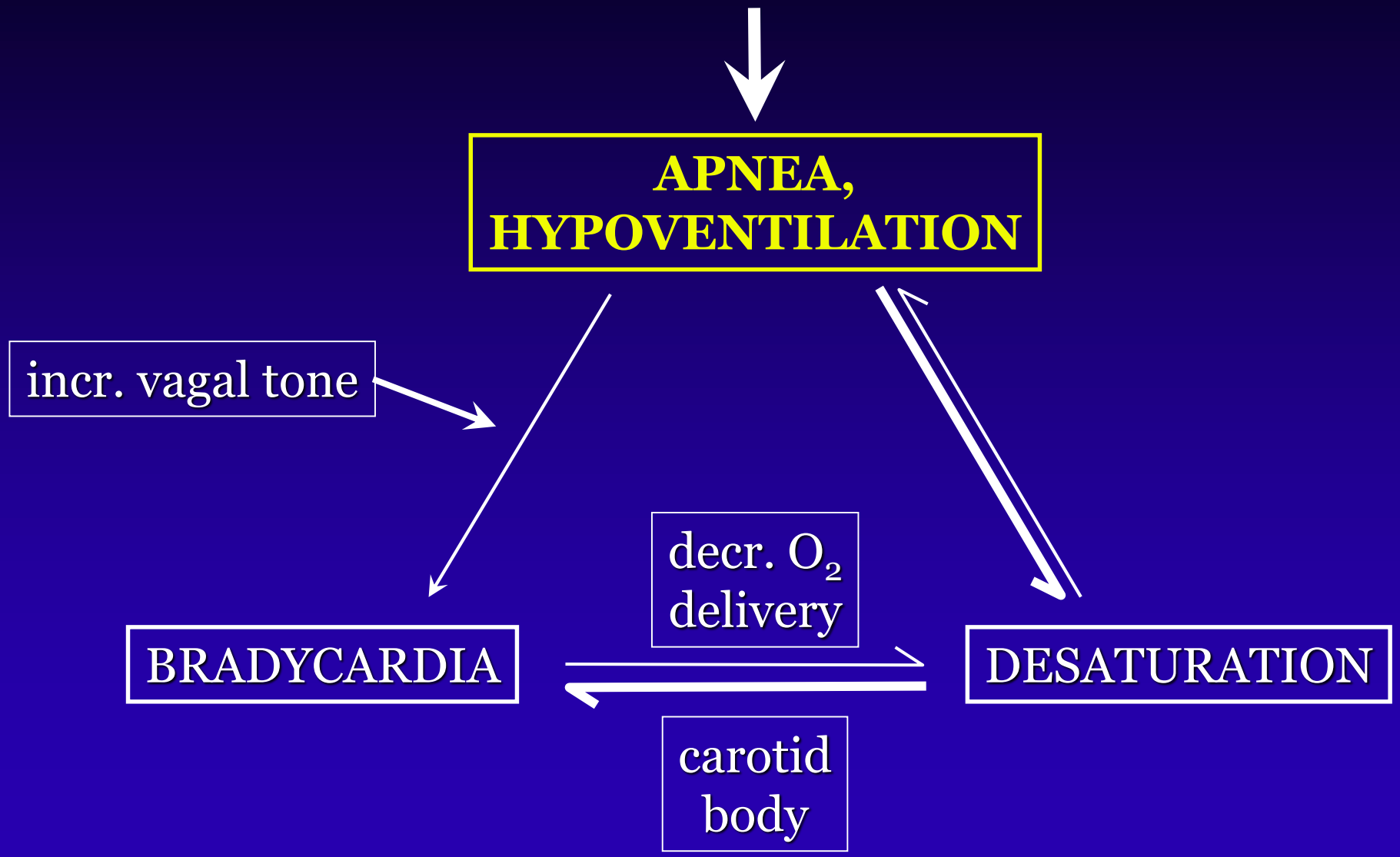
Mid 1970s


CPAP
Apnea of Prematurity
Physiologic Mechanisms
Xanthines
Intermittent Hypoxia

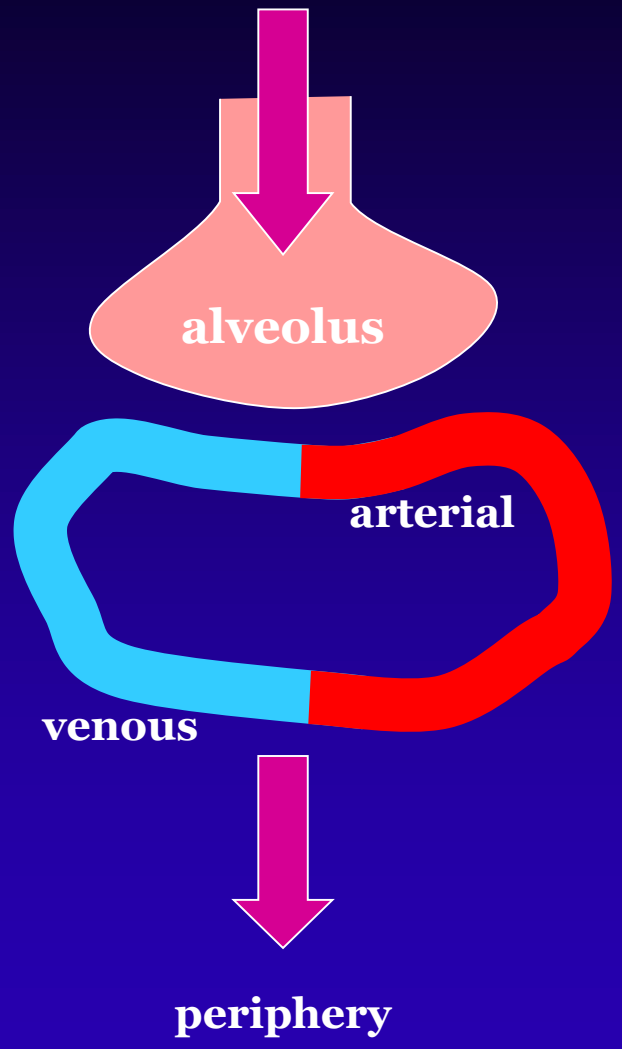
A Role for Intermittent Hypoxia

- **Magnitude of the problem**
- Intermittent hypoxia, oxidant stress and inflammation
- Proposed morbidity
- Treatment and future directions

Decreased Respiratory Drive



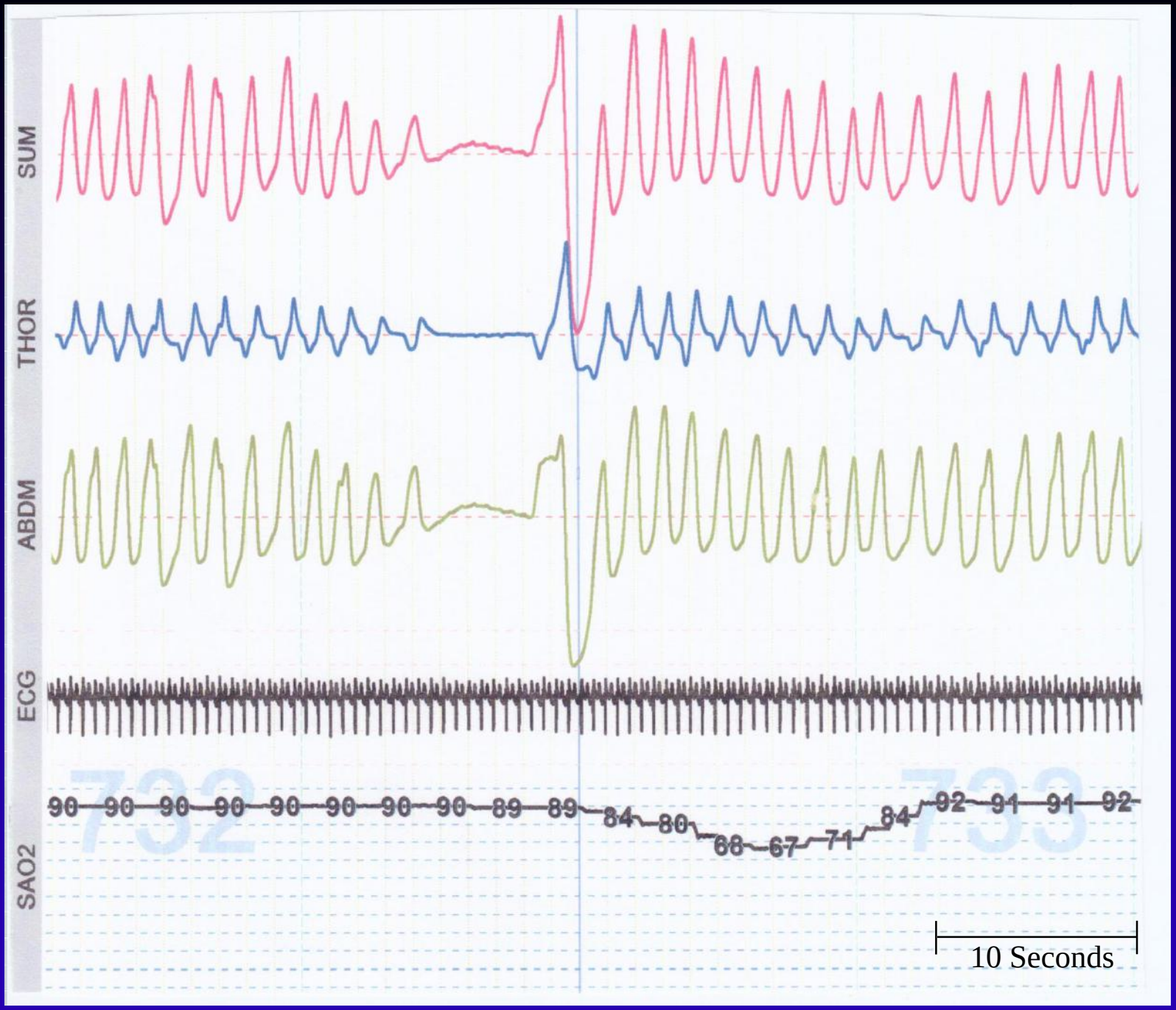
Factors Influencing Arterial O_2 Desaturation during Apnea of Prematurity



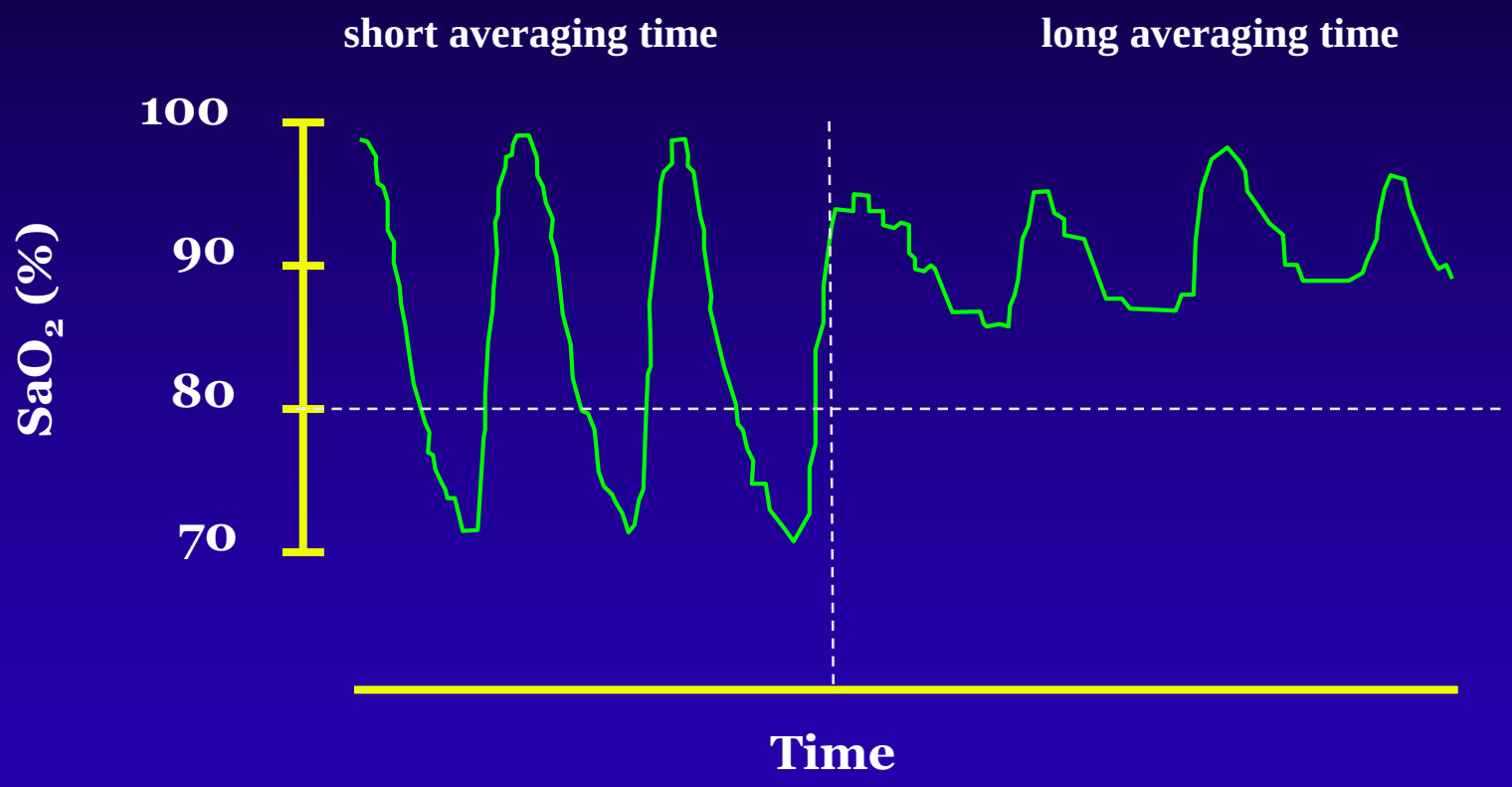
Alveolar O_2 Stores

Pulmonary Hypertension

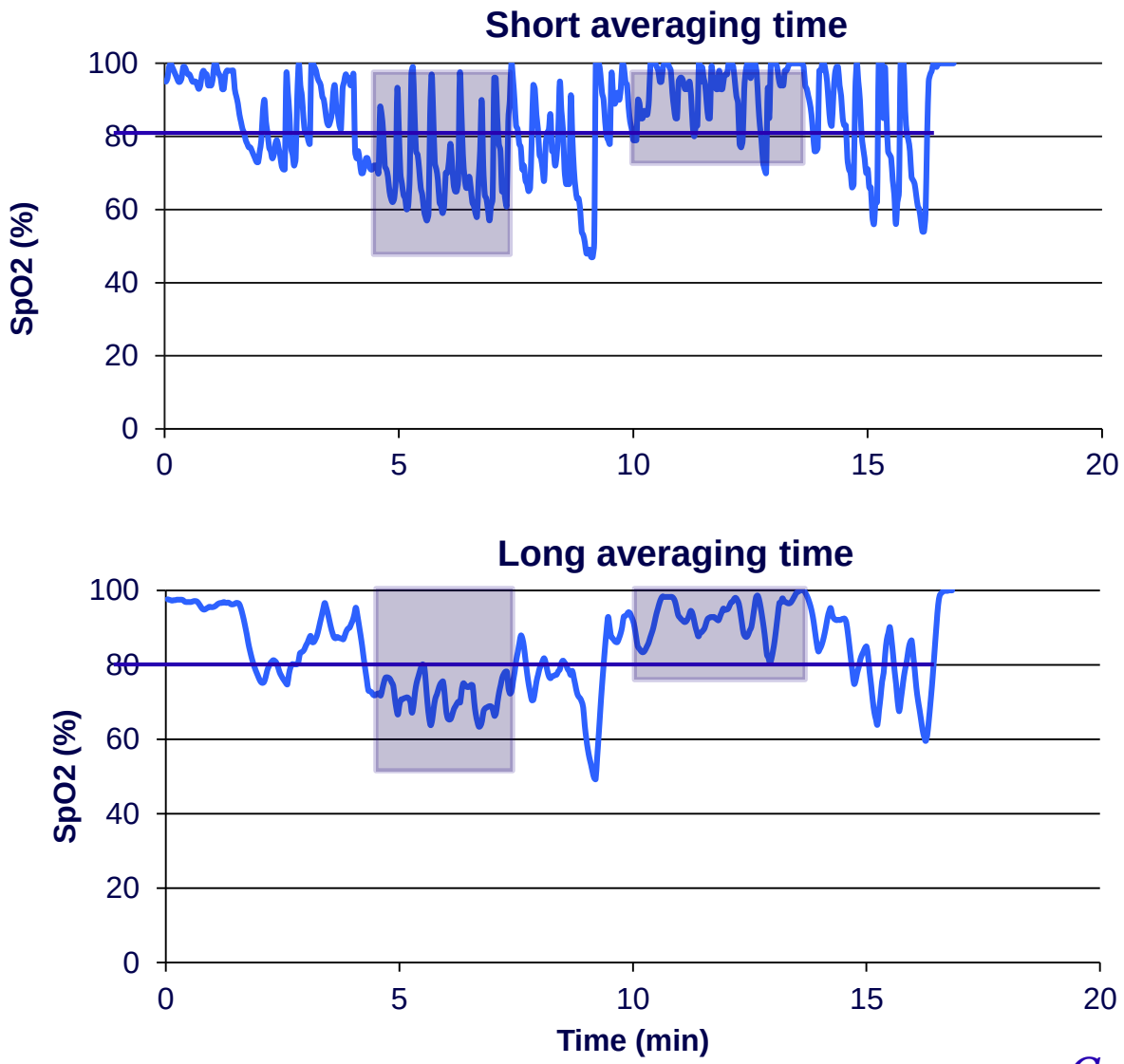
Total Blood O_2 Capacity


SUM
THOR
ABDM
ECG
SAO2
90 90 90 90 90 90 90 90 89 89 84 80 68 67 71 84 92 91 91 92
10 Seconds

Importance of Pulse Oximeter Averaging Time When Measuring Oxygen Desaturation Episodes



Importance of Pulse Oximeter Averaging Times

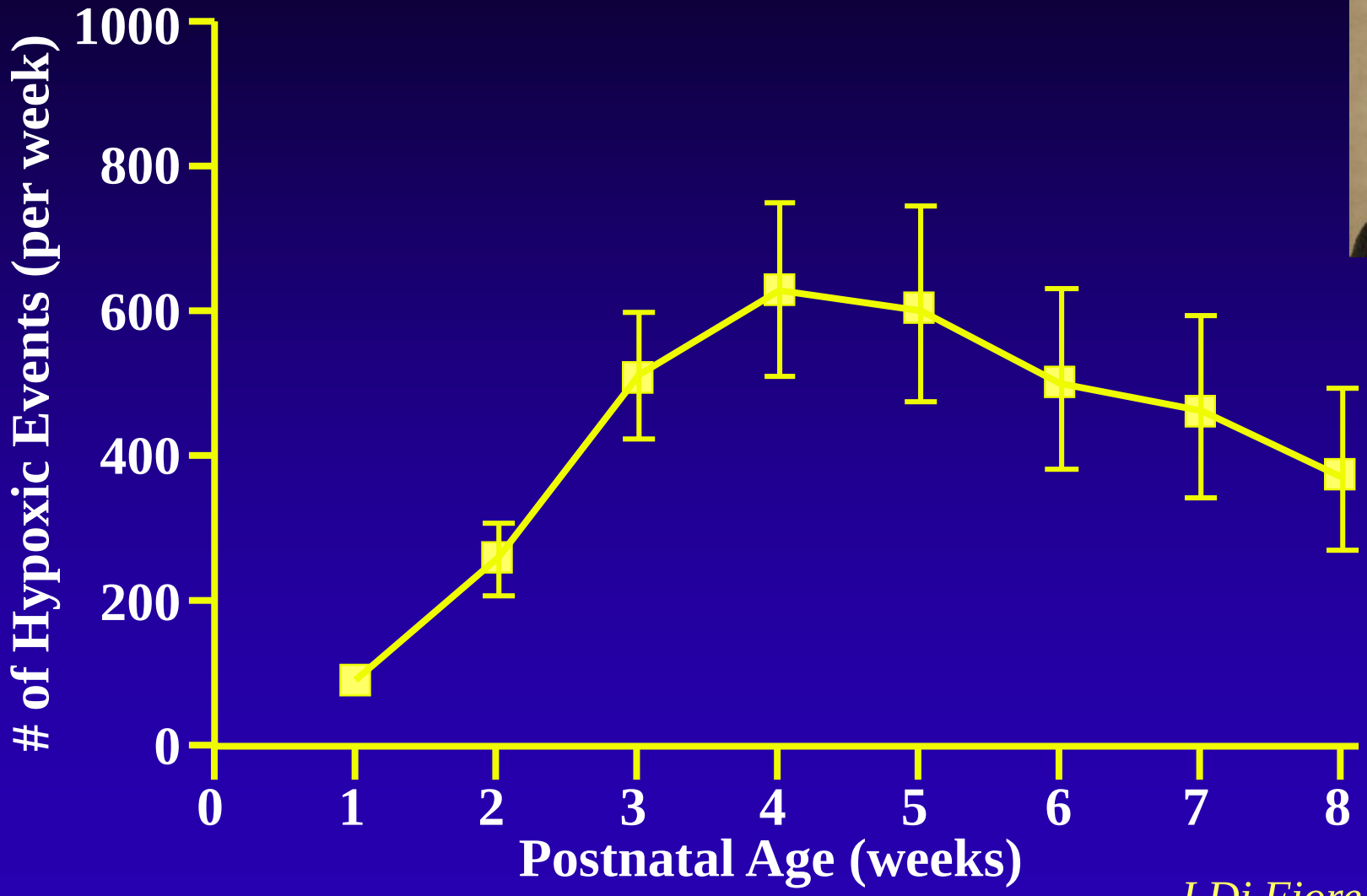


Courtesy: J. Di Fiore

Intermittent Hypoxic Episodes: What is the Magnitude of the Problem?

- Masimo Radical technology was employed via 2 sec averaging
- Desaturation was defined as <80% [≥10 sec and ≤3 min]
- Pulse oximetry data were continuously recorded from birth to 8 weeks in a preterm cohort

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

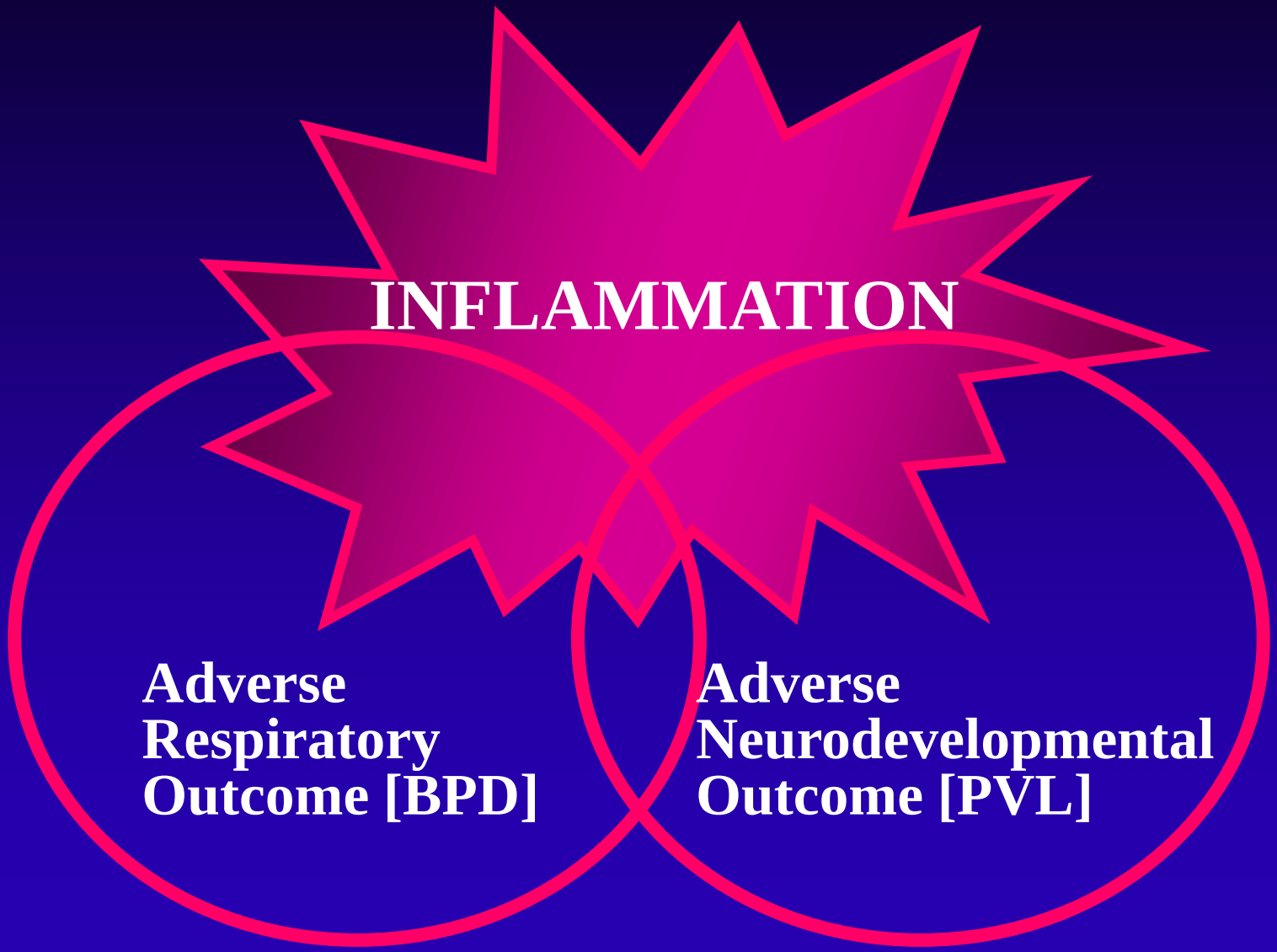


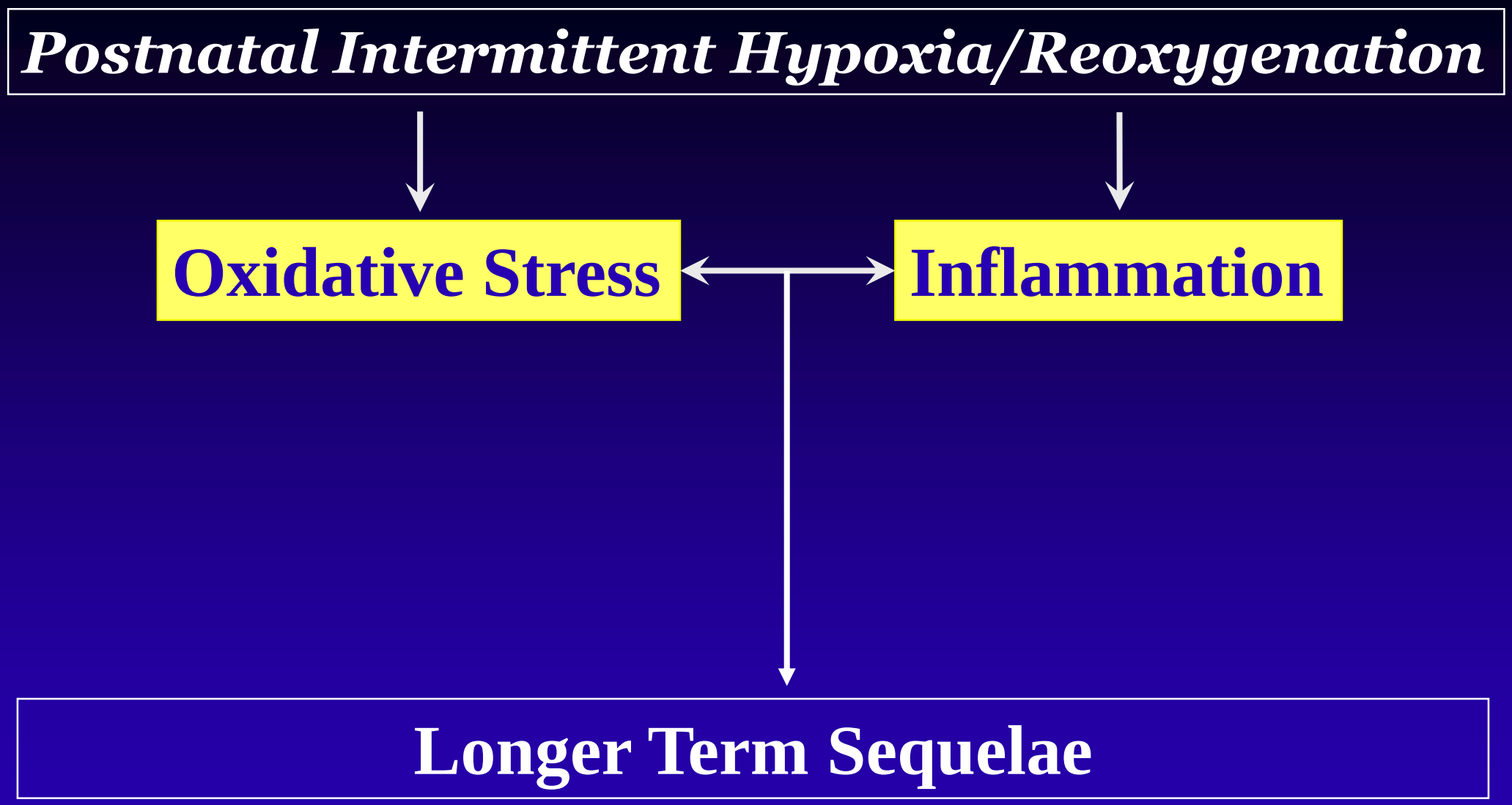
J Di Fiore: J Pediatr 2010

A Role for Intermittent Hypoxia

- Magnitude of the problem
- **Intermittent hypoxia, oxidant stress and inflammation**
- Proposed morbidity
- Treatment and future directions

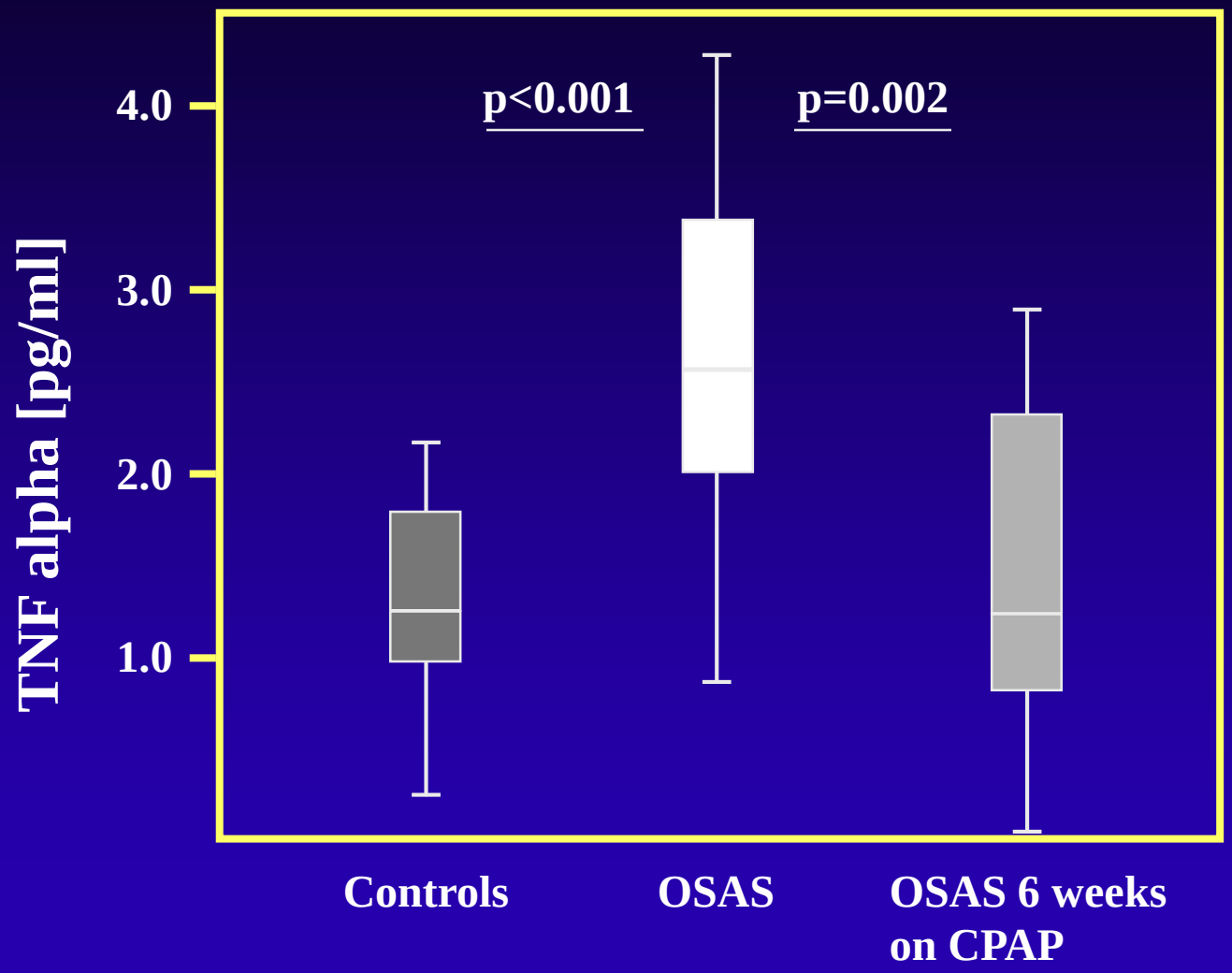
Central Role of Inflammatory Mechanisms on the Immature Lung and Brain



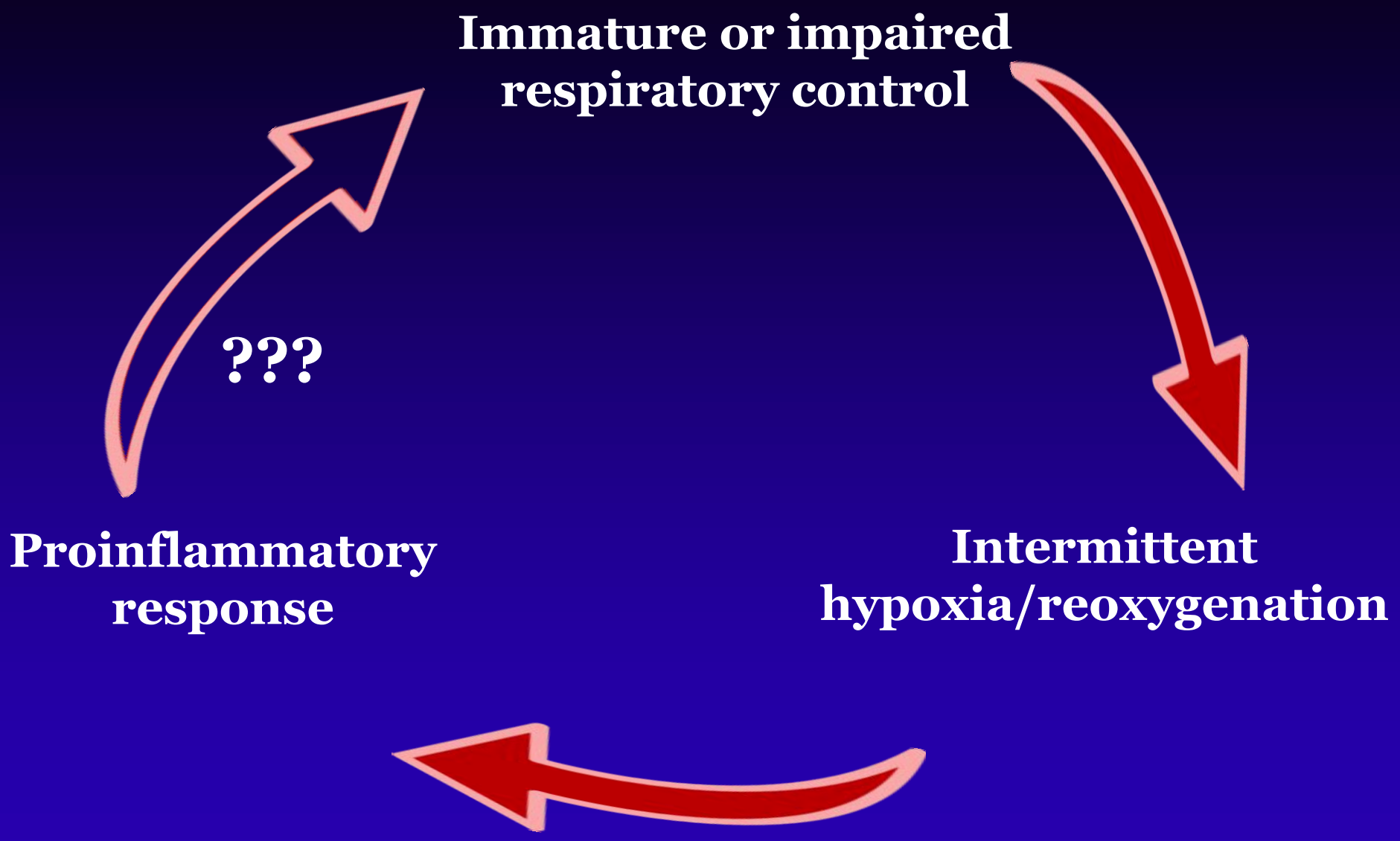


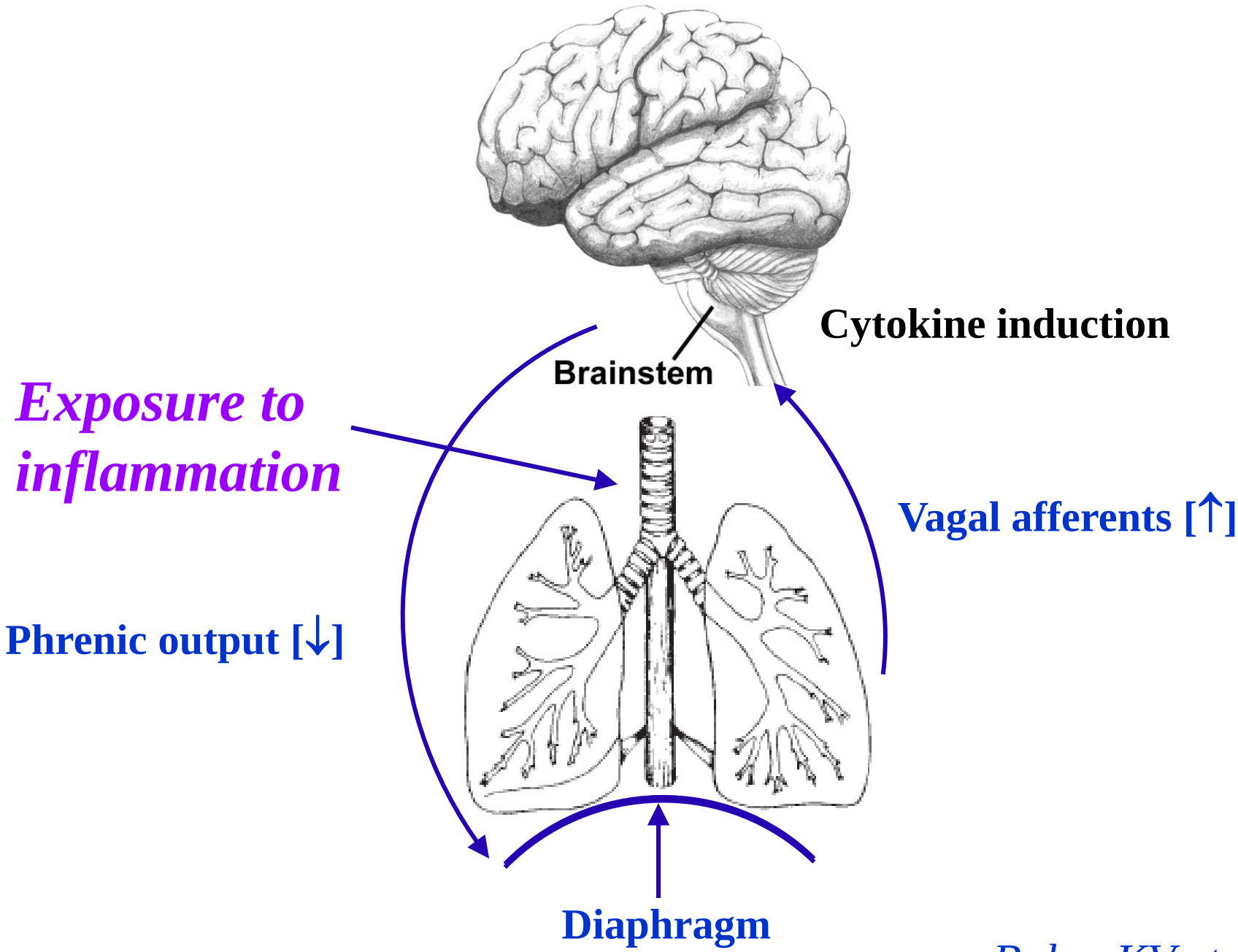
Adapted from Ryan S, et al: Thorax 2009

Inflammatory Pathways Associated with Intermittent Hypoxia in Obstructive Sleep Apnea



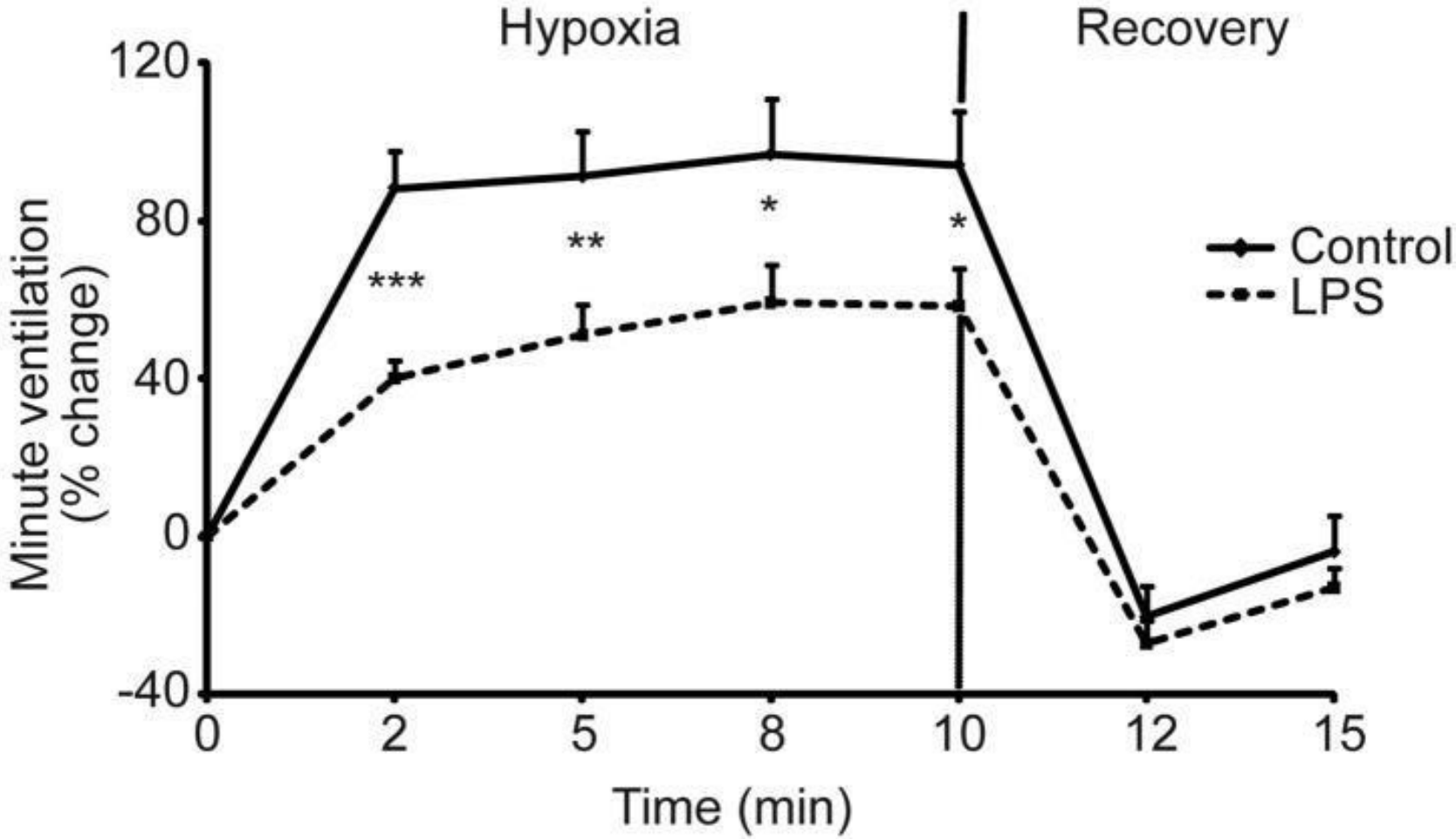
Ryan: Circulation 2005


Immature or impaired respiratory control
???
Proinflammatory response
Intermittent hypoxia/reoxygenation

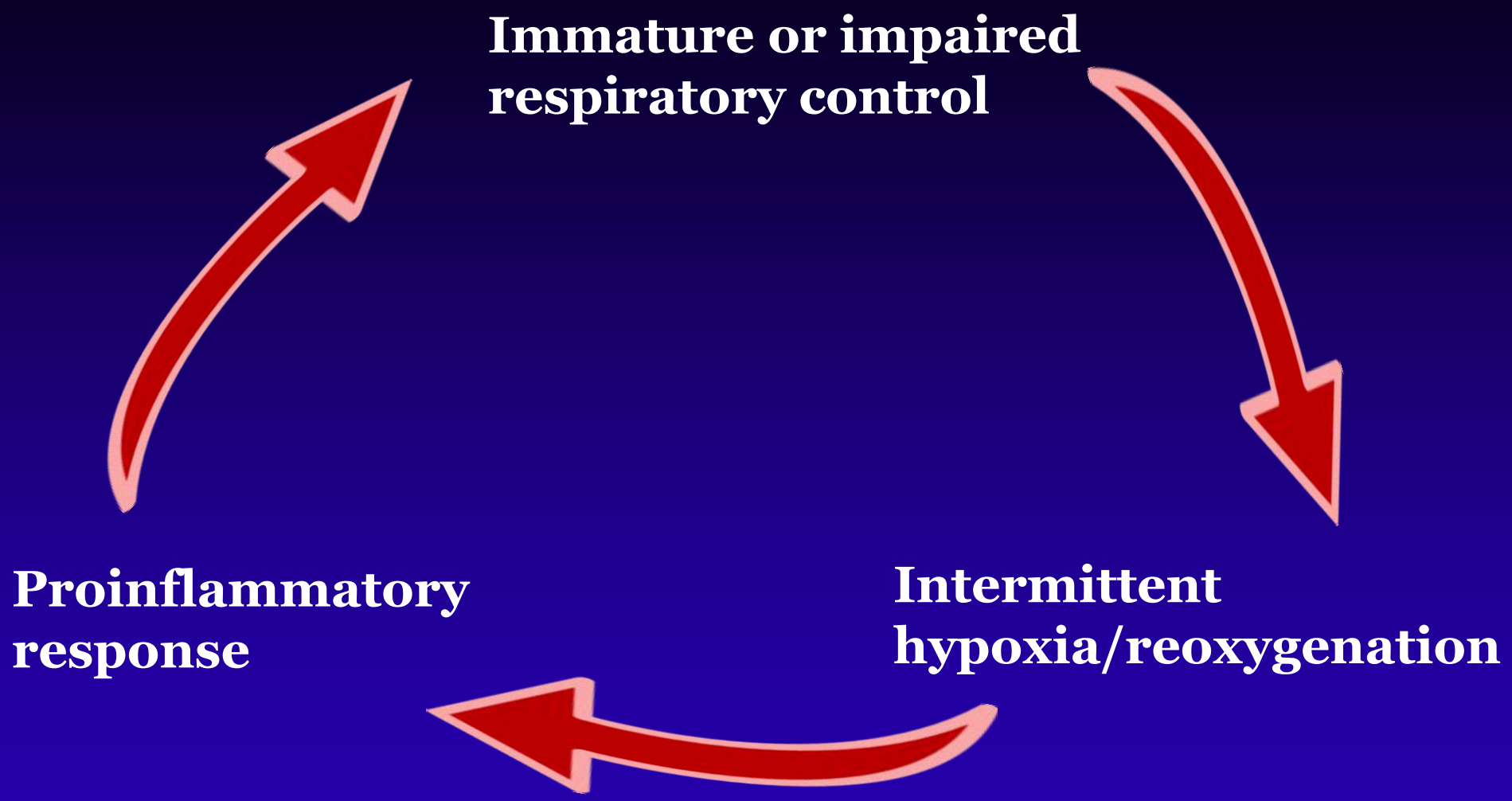


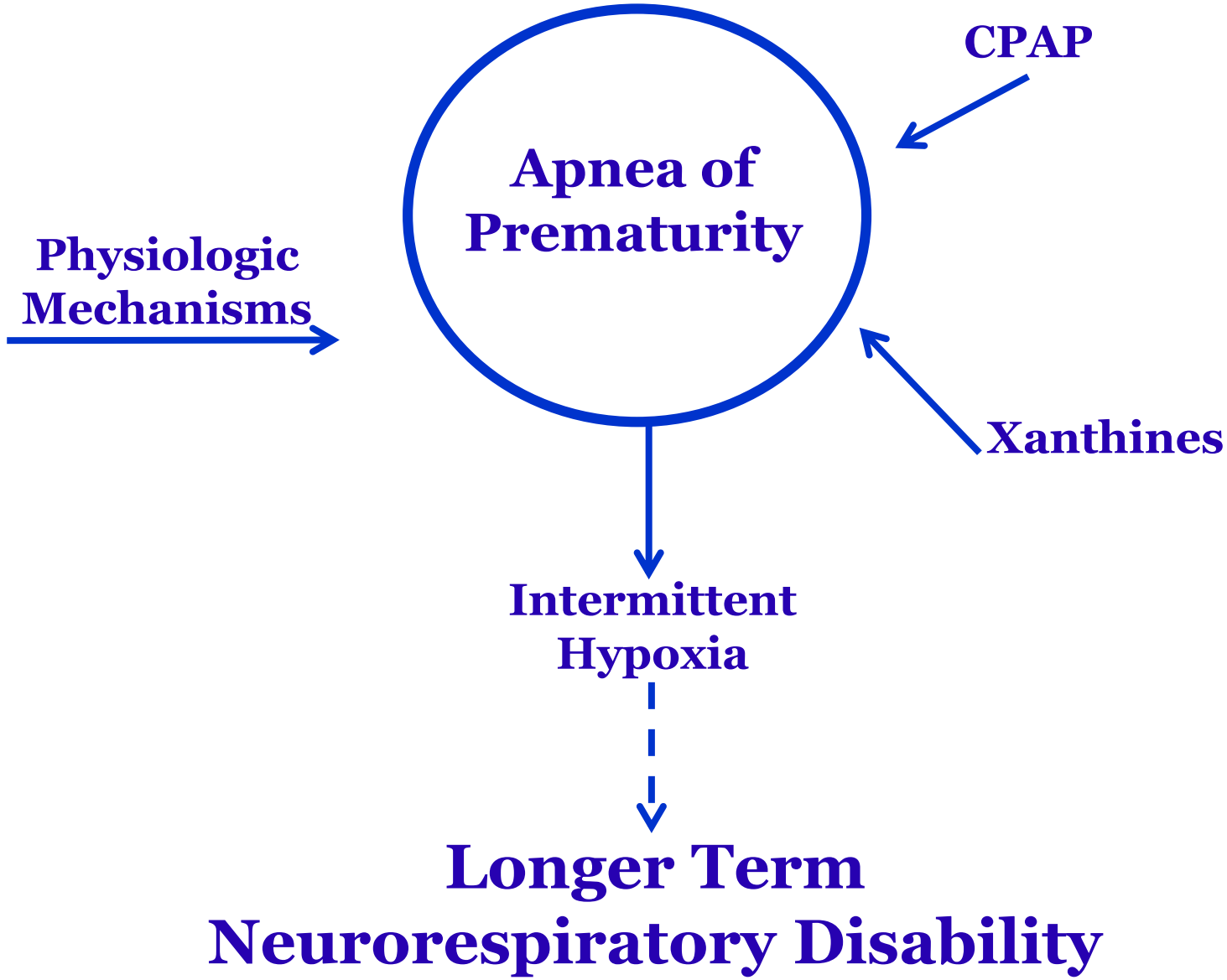
Balan KV et al 2012

Effect of Intratracheal LPS on Hypoxic Ventilatory Response

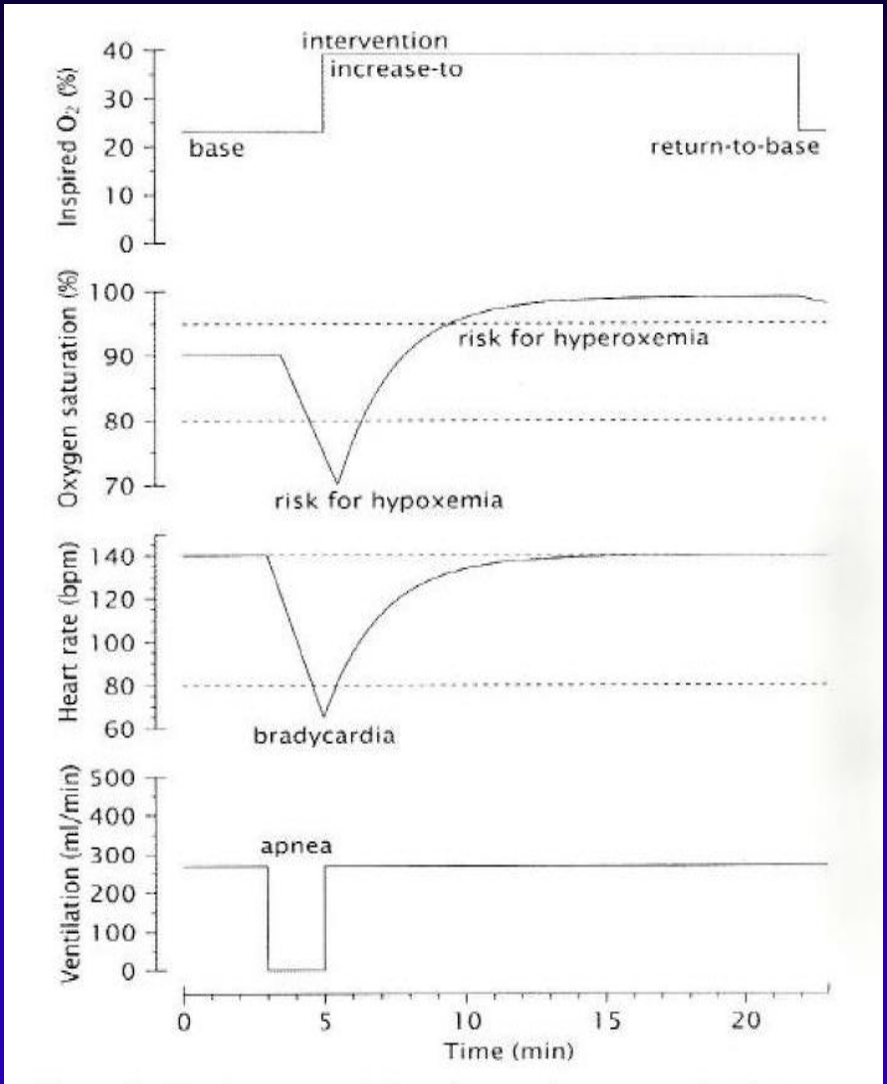


Balan KV: Respir Physiol Neurobiol 2011


Immature or impaired respiratory control
Intermittent hypoxia/reoxygenation
Proinflammatory response


CPAP
Apnea of Prematurity
Physiologic Mechanisms
Xanthines
Intermittent Hypoxia
Longer Term Neurorespiratory Disability

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

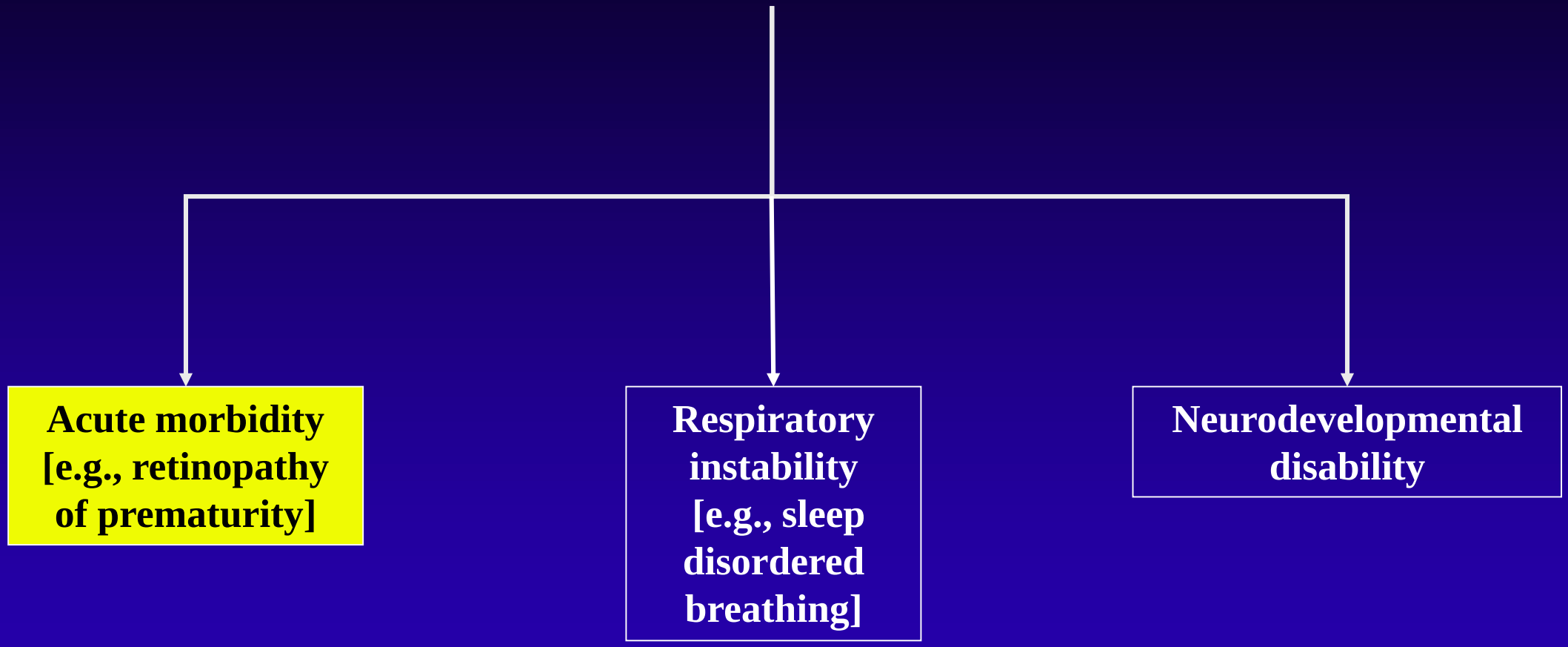


van Zanten HA: Arch Dis Child, 2014

A Role for Intermittent Hypoxia

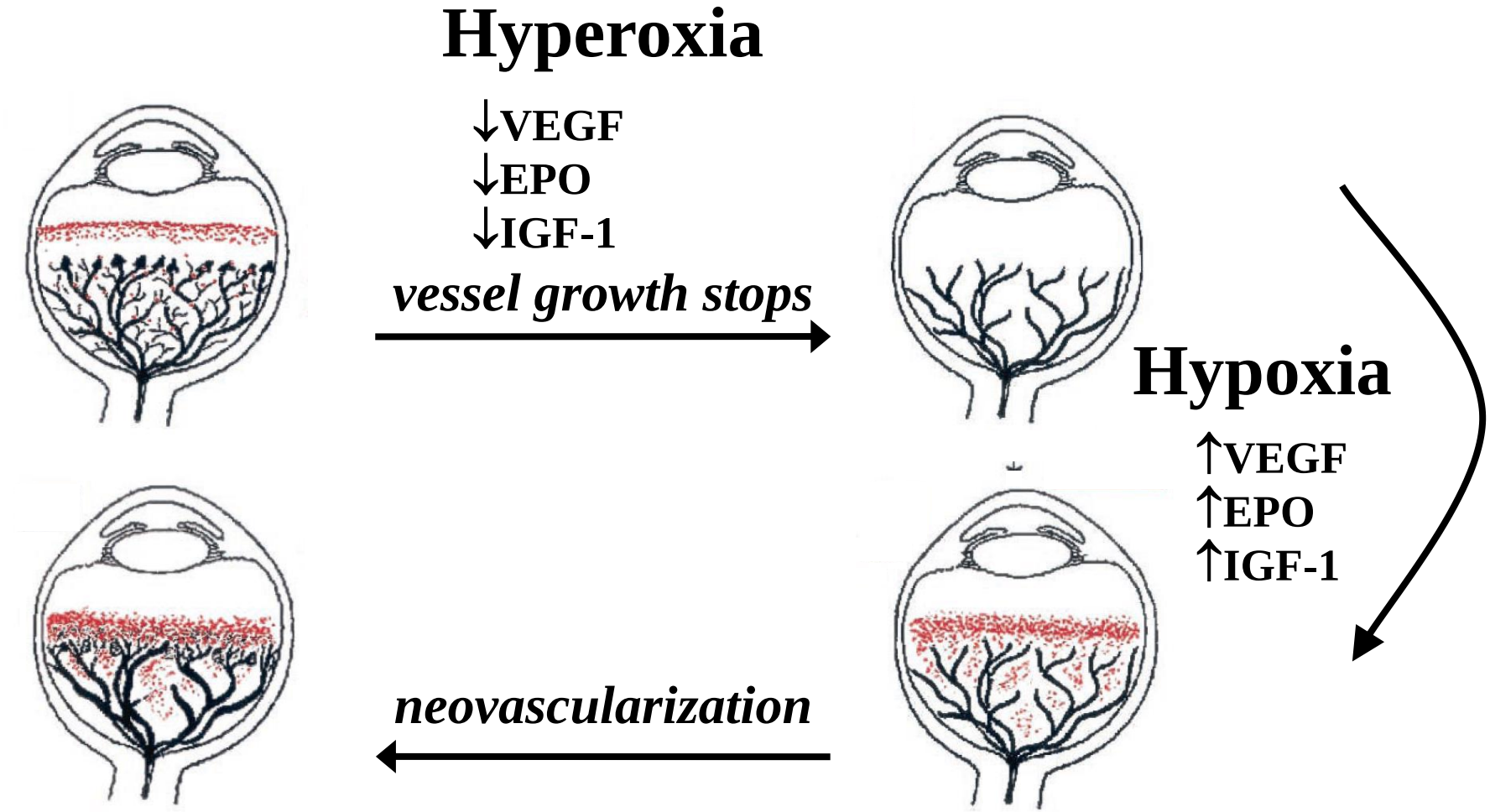
- Magnitude of the problem
- Intermittent hypoxia, oxidant stress and inflammation
- **Proposed morbidity**
- Treatment and future directions

Proposed Morbidities of Intermittent Hypoxia



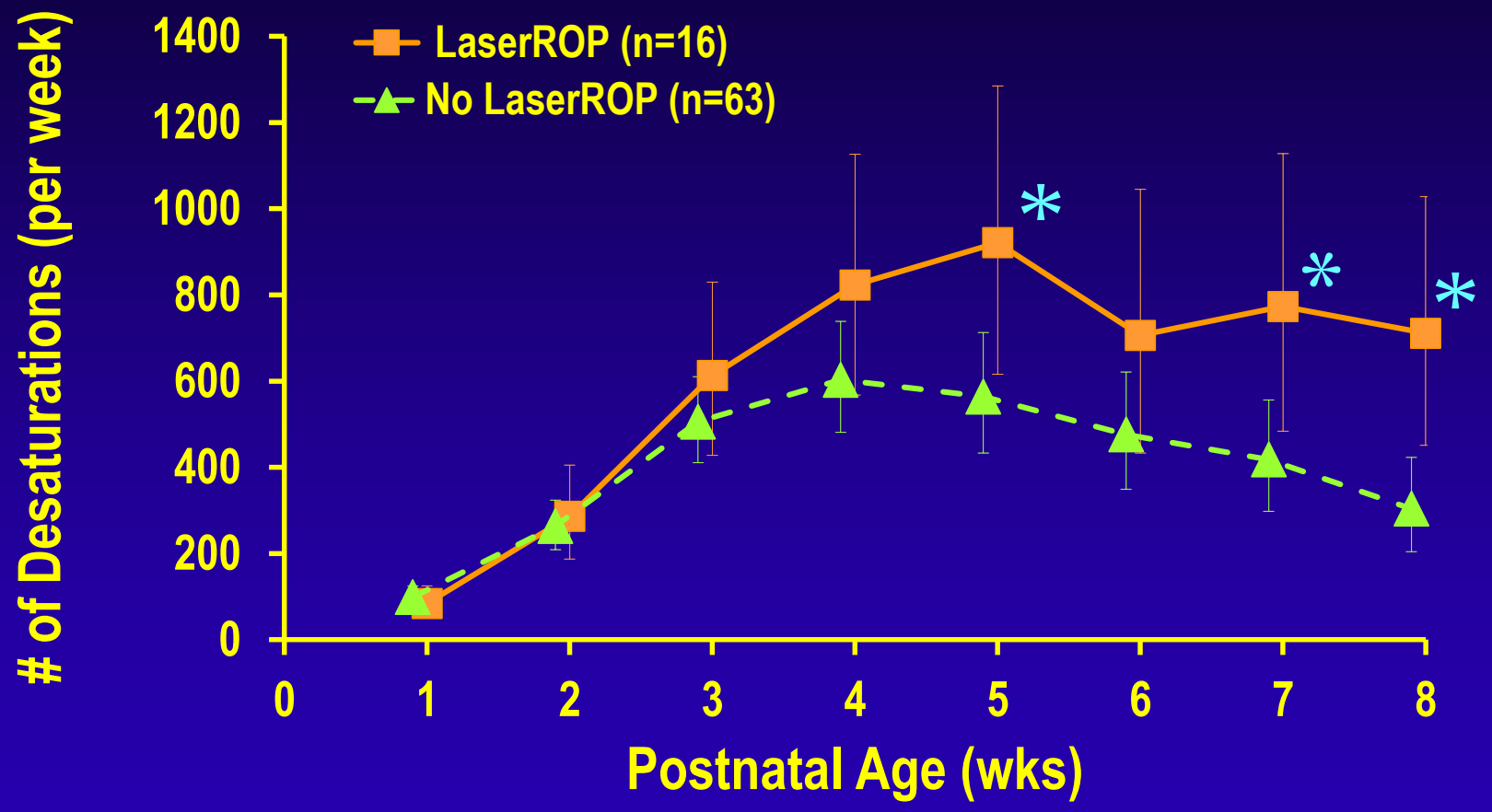
Martin RJ and Wilson C: J Appl Physiol 2009

Role of Oxygenation in Genesis of ROP



Adapted from Chow, Pediatrics 2003

Model Based Estimate of Desaturation Episodes in Infants with and without Laser Therapy for ROP



* p<.05

Mean± 95% confidence Interval

J Di Fiore: J Pediatr 2010

Proposed Morbidities of Intermittent Hypoxia

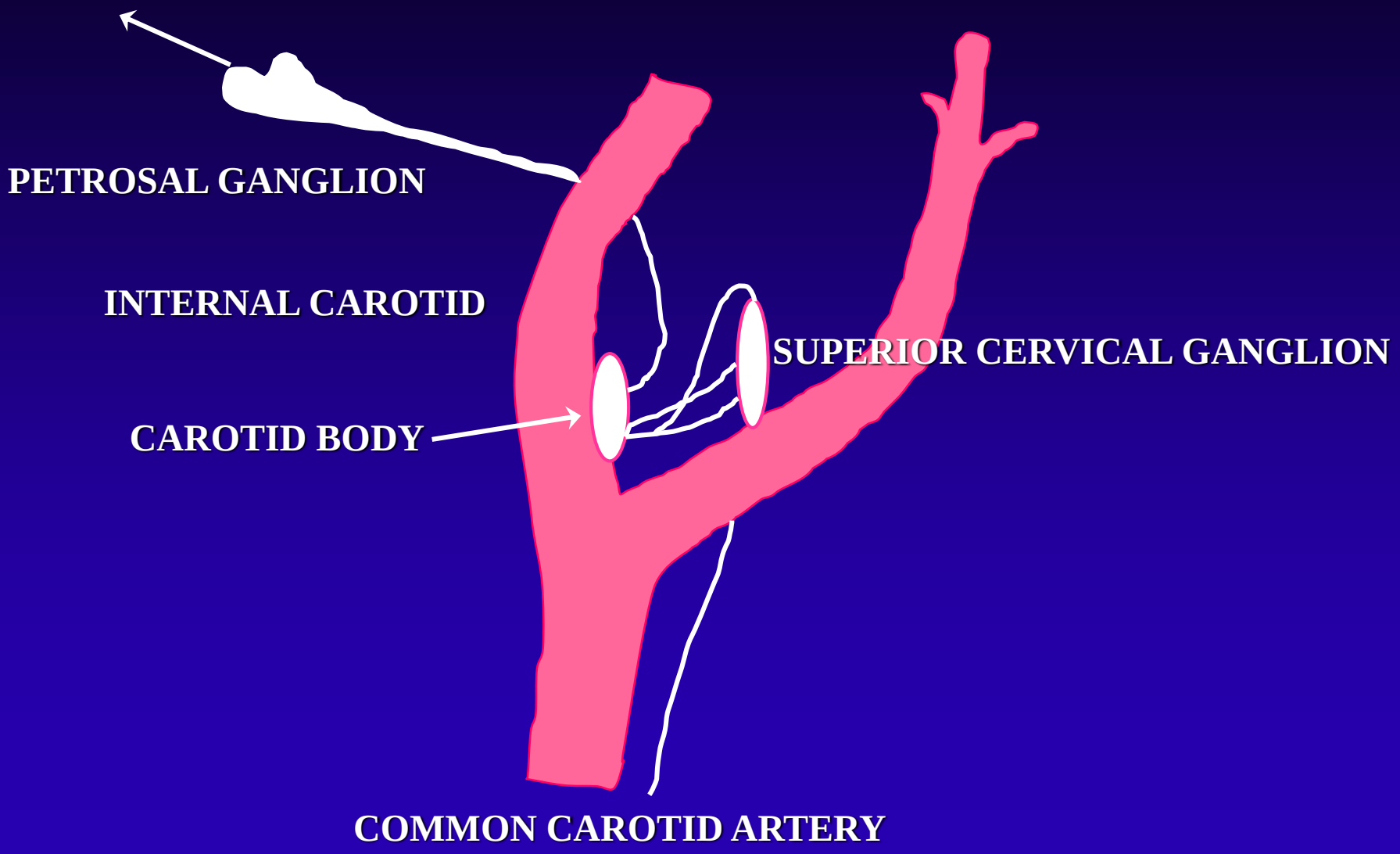
Acute morbidity [e.g., retinopathy of prematurity]

Respiratory instability [e.g., sleep disordered breathing]

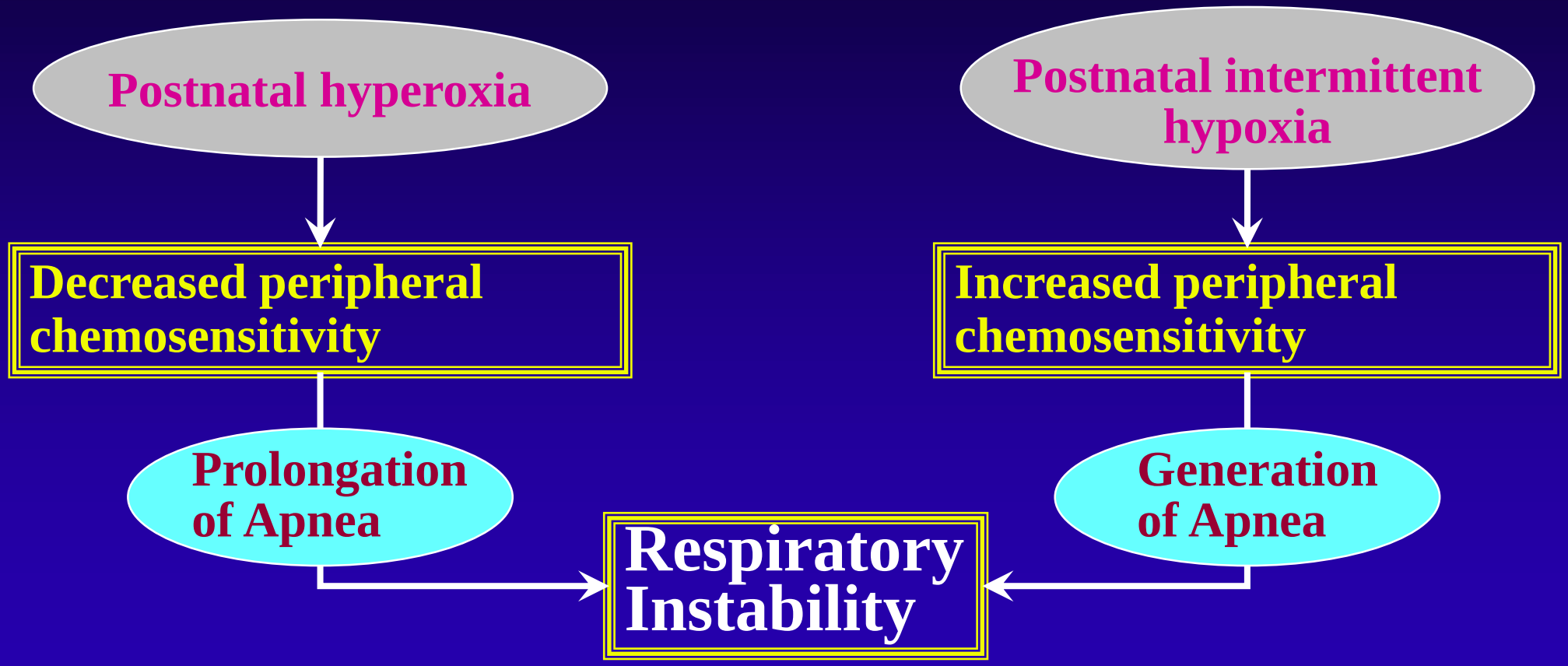
Neurodevelopmental disability

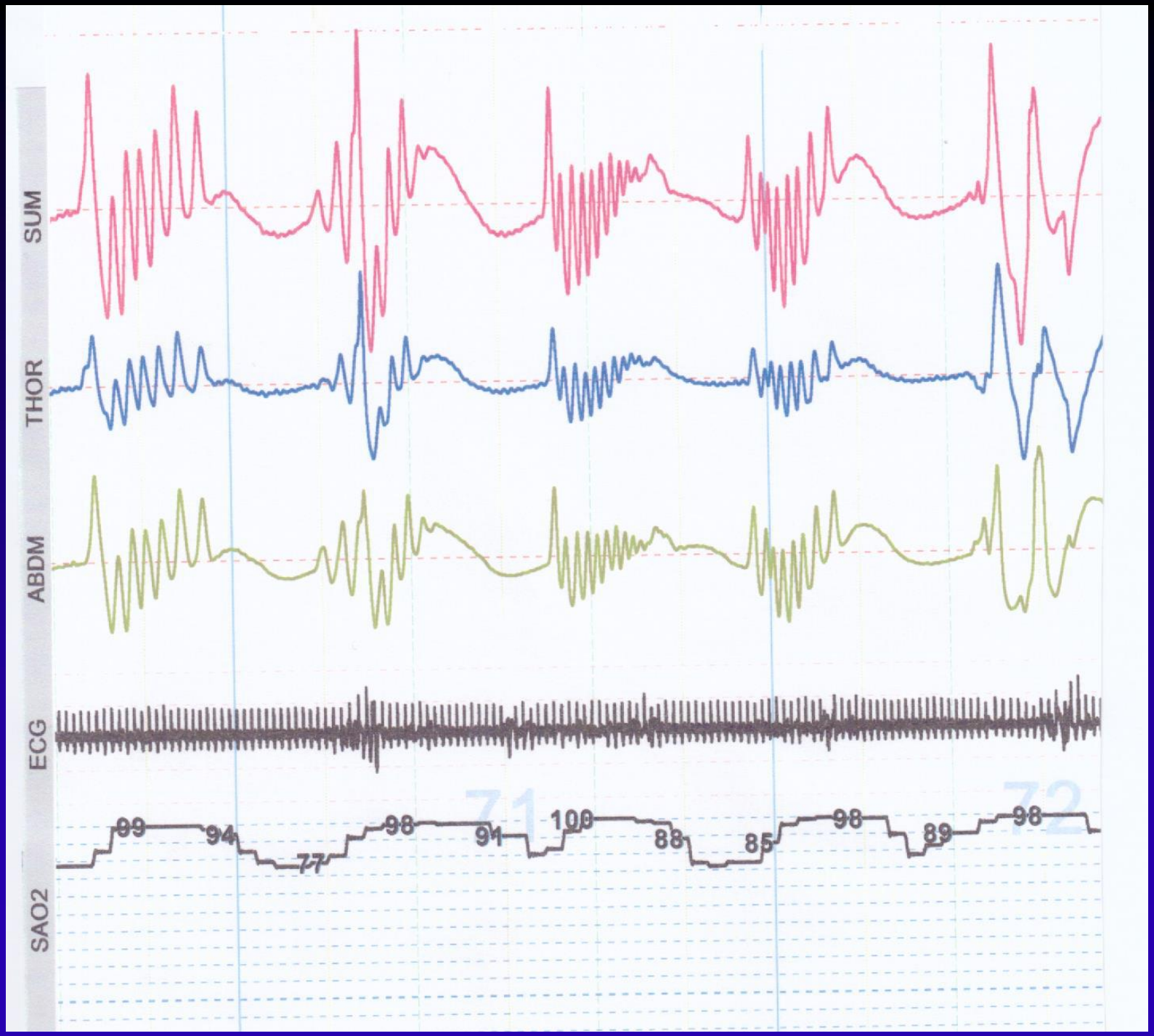
Martin RJ and Wilson C: J Appl Physiol 2009

Anatomy of Carotid Bodies

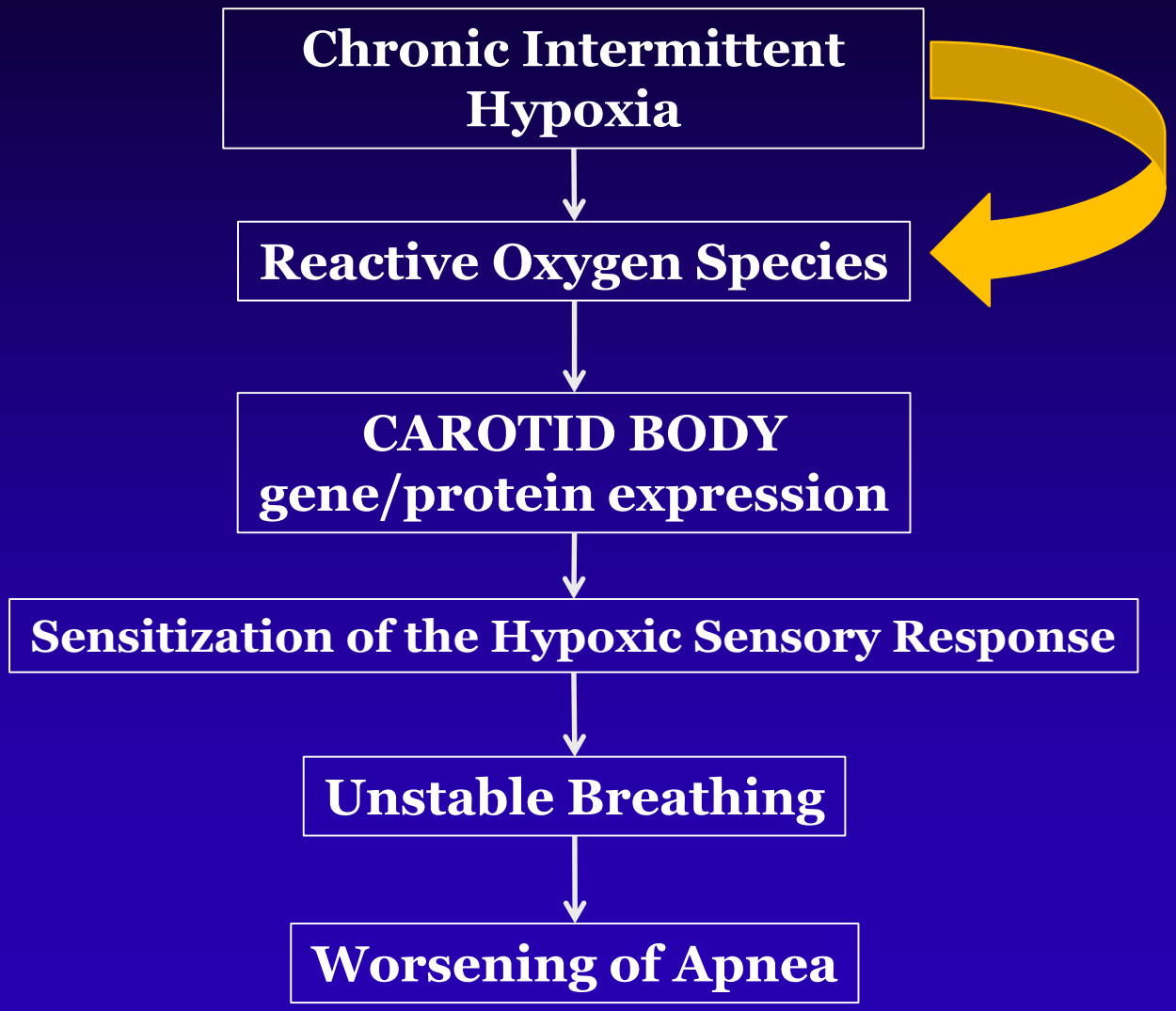


Modulation of Peripheral Chemoreceptor Function During Development




SUM
THOR
ABDM
ECG
SAO2
99
94
77
98
91
100
88
85
98
89
98

Respiratory Consequences of Chronic Intermittent Hypoxia



Risk for Sleep Disordered Breathing [Combined Apnea, Hypopnea Measure] at 8-11 years

	OR (95% CI)	p-value
Preterm	3.0 (1.5-6.5)	0.002

CL Rosen, et al: J Pediatr 2003

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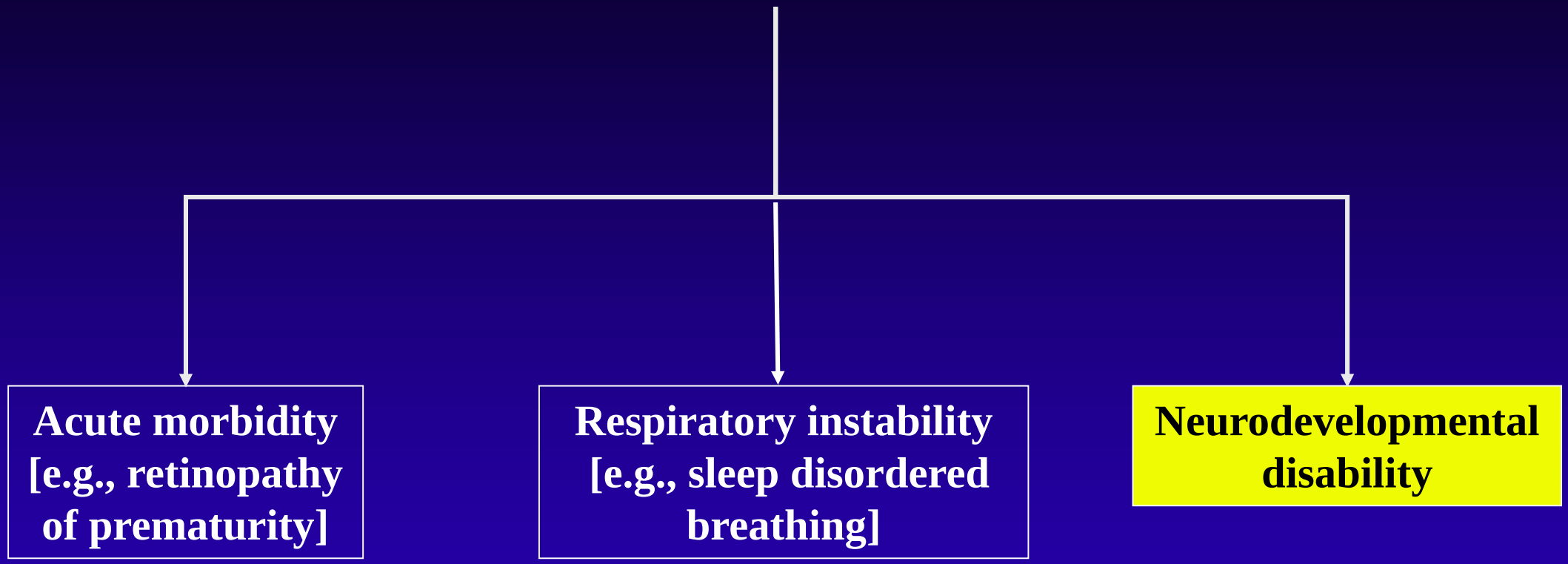
Very Low Birth Weight Increases Risk for Sleep-Disordered Breathing* in Young Adulthood: The Helsinki Study of Very Low Birth Weight Adults

E. Juulia Paavonen, MD, PhD, BSocSc[a], Sonja Strang-Karlsson, MD[b,c], Katri Räikkönen, PhD[a], Kati Heinonen, PhD[a], Anu-Katriina Pesonen, PhD[a], Petteri Hovi, MD[b,c], Sture Andersson, MD, PhD[c], Anna-Liisa Järvenpää, MD, PhD[c], Johan G. Eriksson, MD, PhD[b,d], Eero Kajantie, MD, PhD[b,c]

PEDIATRICS October 2007

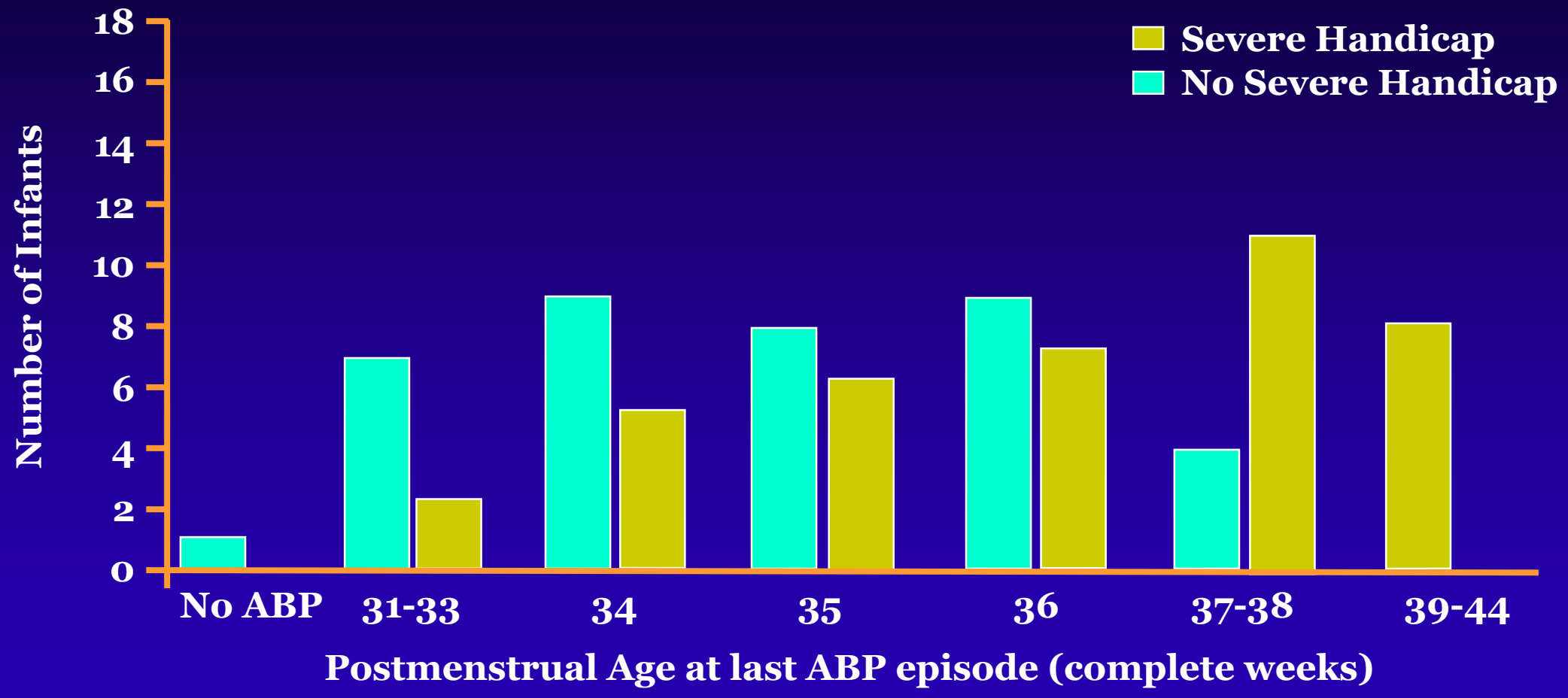
**** via Questionnaire***

Proposed Morbidities of Intermittent Hypoxia



Martin RJ and Wilson C: J Appl Physiol 2009

Persistence of Apnea and Bradycardia of Prematurity (ABP) is Associated with Poor Neurodevelopmental Outcome



More Recent Trials of Oxygen Targeting in ELBWs

- **SUPPORT [n=1316]**
- **BOOST II [n=1187]**
- **COT [n=1201]**

[randomization of preterm infants 24-28 wk GA to 85-89% vs 91-95% O_2 saturation]

Association between Intermittent Hypoxemia or Bradycardia and Late Death or Disability [including ROP] in Extremely Preterm Infants

"This association was significant only for **prolonged hypoxemic episodes** lasting at least 1 minute…Bradycardia did not alter the prognostic value of hypoxemia."

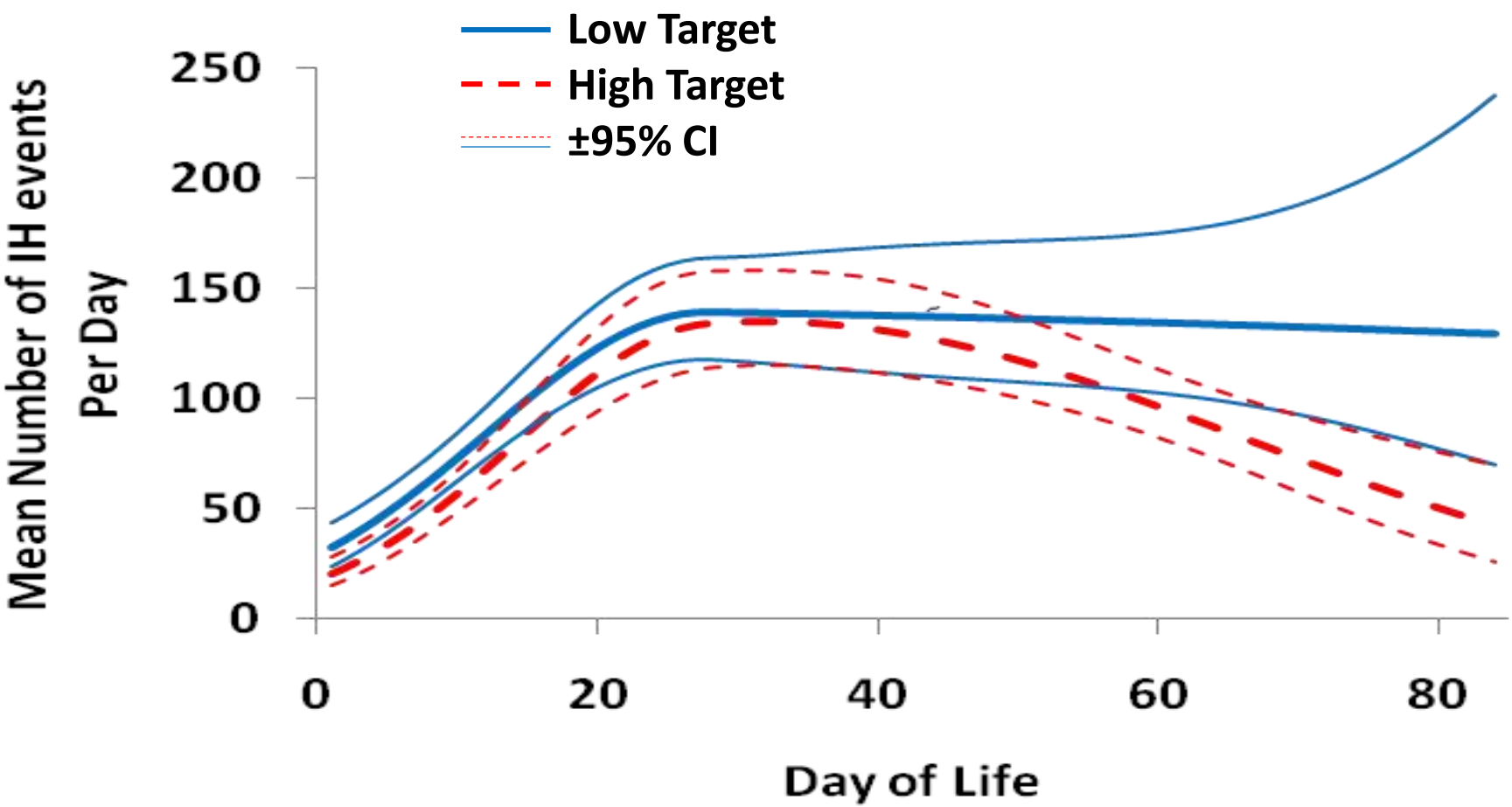
Poets CF et al: JAMA, 2015

Time with SpO_2 <80% and Outcome at 18 months of Age

	IH <1min			IH≥1min		
Outcomes	**OR (95% CI)**	**RR (95% CI)**	**P value**	**OR (95% CI)**	**RR (95% CI)**	**P value**
Late Death or Disability	1.04 (.61-1.77)	1.01 (.77-1.32)	.88	3.4 (1.95-5.93)	1.66 (1.35-2.05)	<.001
Cognitive/ language delay	.96 (.56-1.64)	.96 (.72-1.29)	.87	2.88 (1.65-5.02)	1.61 (1.29-2.03)	<.001
Motor Impairment	2.27 (.90-5.74)	1.90 (.90-4.04)	.08	5.20 (2.48-10.92)	3.51 (2.16-5.72)	<.001
Severe ROP	1.84 (0.86-3.95)	1.46 (0.86-2.47)	.12	2.95 (1.47-5.90)	1.93 (1.26-2.98)	.002

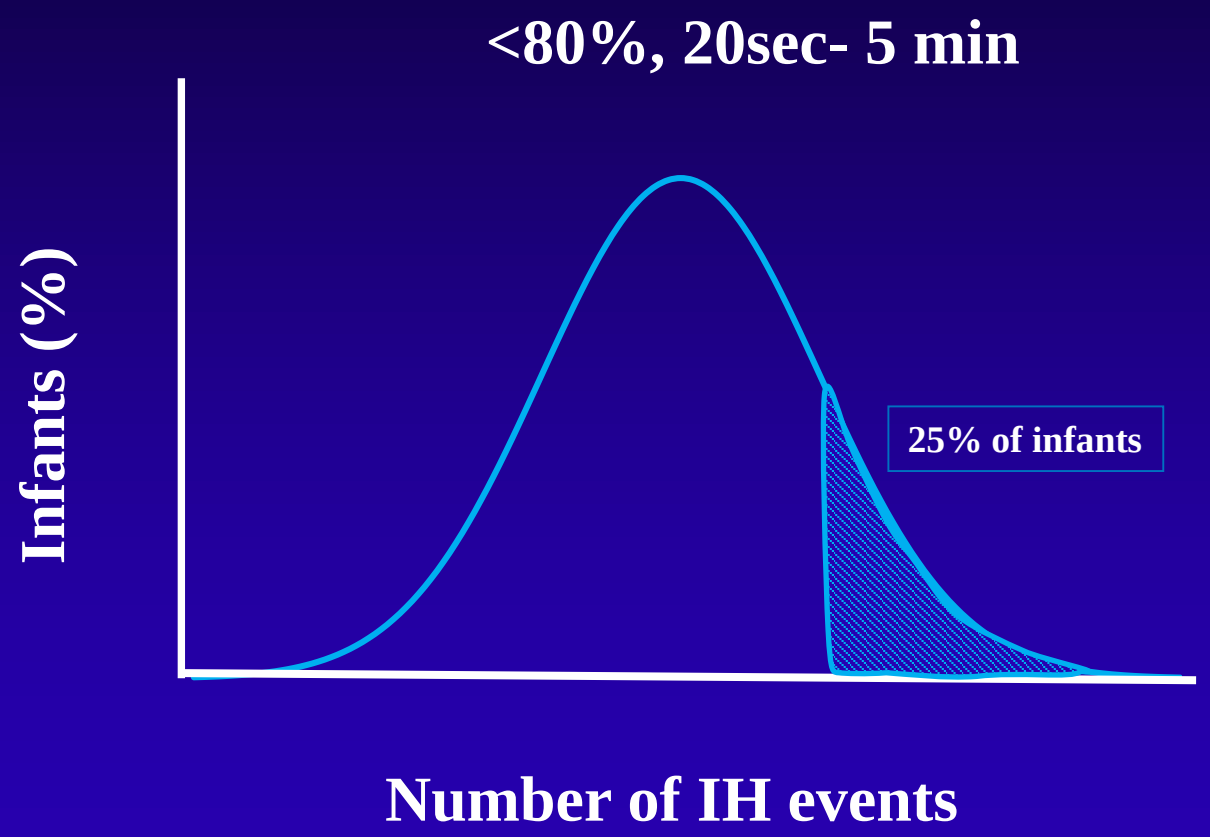
Poets: JAMA 2015

The Incidence of Intermittent Hypoxia in the Low and High Target Groups

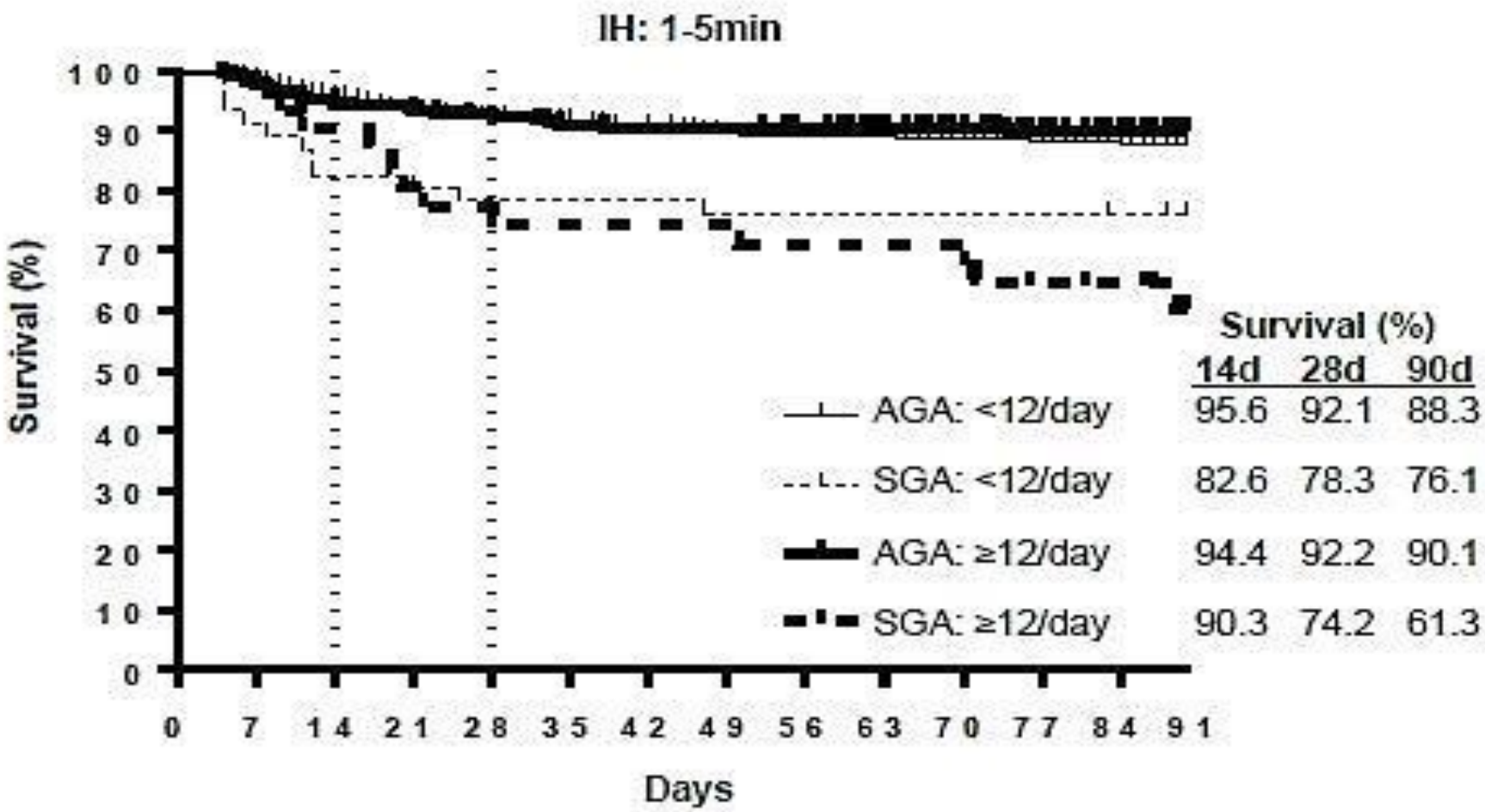


Di Fiore et al: J Pediatr, 2012

Intermittent Hypoxemic Events During the First 3 Days of Life

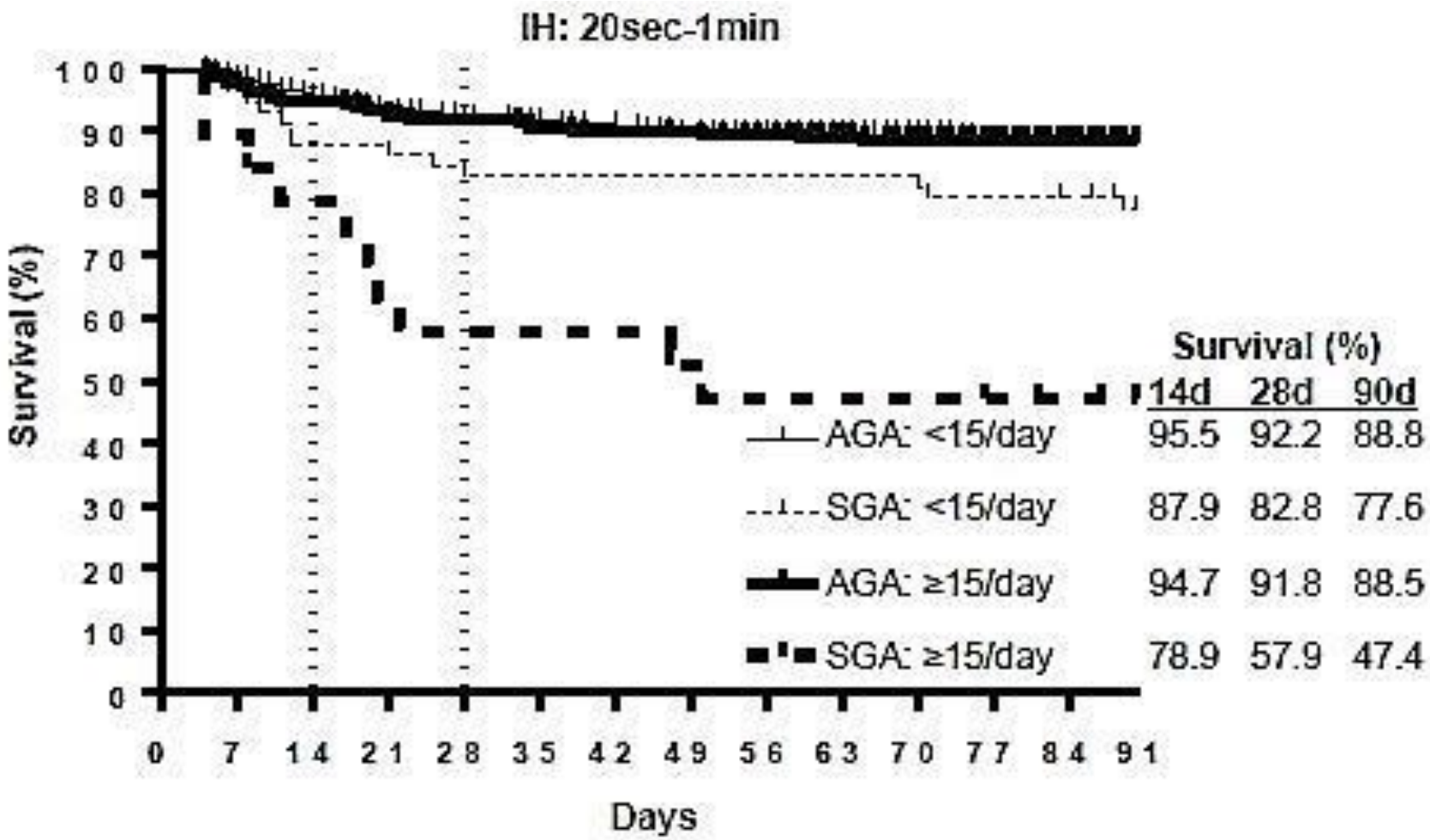


Effect of Growth Status and Longer IH Events in Days 1-3 on Survival



Di Fiore JM: J Pediatr 2017

Effect of Growth Status and Shorter IH Events in Days 1-3 on Survival



Di Fiore JM: J Pediatr 2017

A Role for Intermittent Hypoxia

- Magnitude of the problem
- Intermittent hypoxia, oxidant stress and inflammation
- Proposed morbidity
- **Treatment and future directions**

Treatment Strategies for Intermittent Hypoxia

Xanthines

↓

Enhance Respiratory Control

Supplemental Oxygen

- Manual vs automated FiO_2 control

↓

Optimize Baseline SaO_2

RBC Transfusion

↓

Improve Oxygen Stores

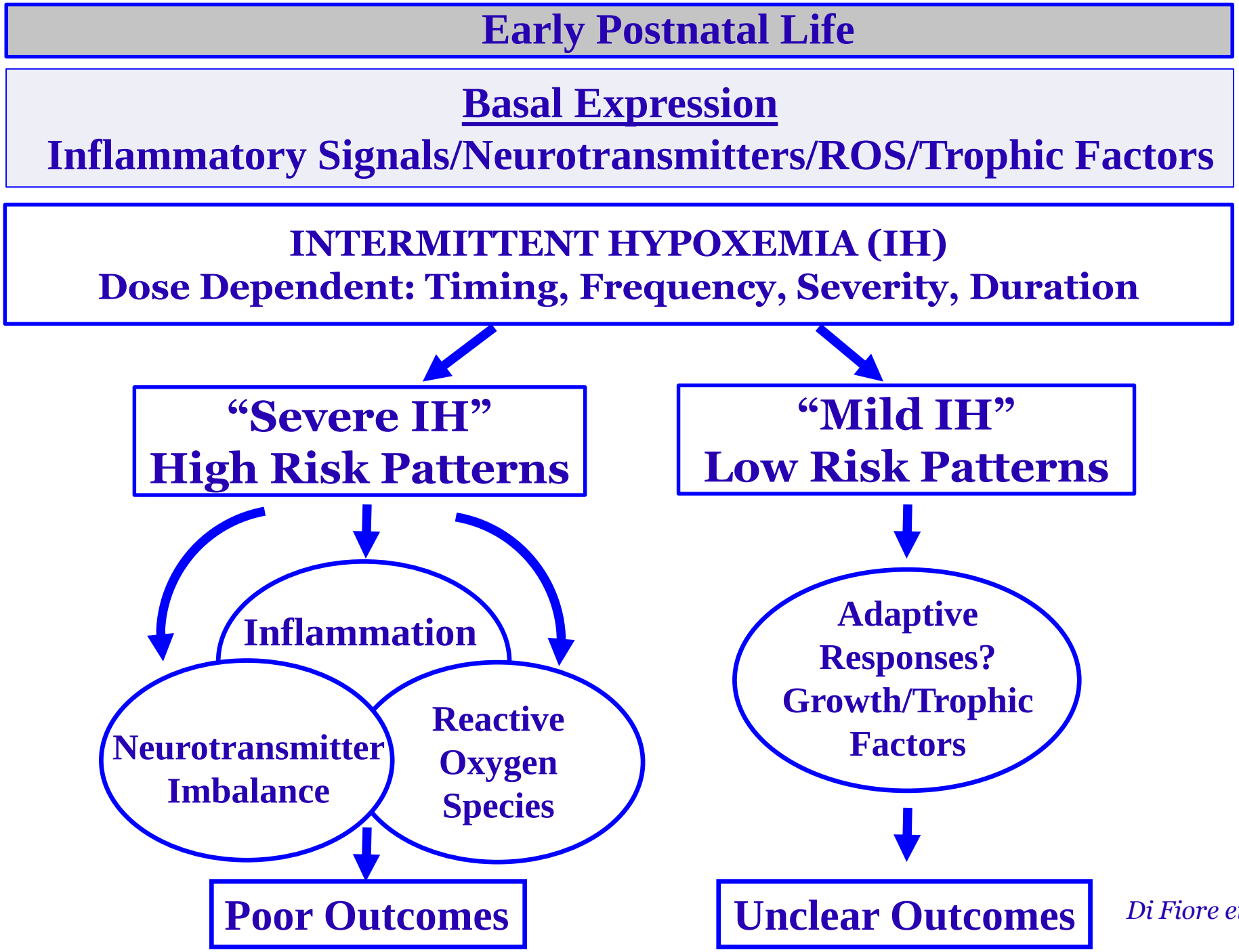
CPAP

- Stabilize lung volume
- Splint upper airway

Novel non-invasive ventilation techniques

Neonatal Caffeine Therapy: Unresolved Issues

	Pro	Con
Early onset	• Improves various morbidities	• Available data are largely based on associations rather than randomized trials • How early is too early?
Prolongation of therapy	• Decreases duration of intermittent hypoxic episodes • May shorten hospitalization [if discharged on caffeine]	• May provide exposure to unnecessary medication • May prolong hospitalization [if discharged off caffeine]
Higher doses	• More strongly enhance respiratory neural output	• Adenosine receptor subtype inhibition of inflammation is variable and dose dependent, raising safety concerns • Preliminary report of cerebellar injury • Likely need for postnatal dose adjustments



Di Fiore et al, in press