Intermittent Hypoxic Episodes: Do They Matter?

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Rainbow Babies
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SCHOOL OF MEDICINE
CASE WESTERN RESERVE
UNIVERSITY

No hablo español, pero, buena comida, buena compañía!

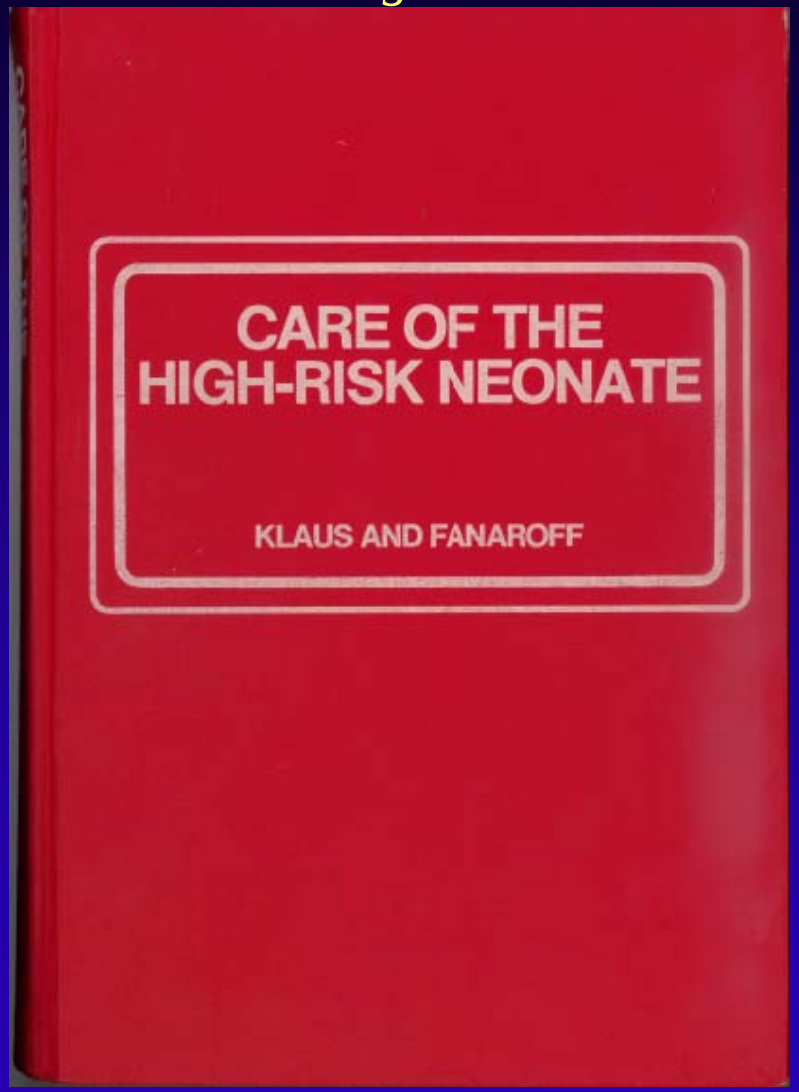
Do Intermittent Hypoxic Episodes Matter?

- ***Historical perspective***
- Magnitude of the problem
- Proposed morbidities
- Treatment strategies

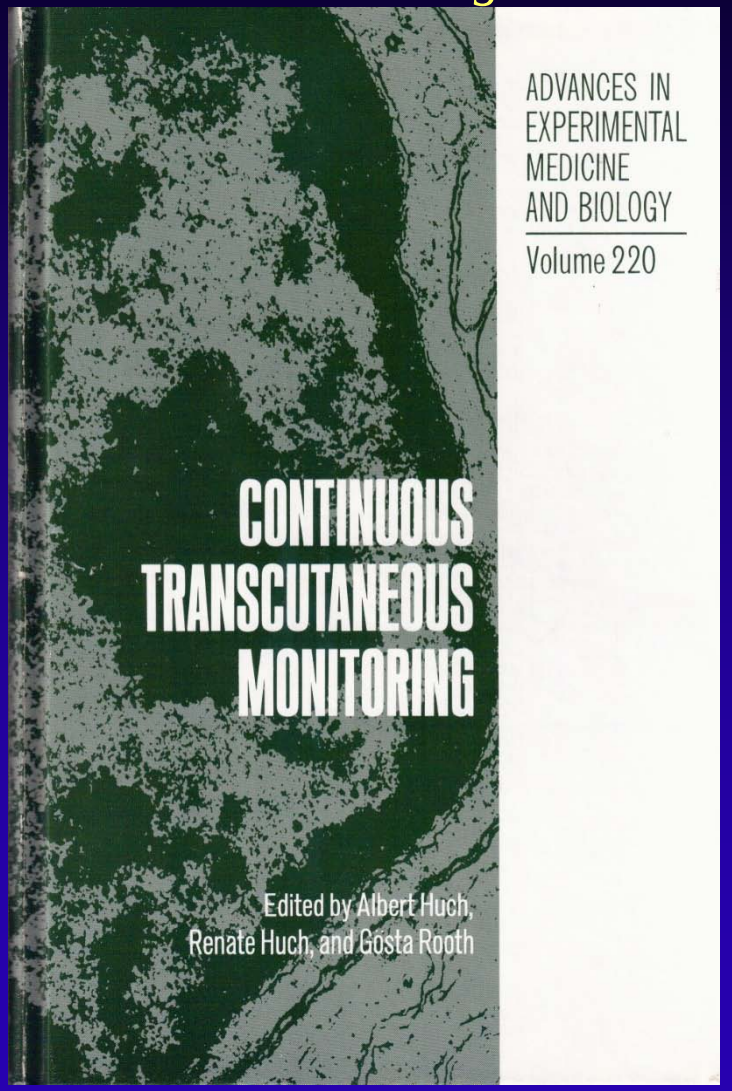
Advent of Umbilical Arterial Lines

1960-1970s

"Maintain PaO_2 between 60-80 mmHg" · Martin RJ



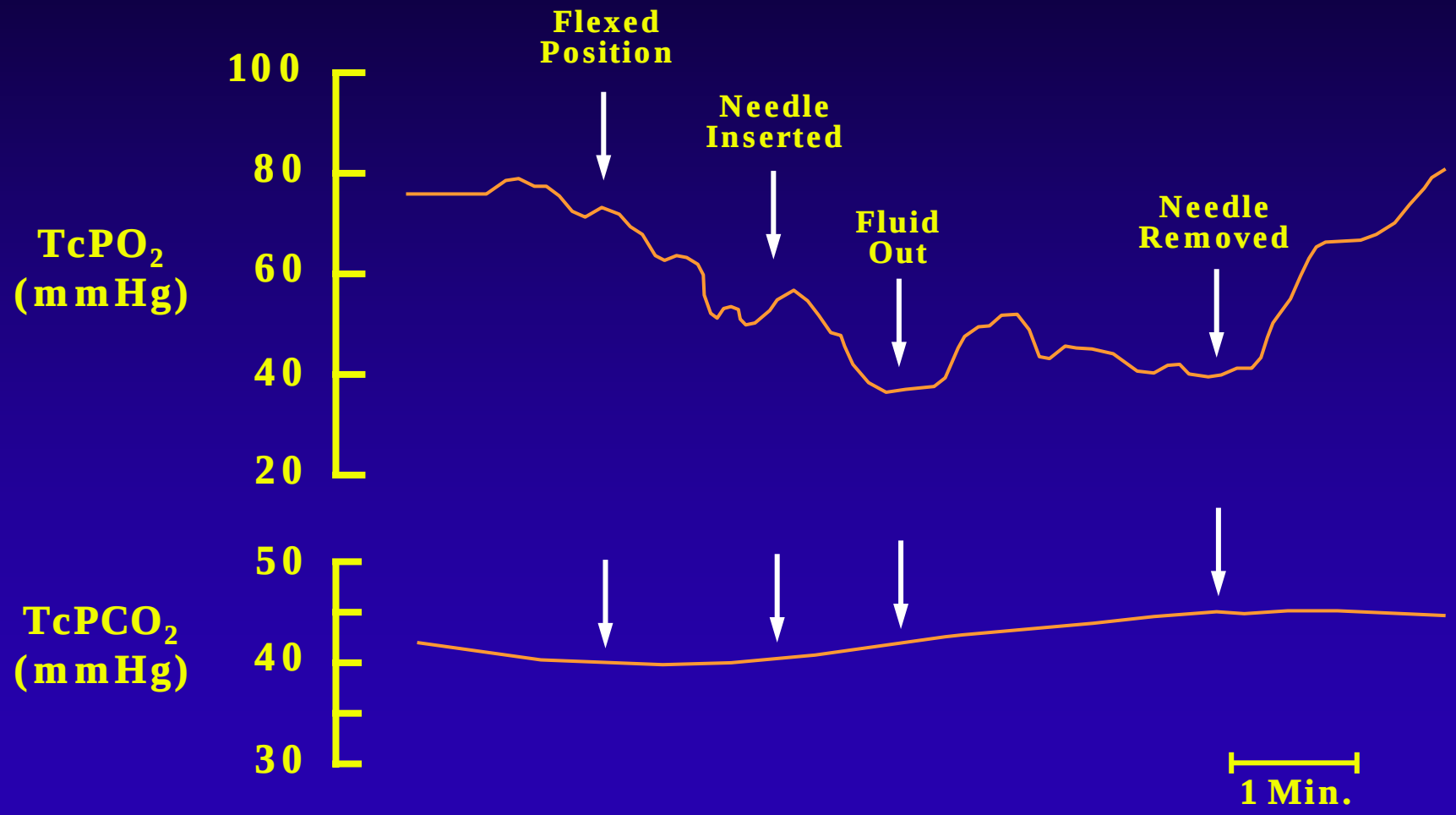
Advent of Non-invasive Monitoring



Transcutaneous PO_2: Lessons Learned

- Magnitude of fluctuations in PO_2
- Effect of procedures, feeding, behavioral state, etc., on oxygenation

Transcutaneous Oxygen and Carbon Dioxide Measurements during a Spinal Tap



Gleason: Pediatrics, 1983

Limitations of Transcutaneous PO_2

- Dependence on skin perfusion
- Skin burns from heated (43.5→44°C) electrodes
- Need for frequent calibrations and repositioning
- Loss of accuracy with advancing postnatal age

Limitations of Transcutaneous PO_2 and PCO_2 Monitoring in Infants with Bronchopulmonary Dysplasia

Ellen S. Rome, Eileen K. Stork, Waldemar A. Carlo, Richard J. Martin

Pediatrics Vol. 74 1984

Pulse Oximetry Advantages in Infants With Bronchopulmonary Dysplasia

Alfonso J. Solimano, MD, John A. Smyth, MD, Tejinder K. Mann, MD,
Susan G. Albersheim, MD, Gillian Lockitch, MD

Pediatrics Vol. 78 No. 5 April 1986

Pulse Oximetry in Very Low Birth Weight Infants With Acute and Chronic Lung Disease

Rangasamy Ramanathan, MD, Manuel Durand, MD, Carlos Larrazabal, MD

Pediatrics Vol. 79 No. 4 April 1987

Oxygen Treatment for Immature Infants beyond the Delivery Room: Lessons from Randomized Studies

"...the switch from $TcPO_2$ monitoring targeting a PaO_2 range of 50-80 mm Hg to SpO_2 monitoring targeting a saturation range 85%-95% ushered in a second era of unrecognized oxygen restriction, unsupported by trial evidence".

Stenson B, Saugstad OD: J Pediatr 2018

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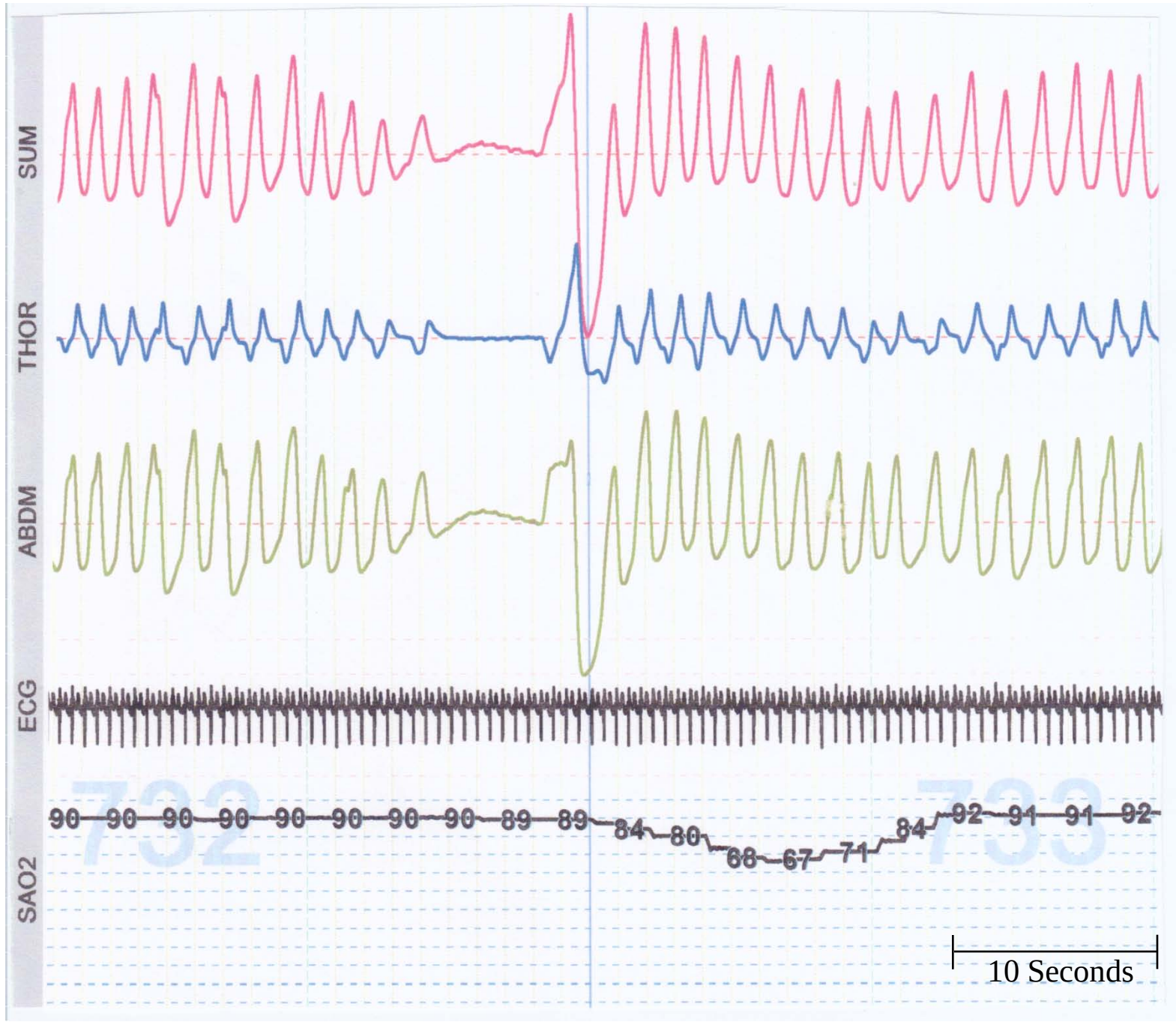
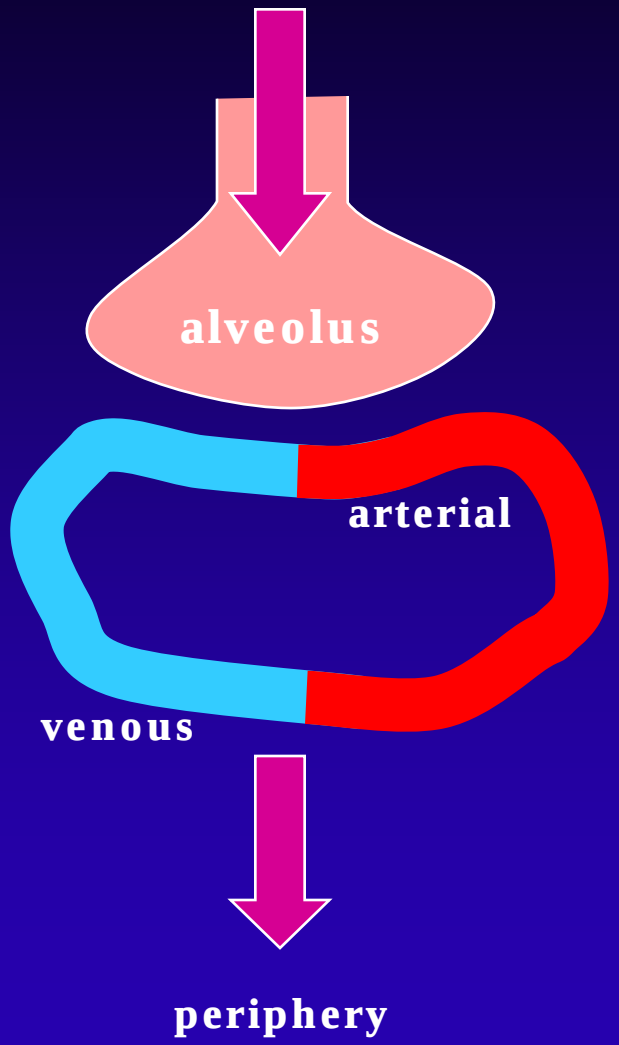

SUM
THOR
ABDM
ECG
SAO2
90 90 90 90 90 90 90 90 89 89 84 80 68 67 71 84 92 91 91 92
732
733
10 Seconds

Factors Influencing Arterial O_2 Desaturation during Apnea of Prematurity

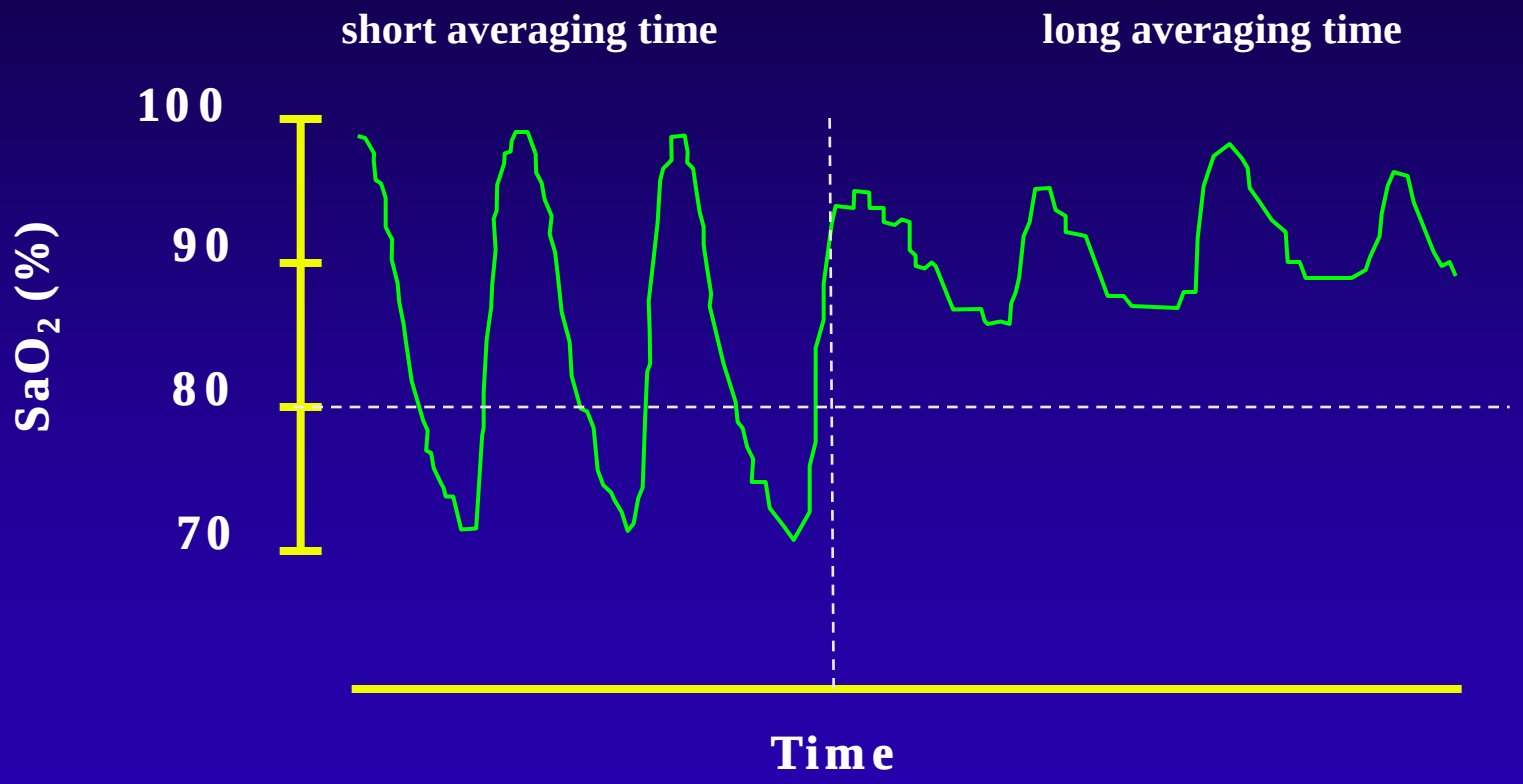


Alveolar O_2 Stores

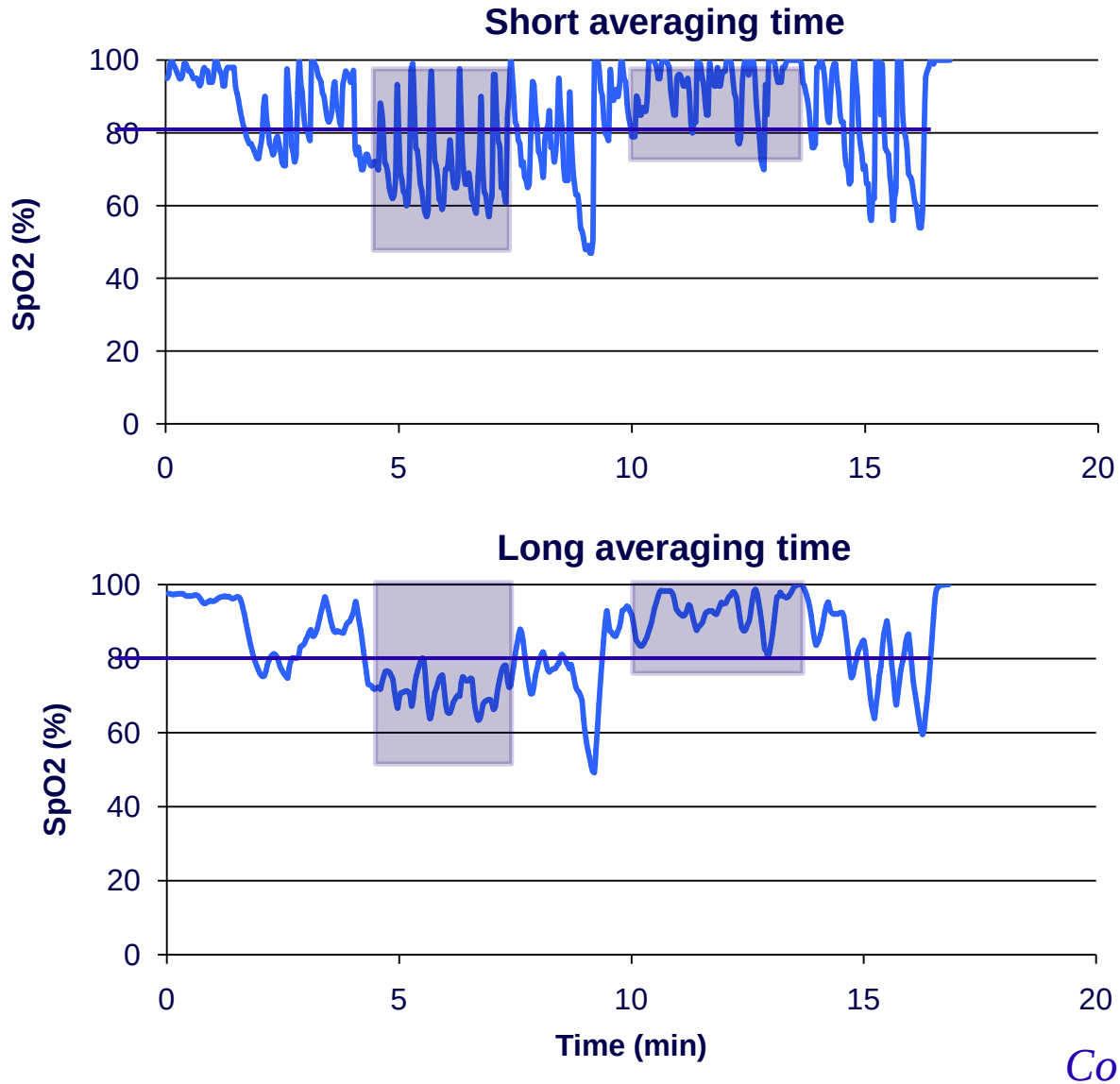
Pulmonary Hypertension

Total Blood O_2 Capacity

Importance of Pulse Oximeter Averaging Time When Measuring Oxygen Desaturation Episodes

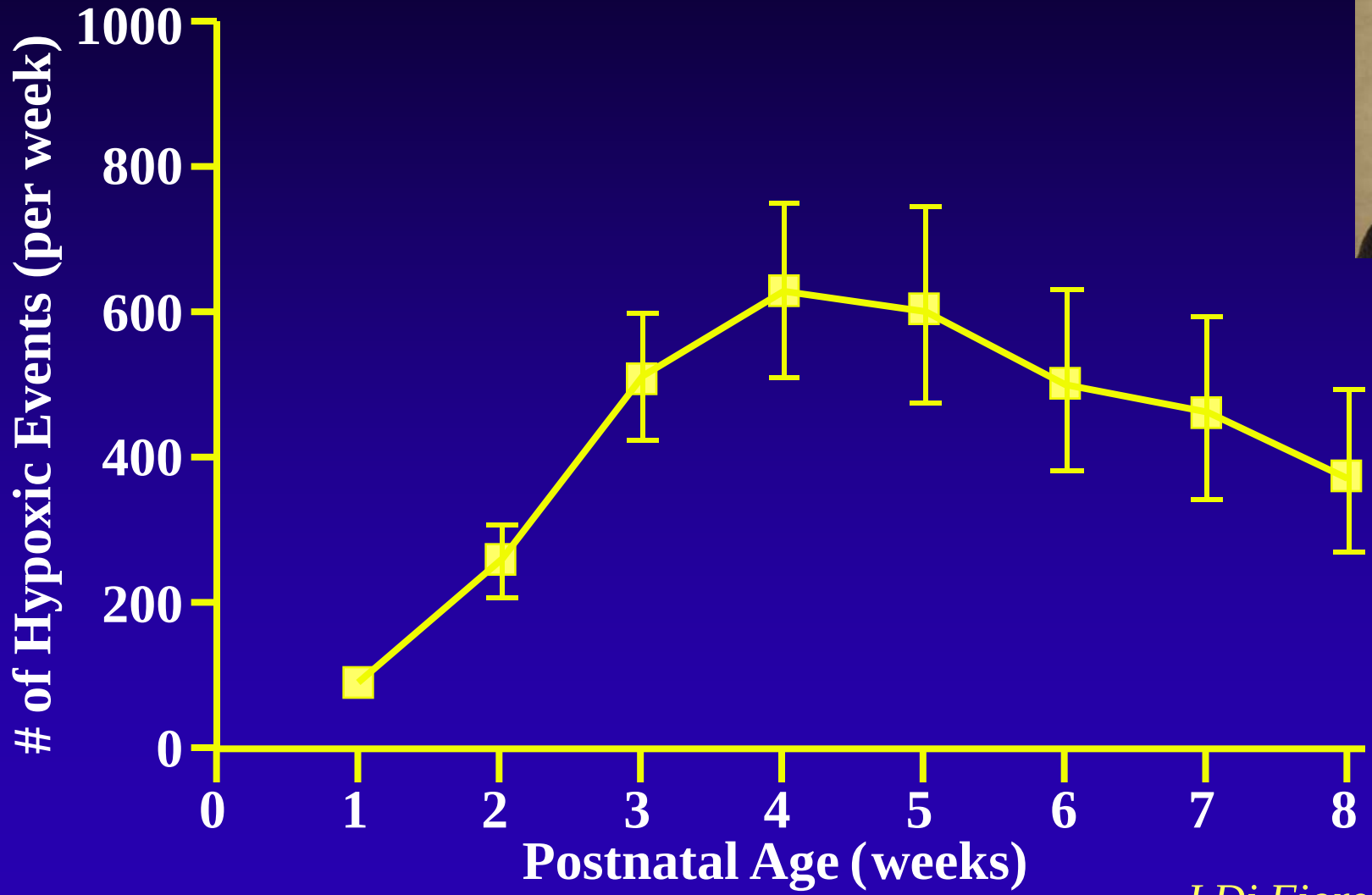


Importance of Pulse Oximeter Averaging Times



Courtesy: J. Di Fiore

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



J Di Fiore: J Pediatr 2010

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Review

Neonatology

Neonatology 2011;100:303–310
DOI: 10.1159/000329922

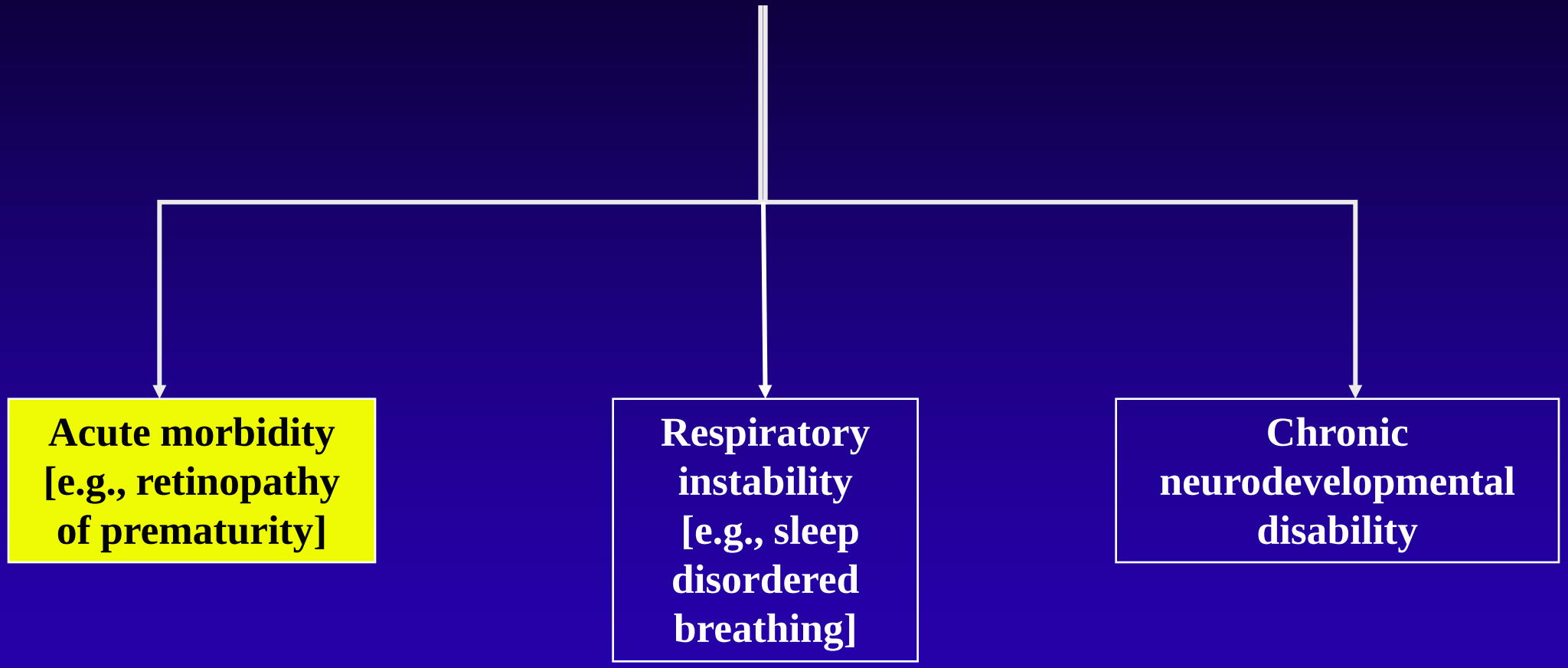
Published online: October 3, 2011

Intermittent Hypoxic Episodes in Preterm Infants: Do They Matter?

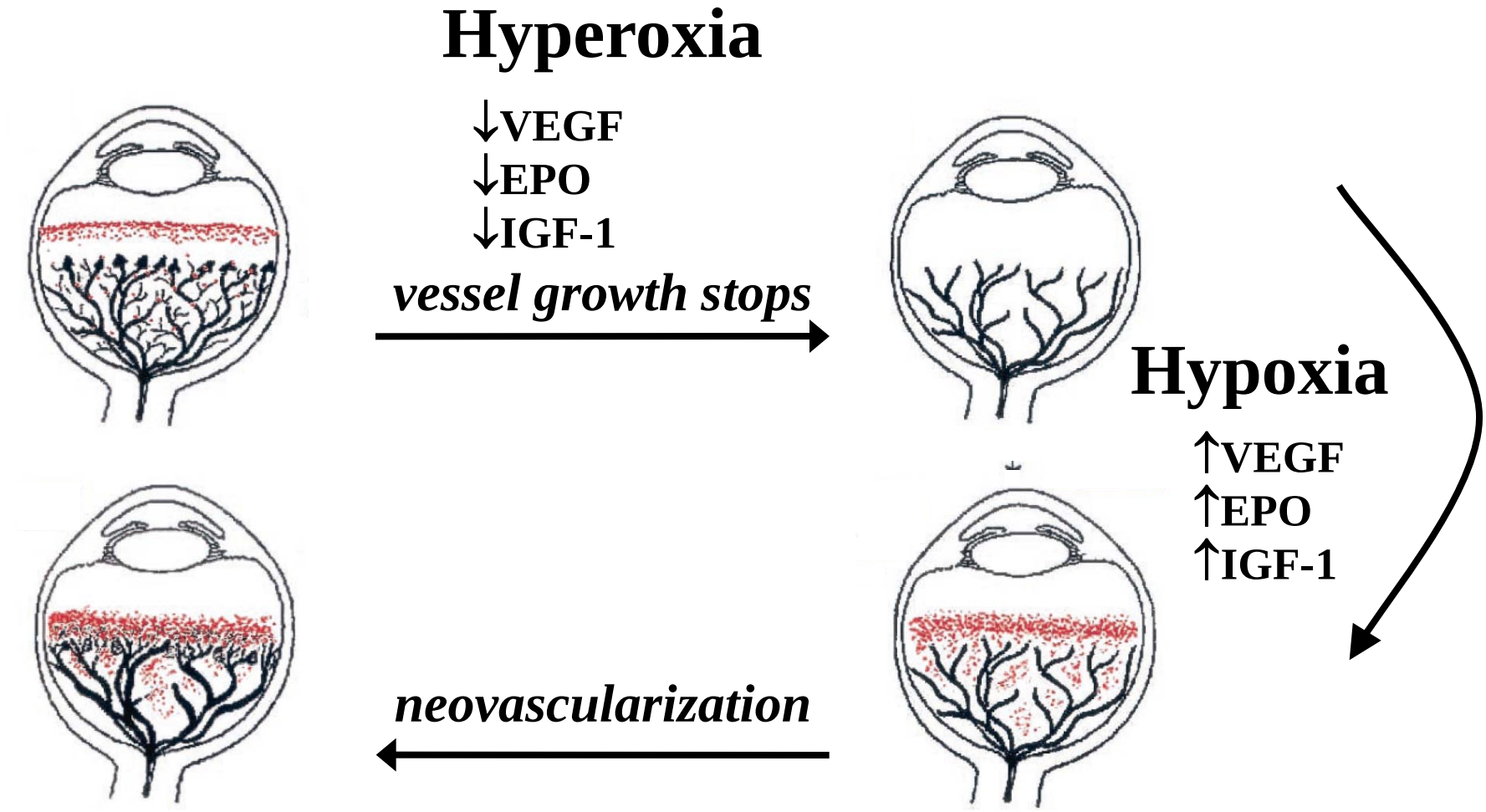
Richard J. Martin Katherine Wang Özge Köroğlu Juliann Di Fiore Prabha Kc

Division of Neonatology, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio, USA

Proposed Morbidities of Intermittent Hypoxia

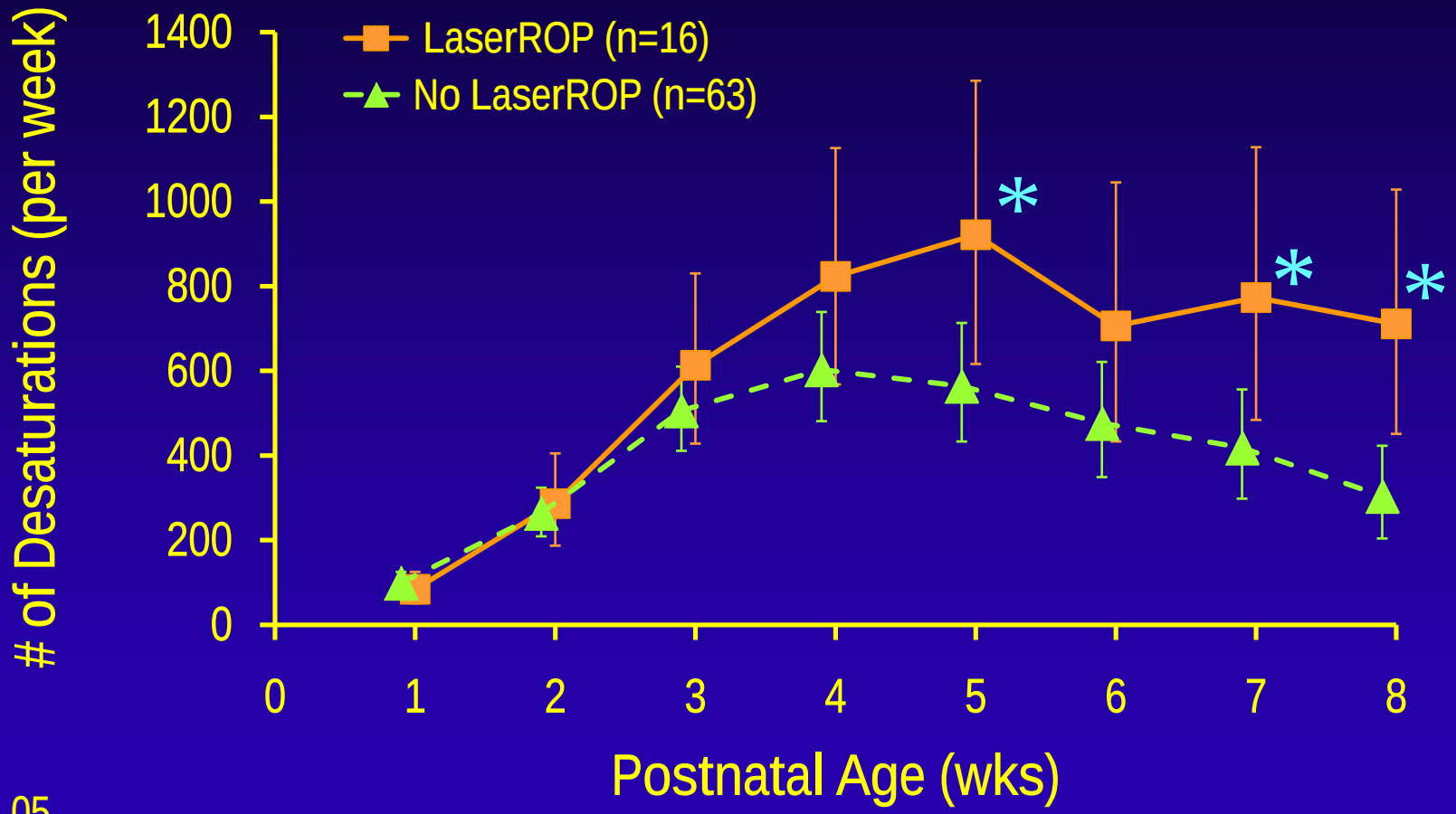


Role of Oxygenation in Genesis of ROP



Adapted from Chow, Pediatrics 2003

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

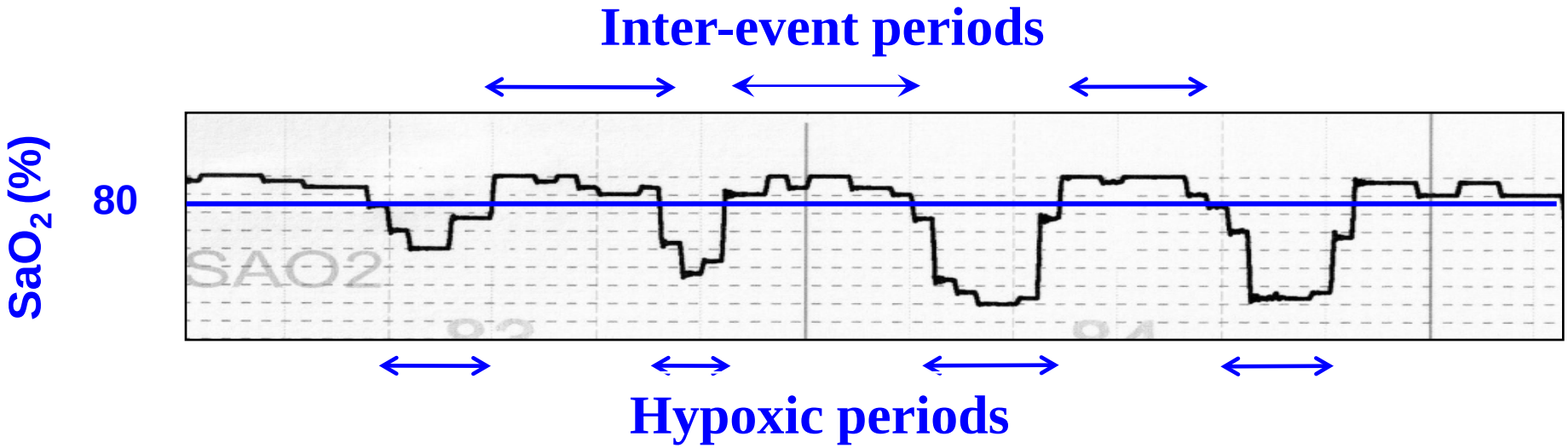


* p<.05

Mean± 95% confidence Interval

J Di Fiore: J Pediatr 2010

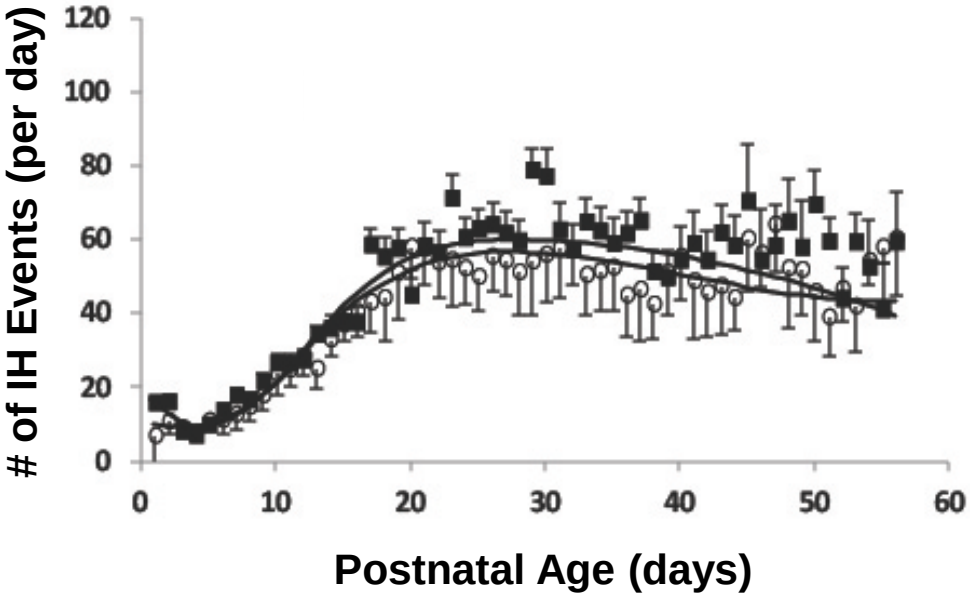
Timing of Intermittent Hypoxic Events



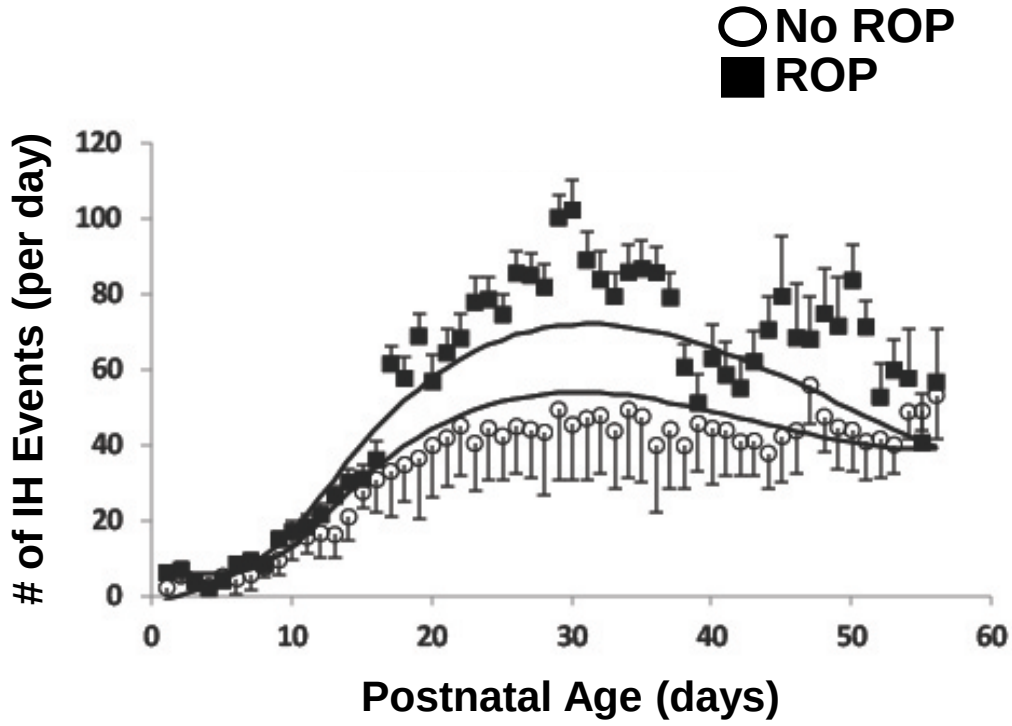
Di Fiore: Pediatr Res 2012

Effect of Time Interval Between Intermittent Hypoxic Events

Time Intervals <1 min

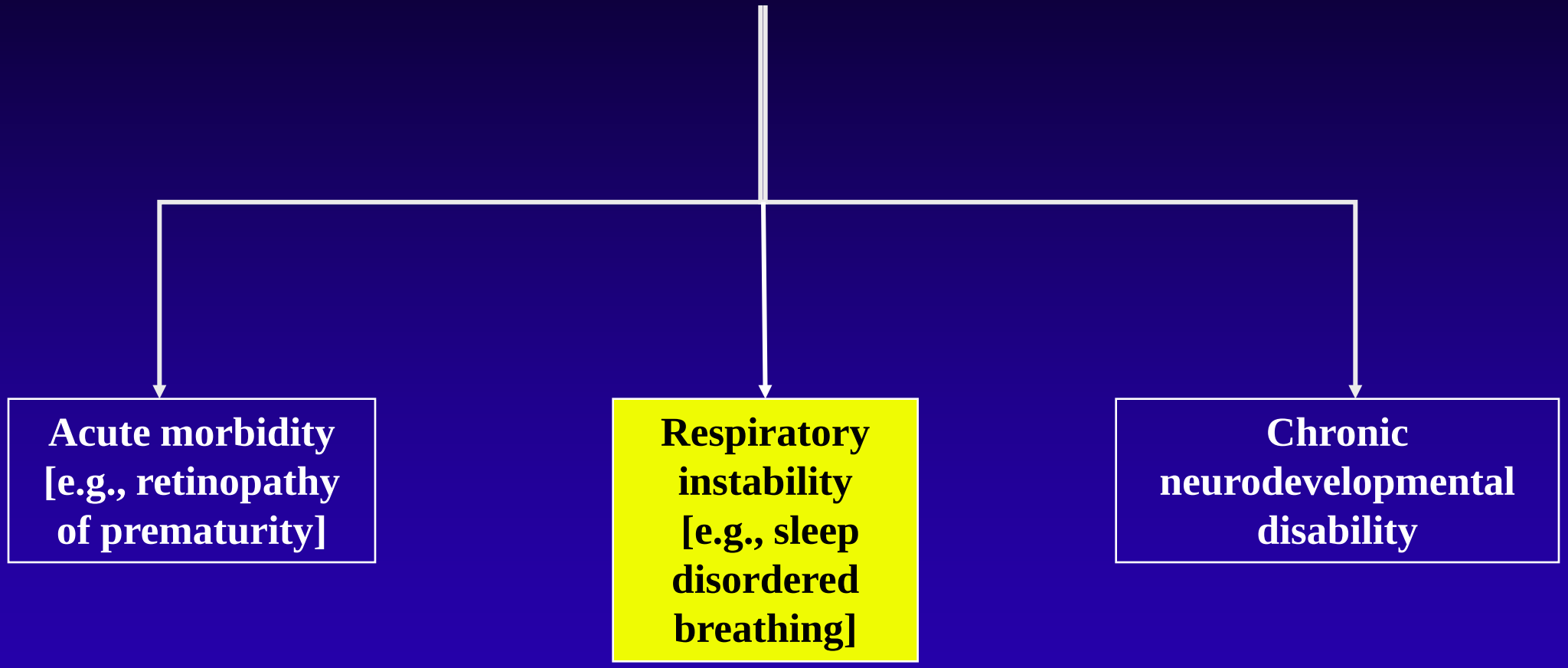


Time Intervals >1 min

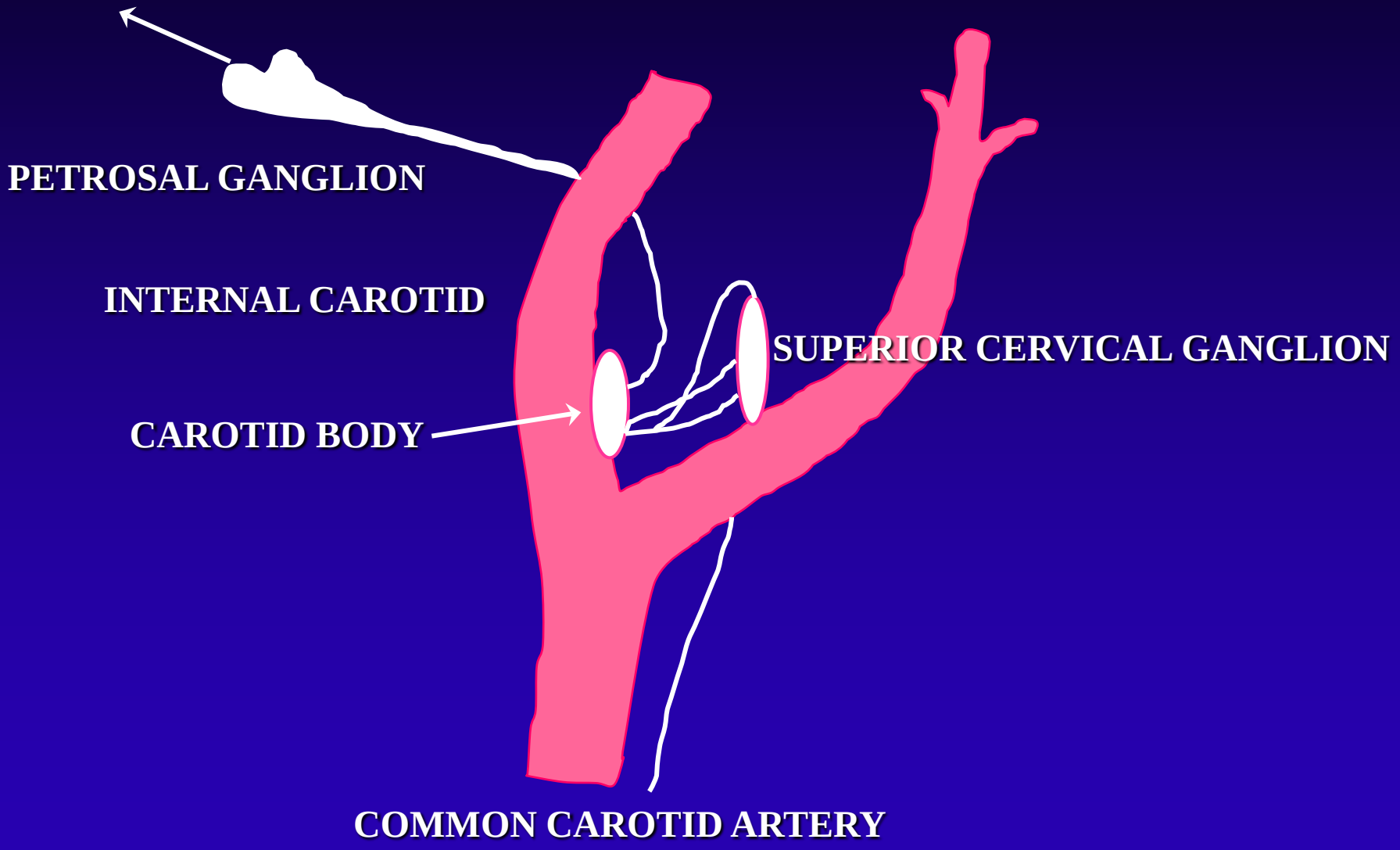


Di Fiore: Pediatr Res 2012

Proposed Morbidities of Intermittent Hypoxia



Anatomy of Carotid Bodies



Neurorespiratory Consequences of Chronic Intermittent Hypoxia

Chronic Intermittent Hypoxia

↓

Reactive Oxygen Species

↓

CAROTID BODY
gene/protein expression

↓

Sensitization of the Hypoxic Sensory Response

↓

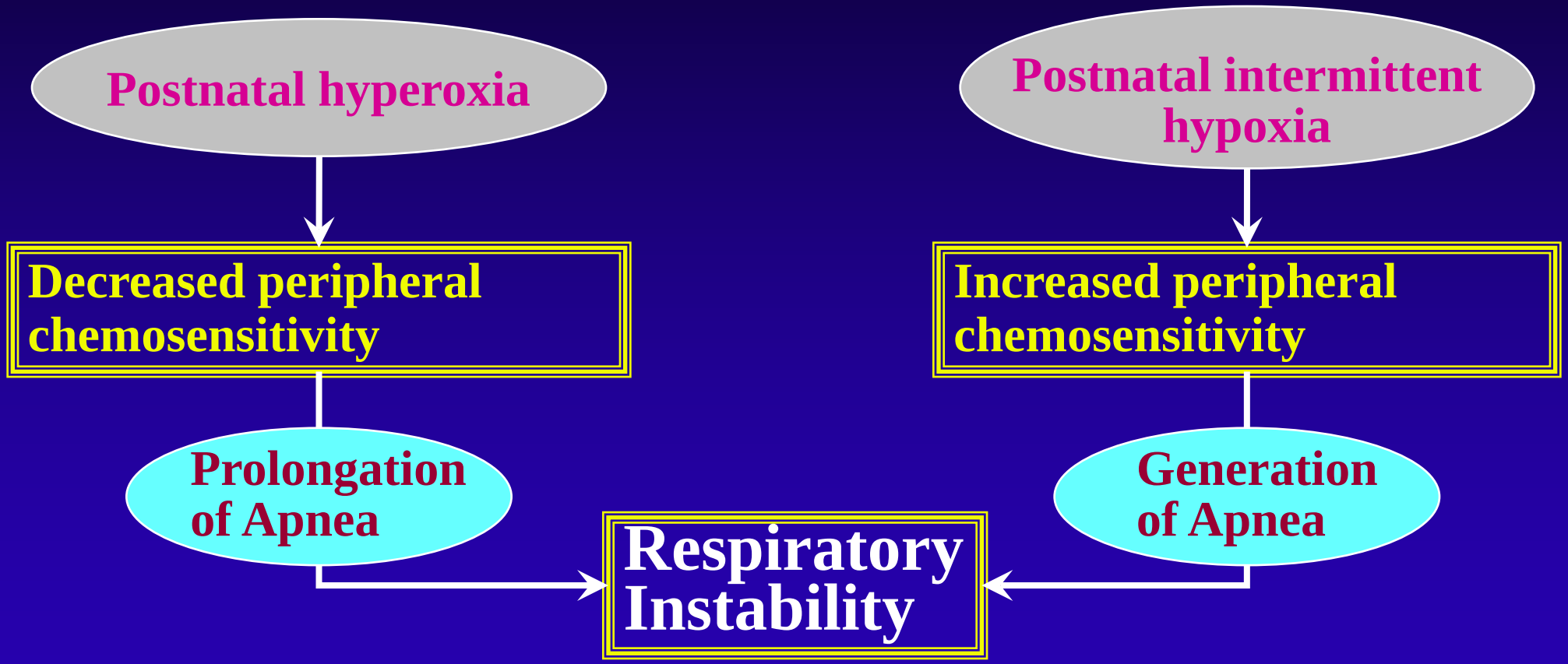
Unstable Breathing

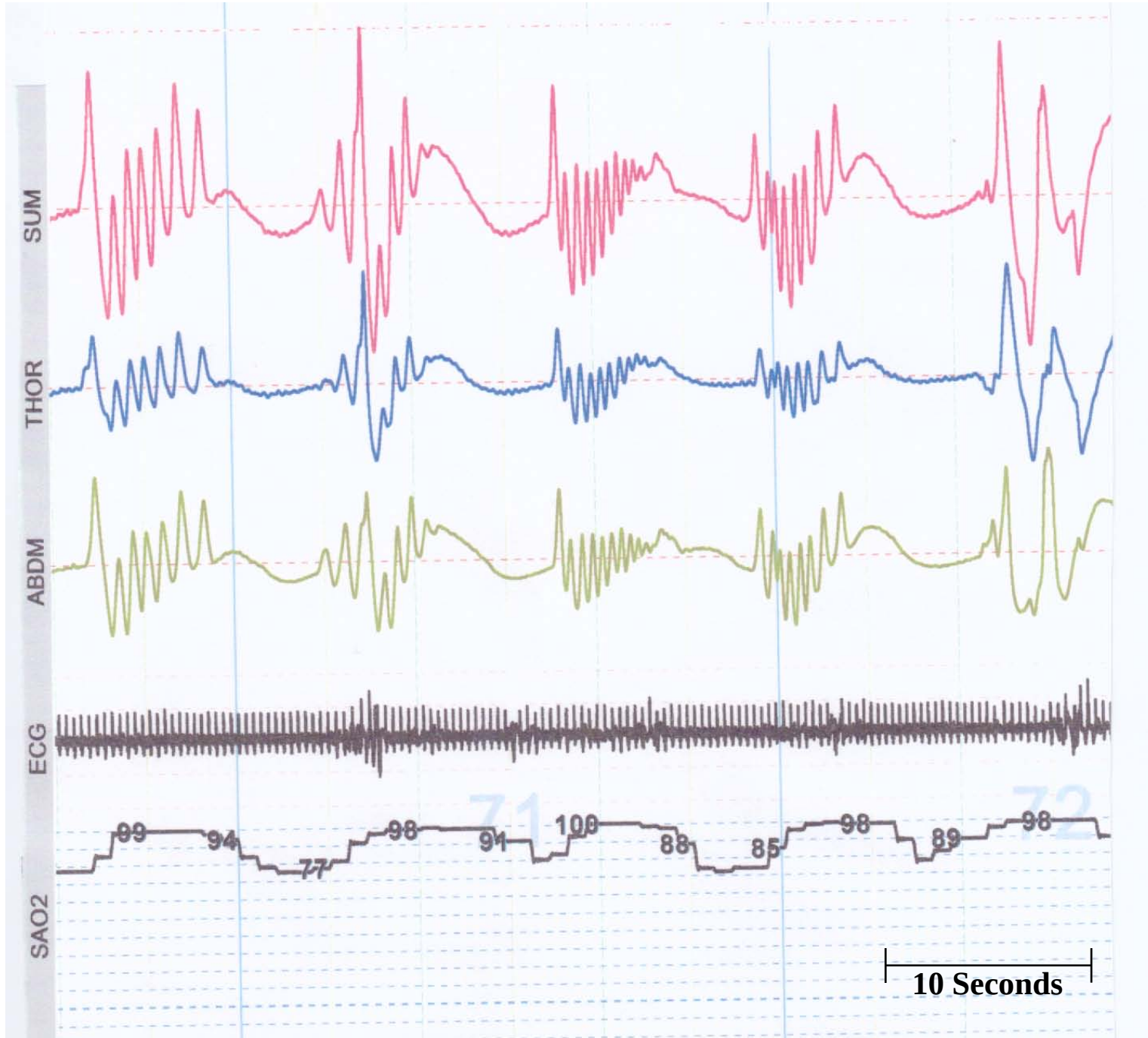
↓

Worsening of Apnea

Prabhakar, Respir Physiol Neurobiol 2007

Modulation of Peripheral Chemoreceptor Function During Development




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

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

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

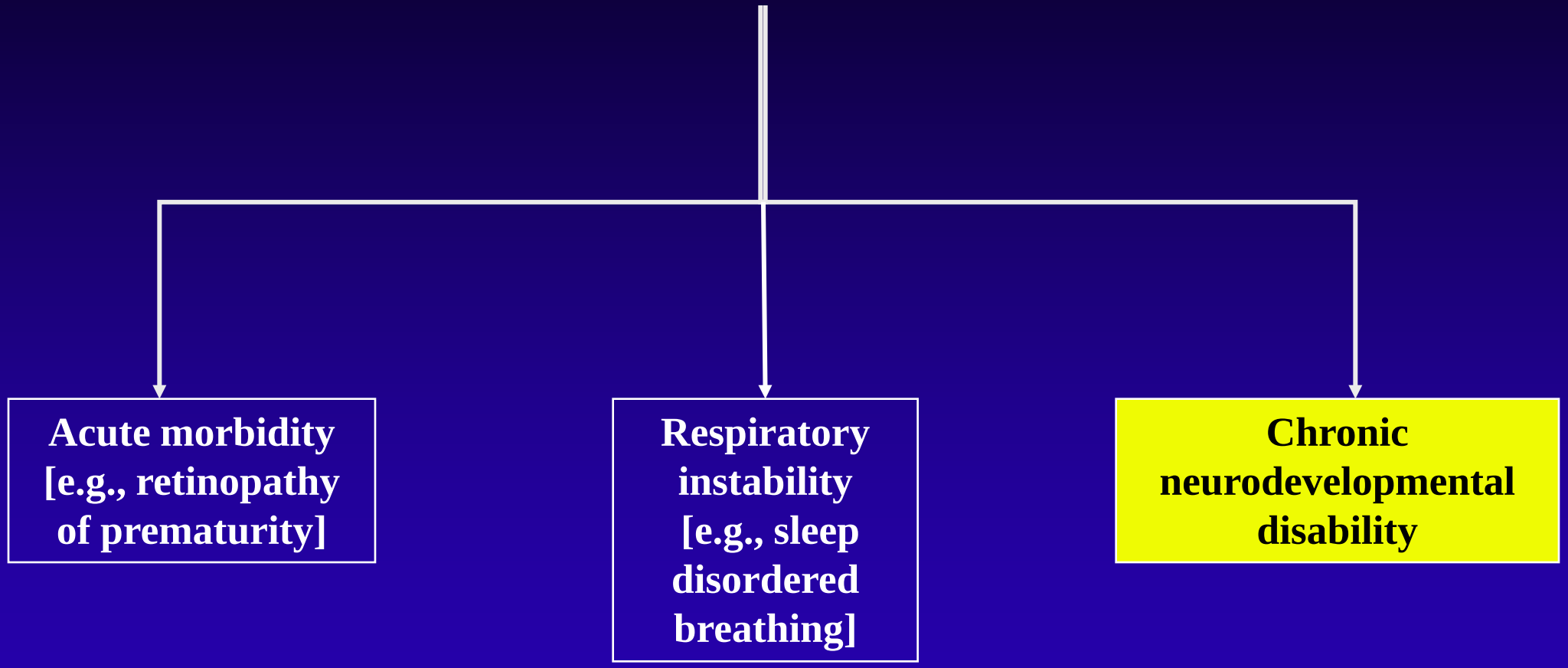
**** via Questionnaire***

Long-Term Effects of Caffeine Therapy for Apnea of Prematurity on Sleep at School Age

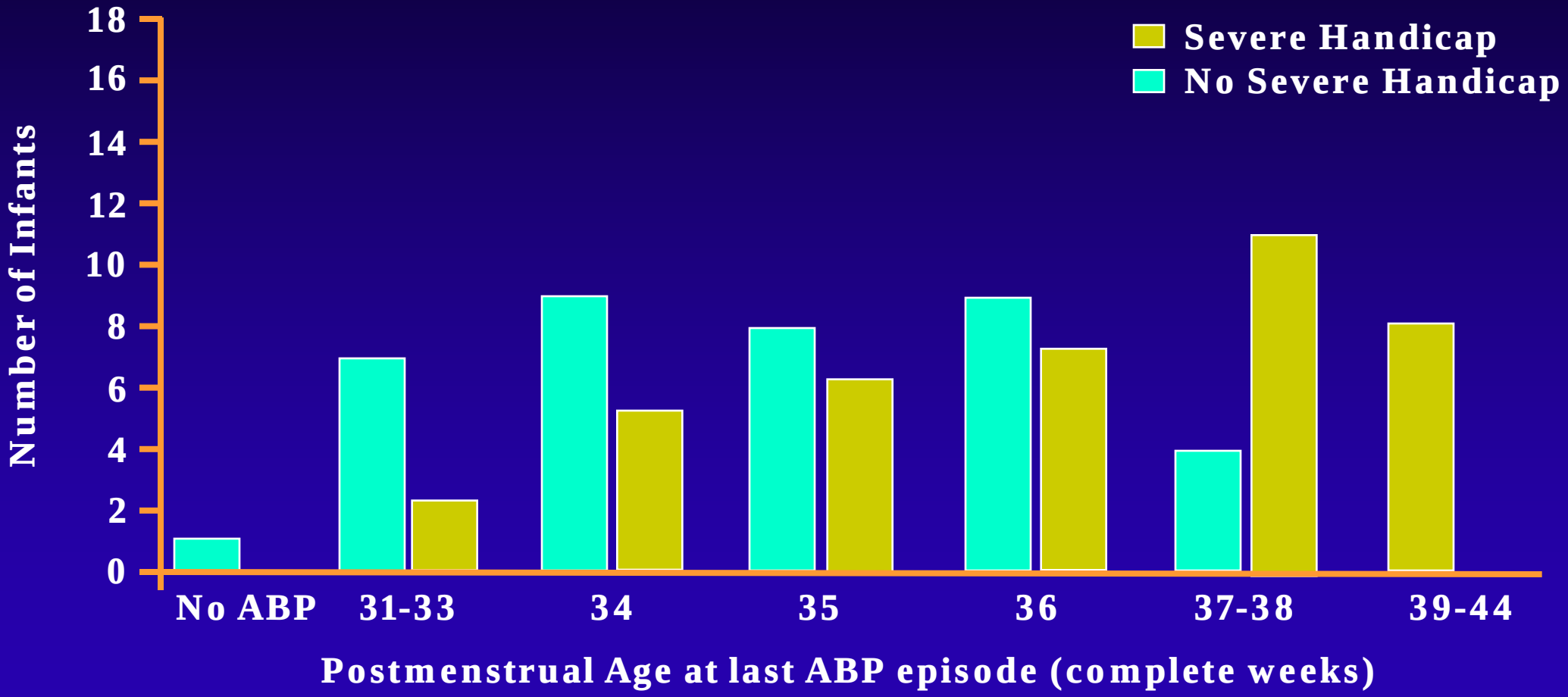
- The percentage of children with obstructive sleep apnea (8.2% of caffeine group versus 11.0% of placebo; $P = 0.22$)....was high, but did not differ significantly between groups.
- Ex-preterm infants, regardless of caffeine status, are at risk for obstructive sleep apnea....in later childhood.

Marcus CL: Am J Respir Crit Care Med 2014

Proposed Morbidities of Intermittent Hypoxia



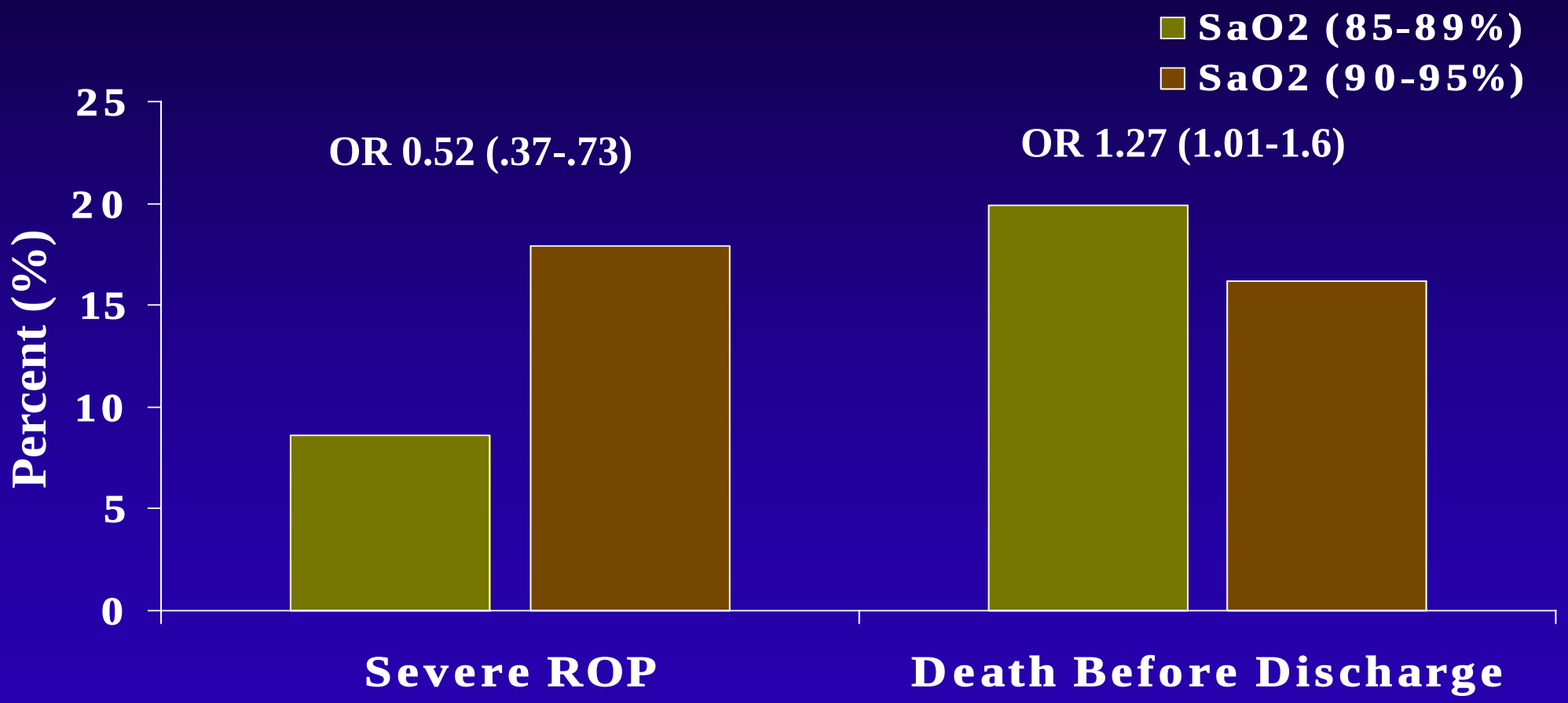
Persistence of Apnea and Bradycardia of Prematurity (ABP) is Associated with Poor Neurodevelopmental Outcome



In ELBWs is Targeting an SaO_2 of 85-89% vs 91-95% Associated with a Difference in Death or a Major Disability at a Corrected Age of 24 Months?

- SUPPORT (n=1316)
- BOOST II (n=1187)
- COT (n=1201)

Lower Baseline Ranges of Oxygen Saturation Decrease ROP but Increase Mortality in ELBW Infants

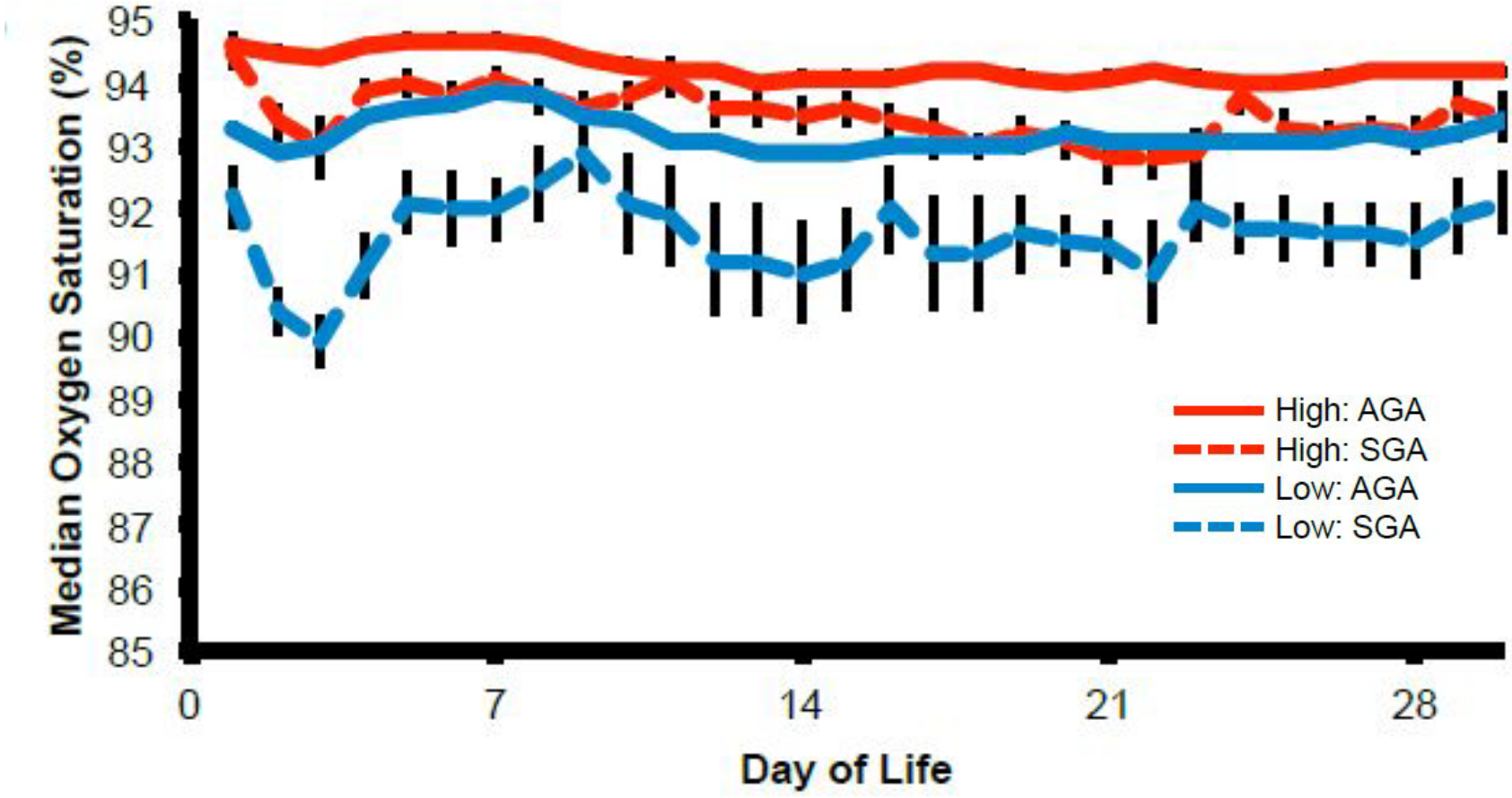


NEJM 2010

Tentative Conclusions

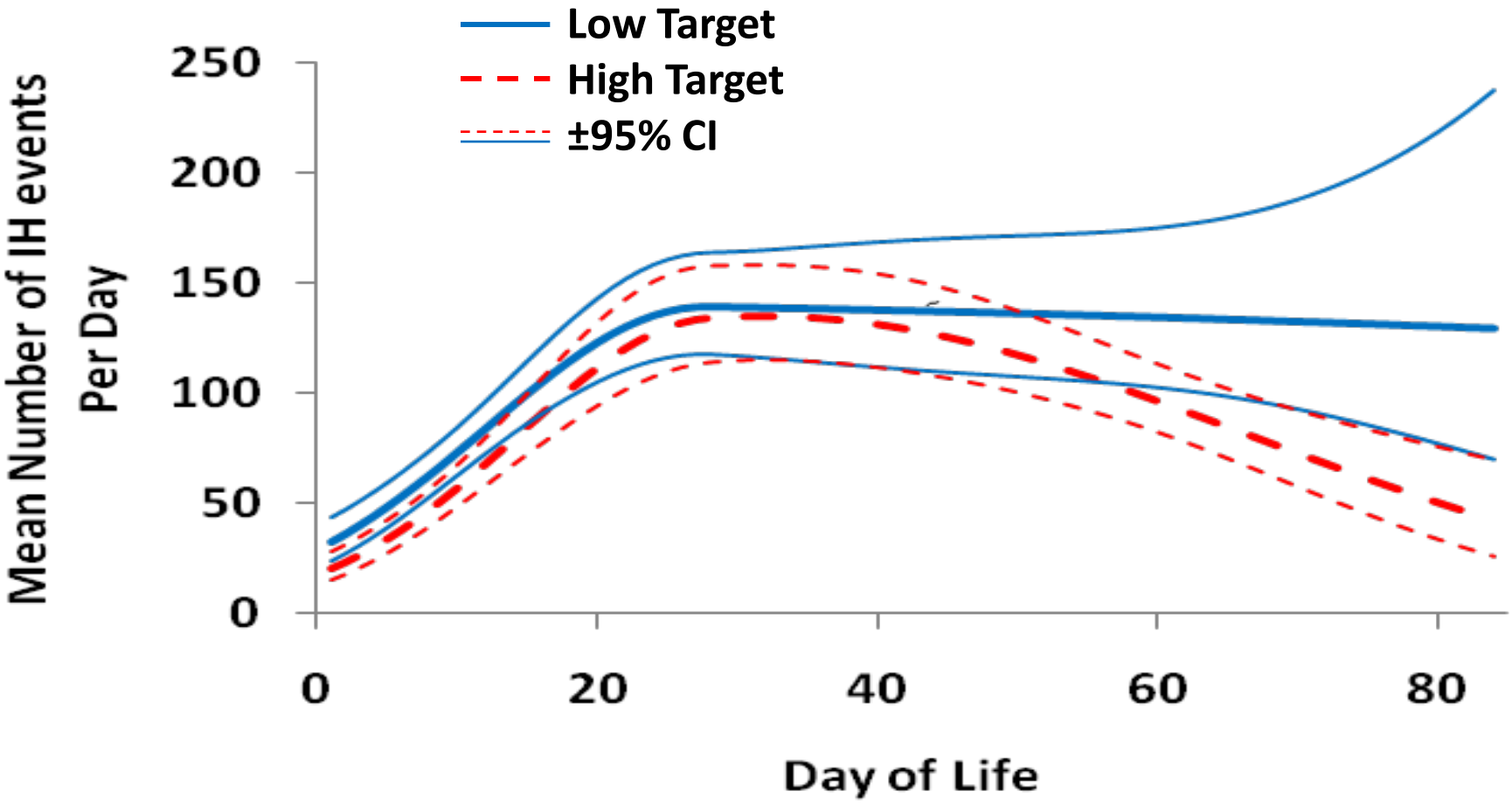
- "Collective data suggest that risks associated with restricting the upper SpO_2 target limit to 89% outweigh the benefits. Quality of evidence was moderate." · *Manja: Pediatrics 2017*
- "Recent RCTs suggest that a targeted oxygen saturation range of 90% to 95% may be safer than 85% to 89%, ***at least for some infants***." *Cummings & Polin: Pediatrics 2016*

Achieved Oxygen Saturation by Target Group and Growth Status



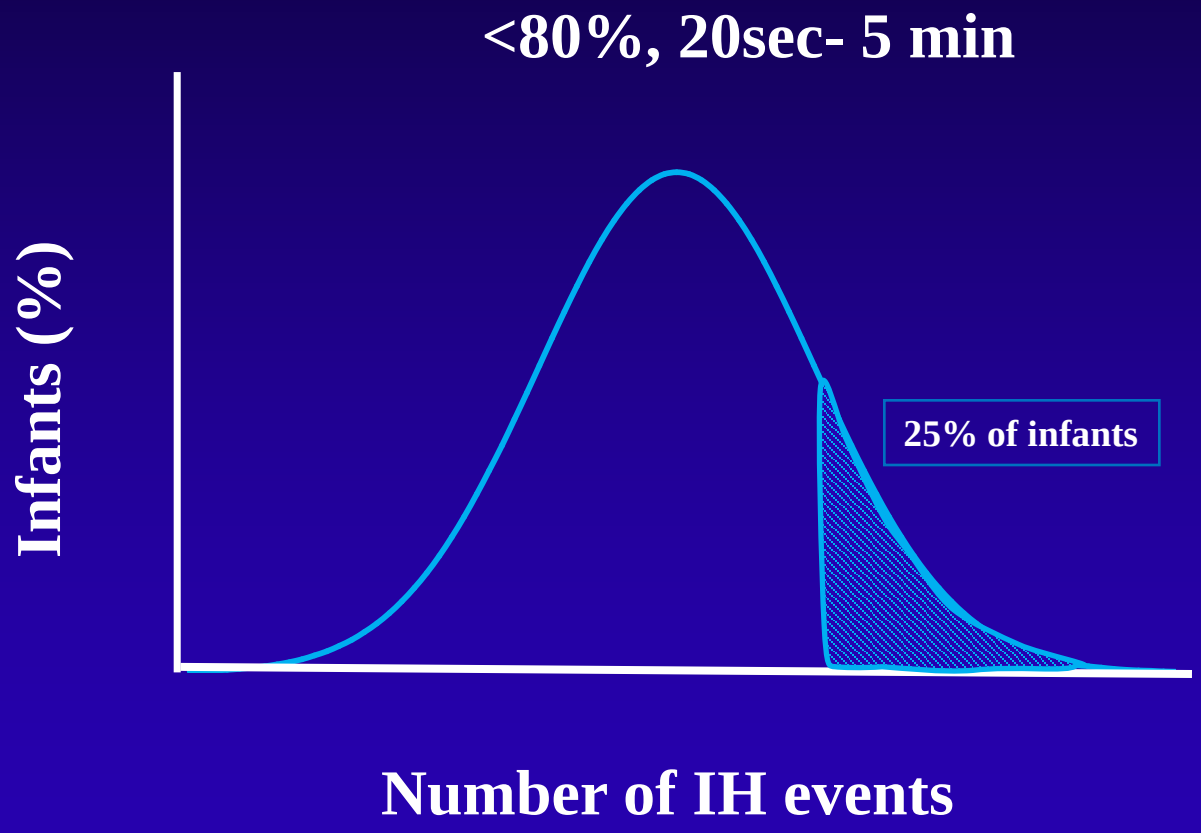
Di Fiore JM: J Pediatr 2017

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

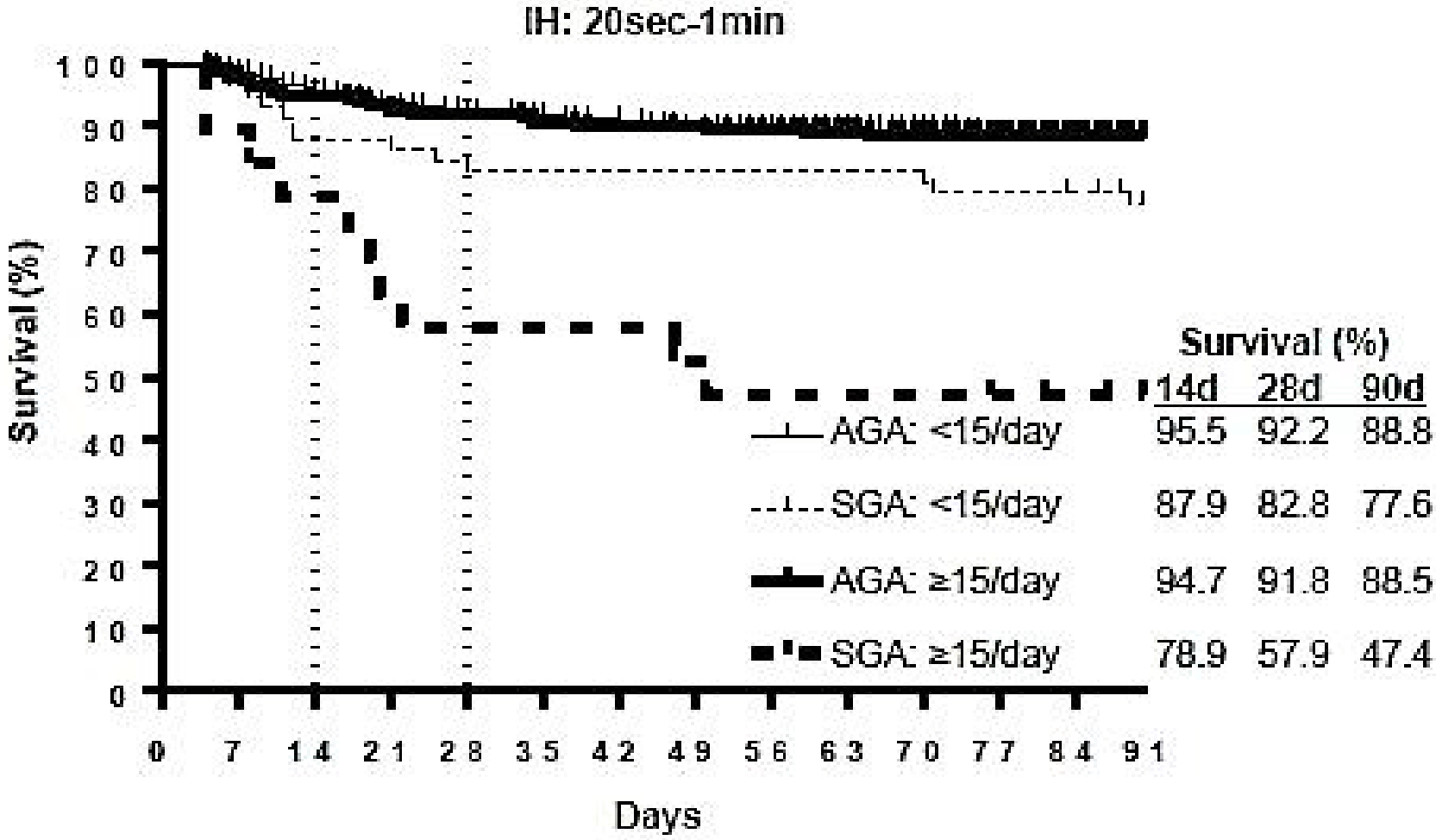


Di Fiore et al: J Pediatr, 2012

Intermittent Hypoxemic Events During the First 3 Days of Life



Effect of Growth Status and Shorter [20 sec-1 min] IH Events in Days 1-3 on Survival



Di Fiore JM: J Pediatr 2017

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."

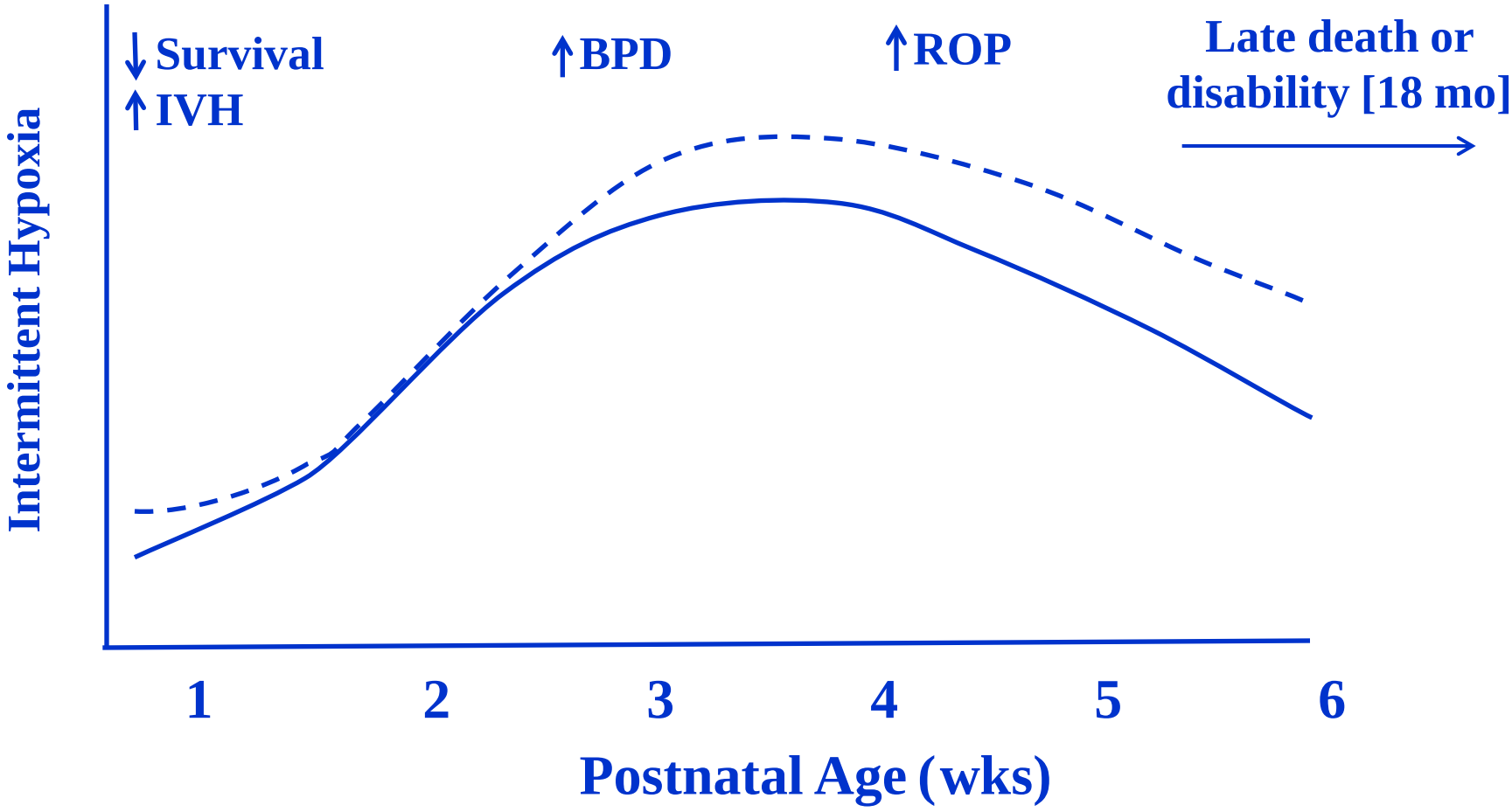
Poets CF et al: JAMA, 2015

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

Association between Intermittent Hypoxia and Adverse Outcomes



Modified from: J Di Fiore

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- Historical perspective
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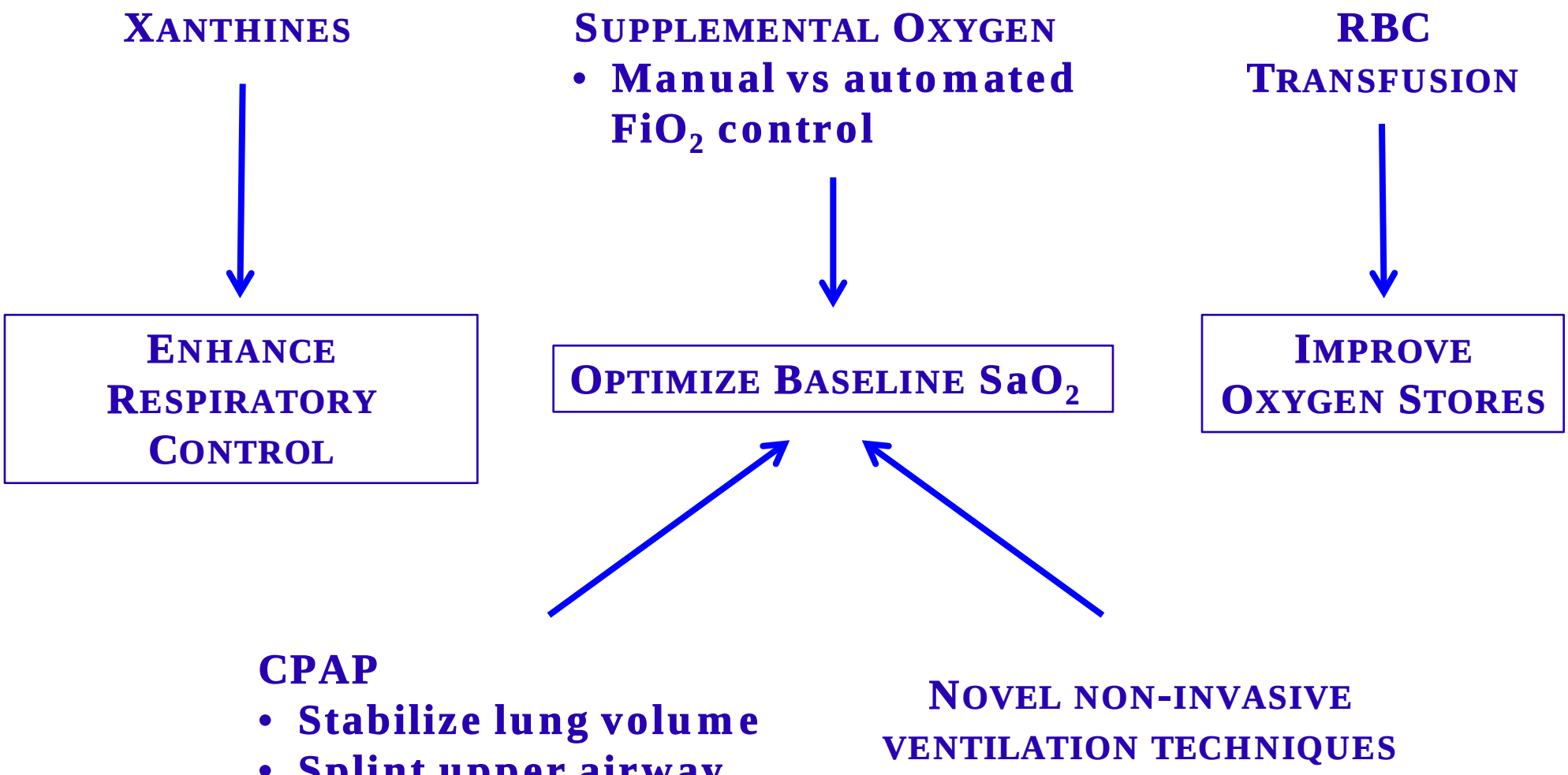
- ***Treatment strategies***

Treatment Strategies for Intermittent Hypoxia



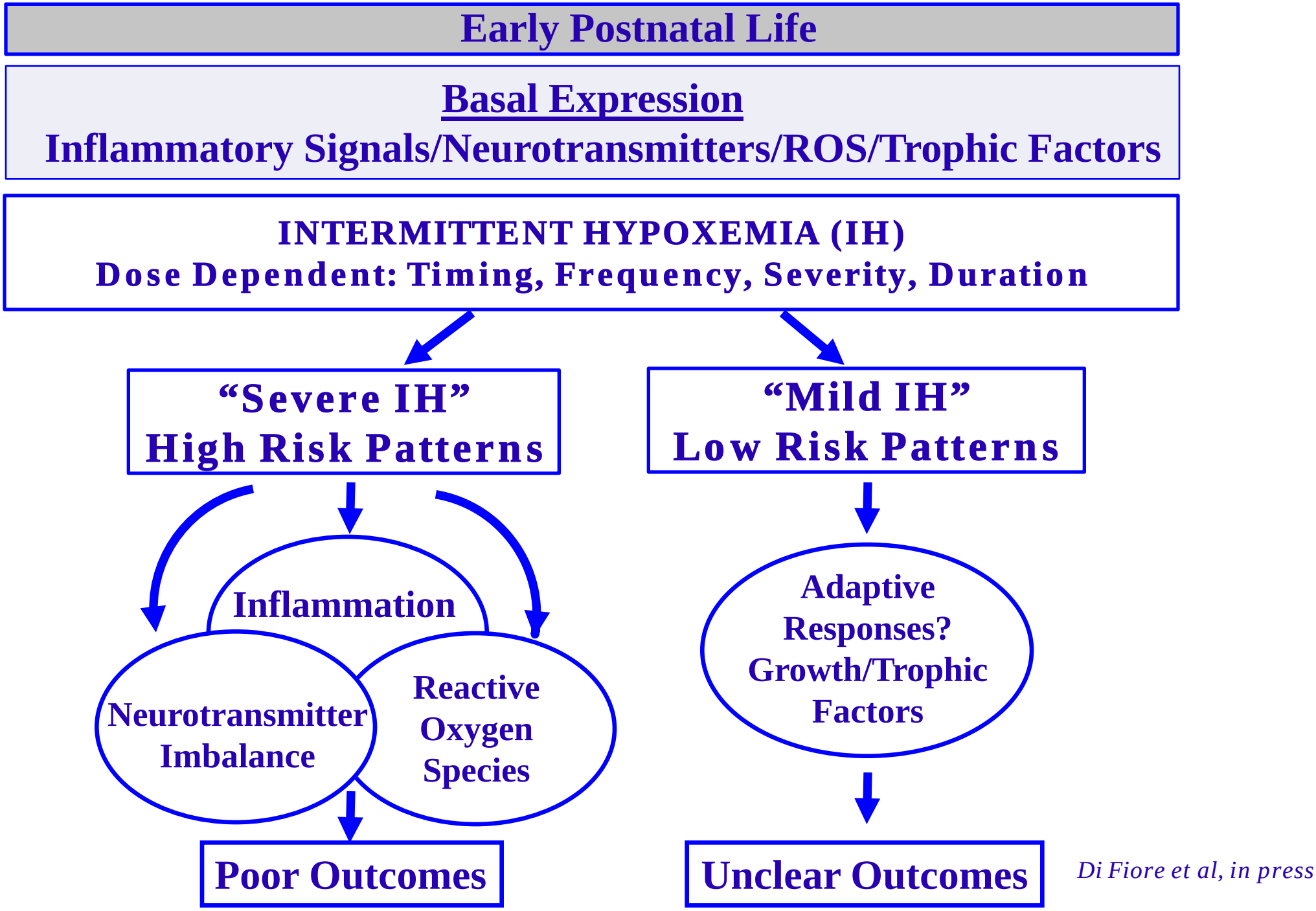
NEONATOLOGY
Karger Publishers

Doxapram Treatment for Apnea of Prematurity: A Systematic Review

Roseanne J.S. Vliegenthart,* Christine H. ten Hove, Wes Onland, and Anton H.L.C. van Kaam

Conclusion:
Based on the limited number of studies and level of evidence, no firm conclusions on the efficacy and safety of doxapram in preterm infants can be drawn. For this reason, routine use cannot be recommended.

Neonatology 2017



Di Fiore et al, in press