Lessons Learned from a Career in Neonatal Research

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Rainbow Babies & Children's Hospital

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

Lessons Learned…

- Seize opportunities and energetic mentorship
- Hang in there and formulate the next question
- Lessons learned from animal models
- Take opportunities to engage in clinical trials

Maureen Hack, M.D., Marshall H. Klaus, M.D., Avroy A. Fanaroff, M.D.

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

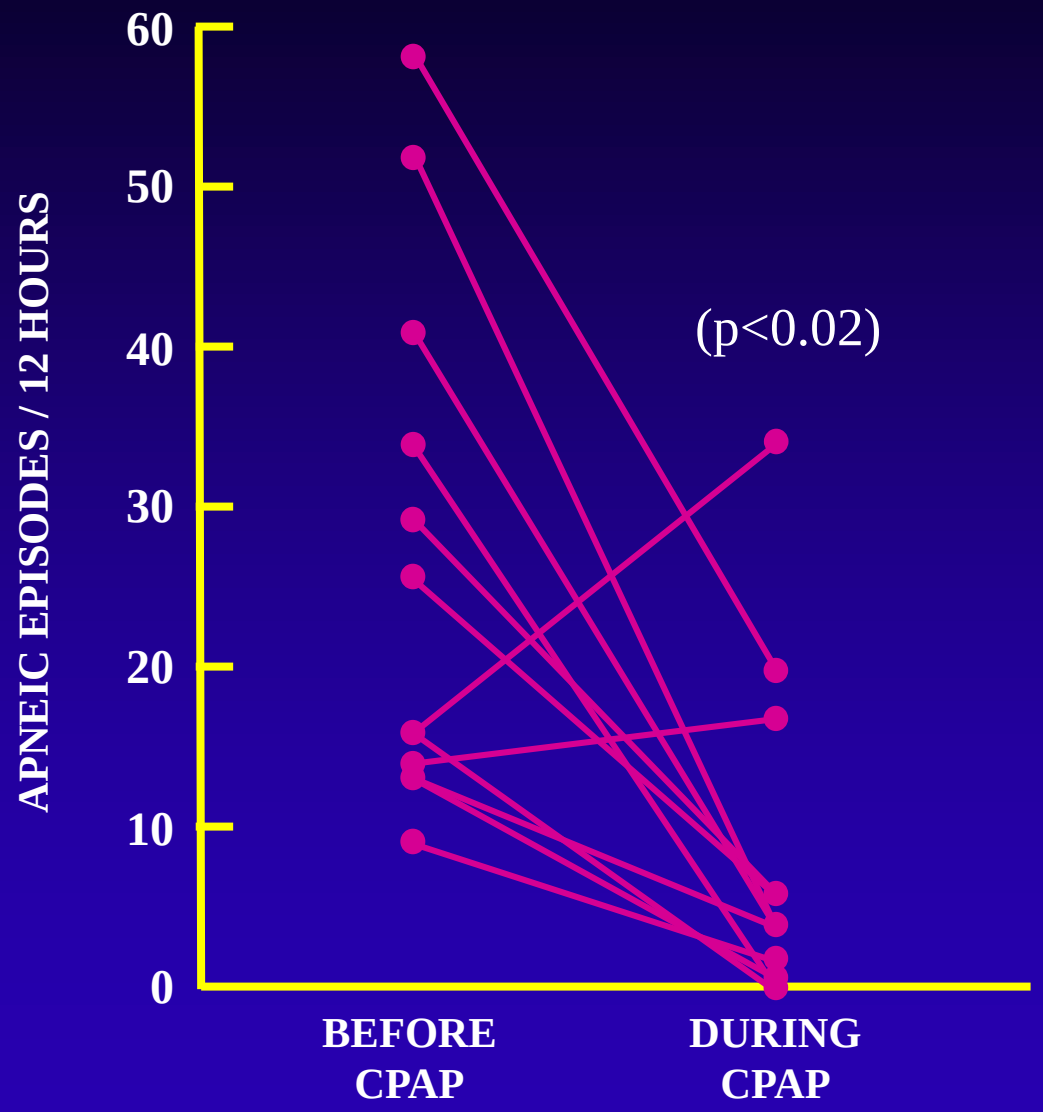
William J. R. Daily, M.A., M.D., Marshall Klaus, M.D., and H. Belton P. Meyer, M.D.

ABSTRACT

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

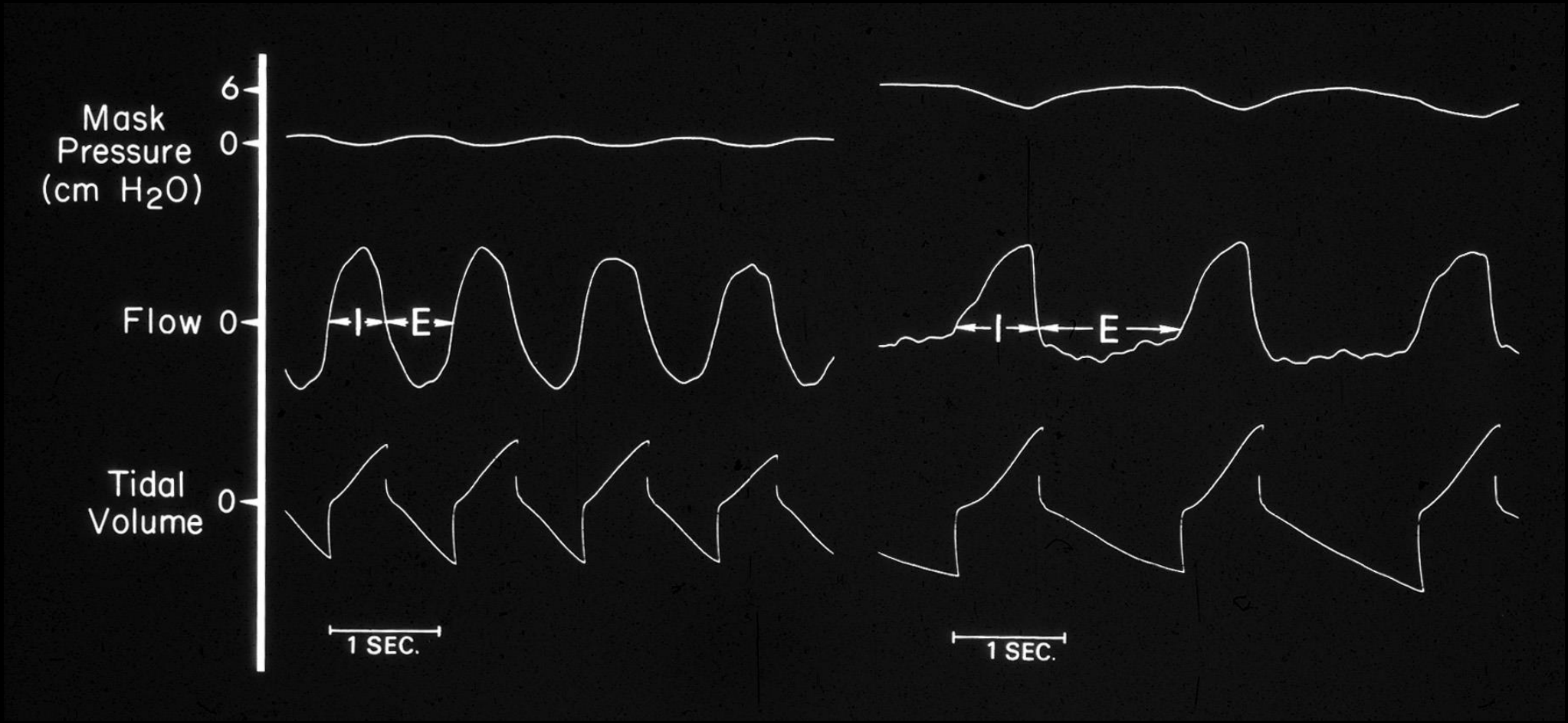
Pediatrics 1969

Effect of CPAP on Incidence of Apnea



Kattwinkel 1975

Effect of CPAP on Respiratory Timing



Martin et al: J Appl Physiol 1978

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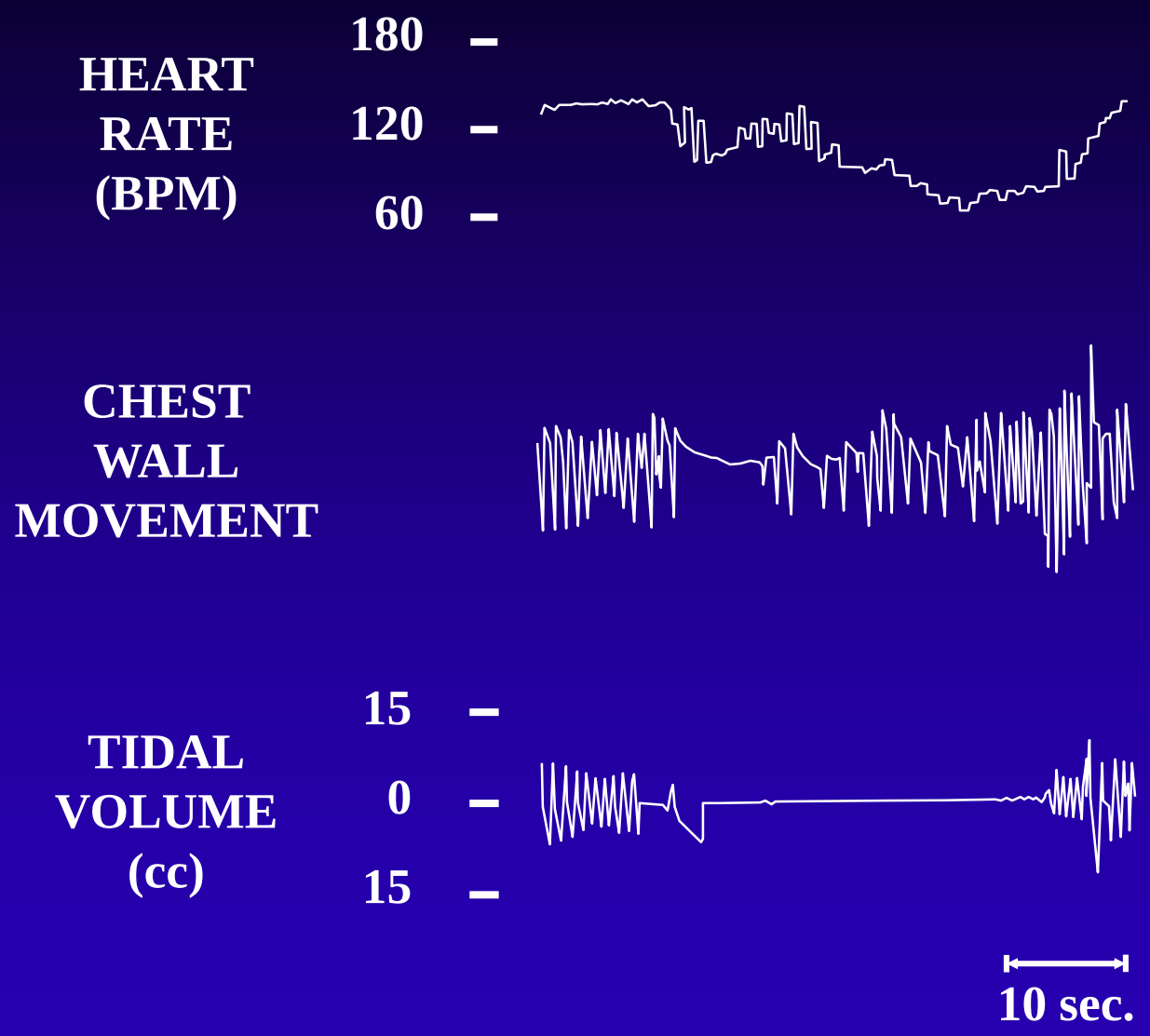
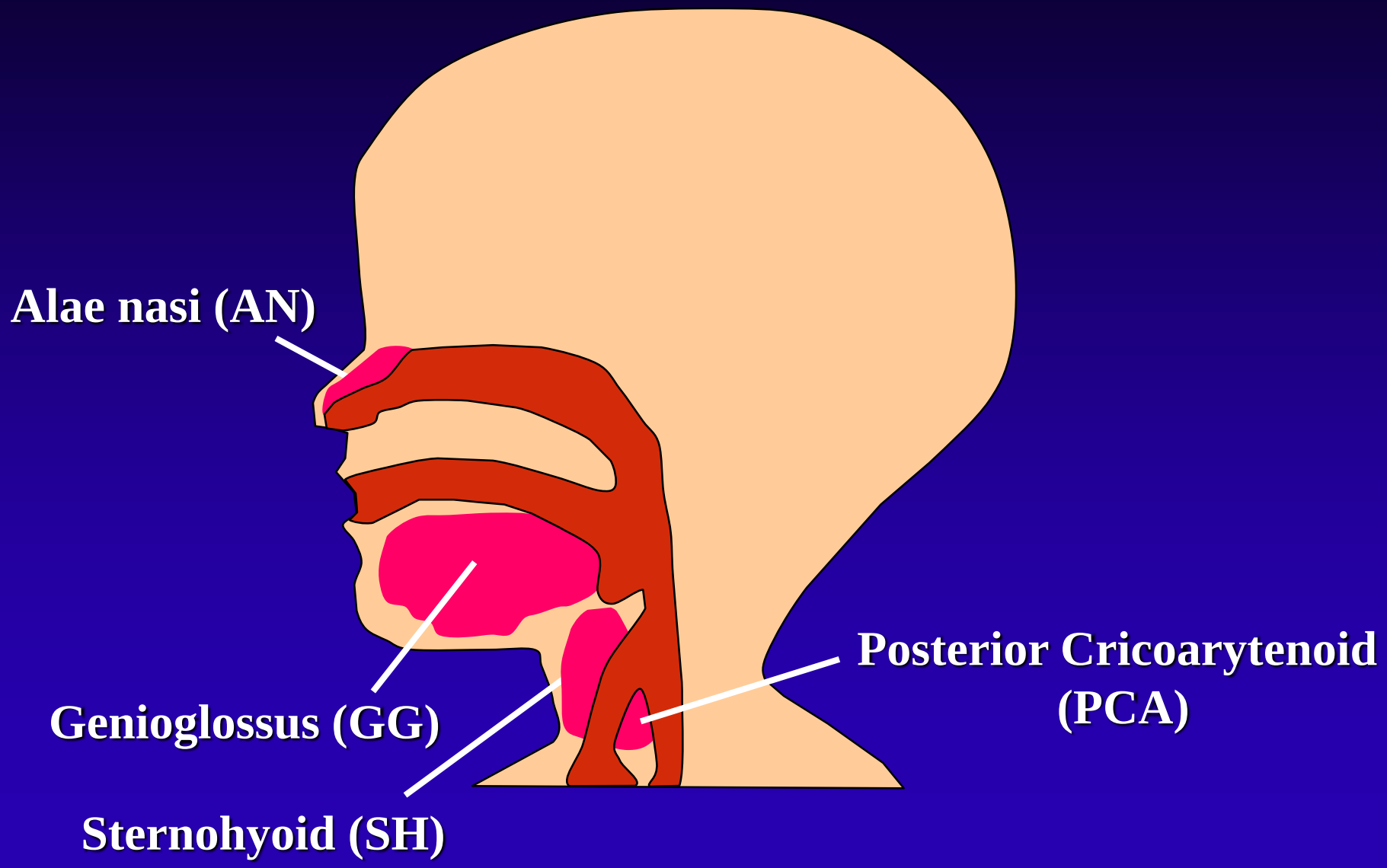
Mixed Apnea


HEART RATE (BPM)
180
120
60
CHEST WALL MOVEMENT
TIDAL VOLUME (cc)
15
0
15
10 sec.

Physiologic Data From Upper Airway Dilator Muscles During Development



Nasal CPAP for Neonatal Apnea

- *Decrease in upper airway resistance*
- Increase in FRC
- Improvement in oxygenation

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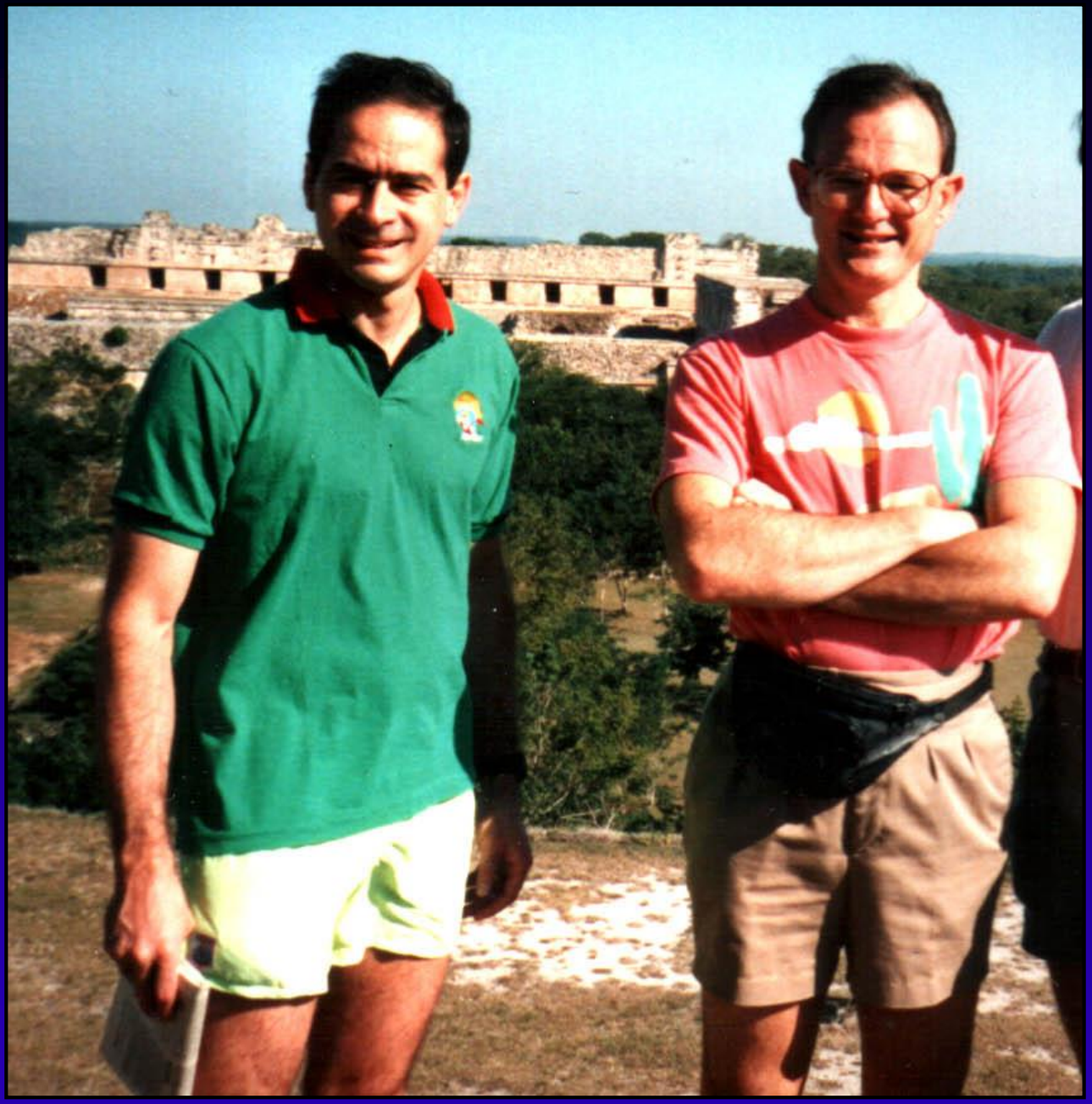
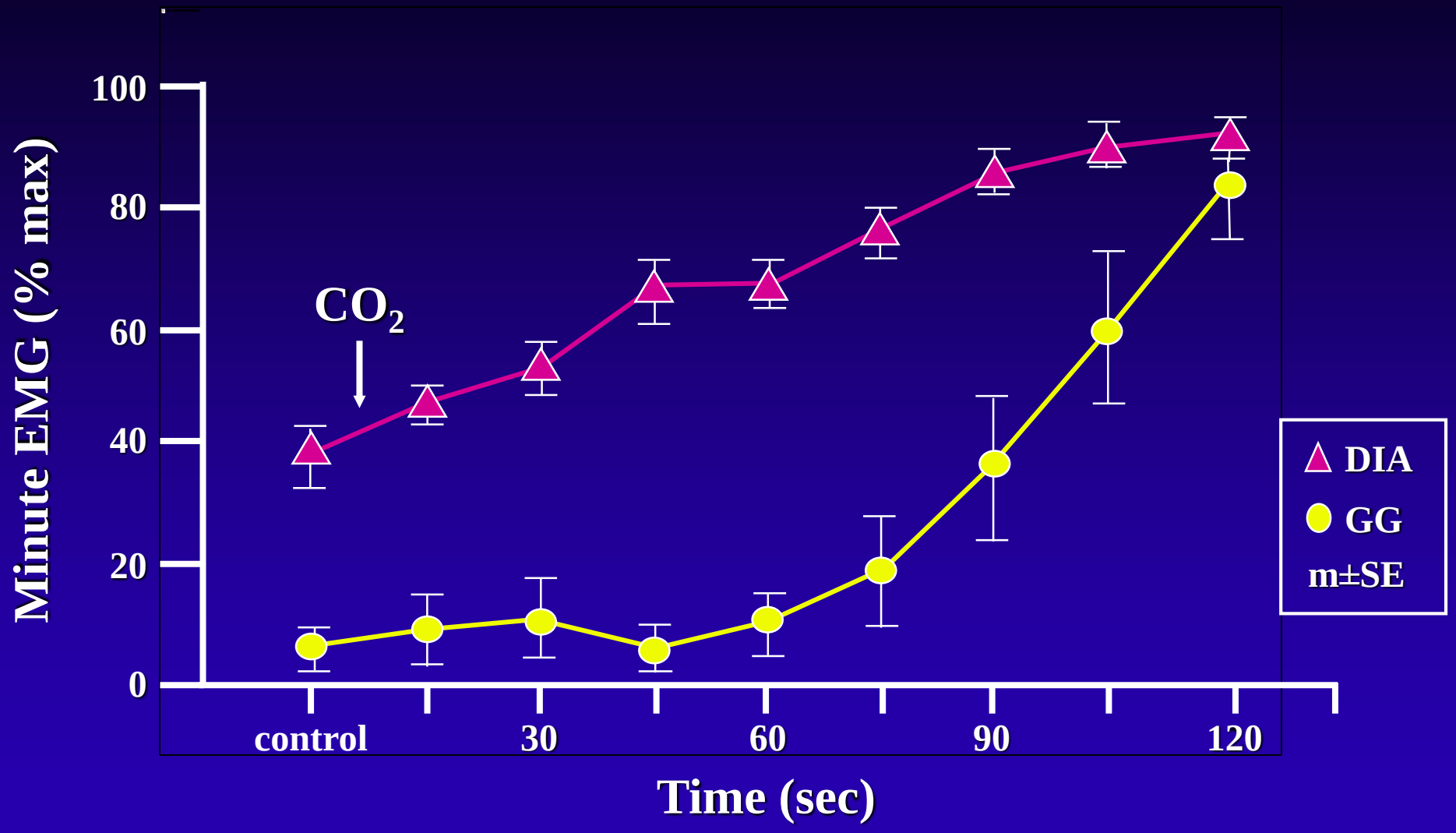


Mexico
[undated]

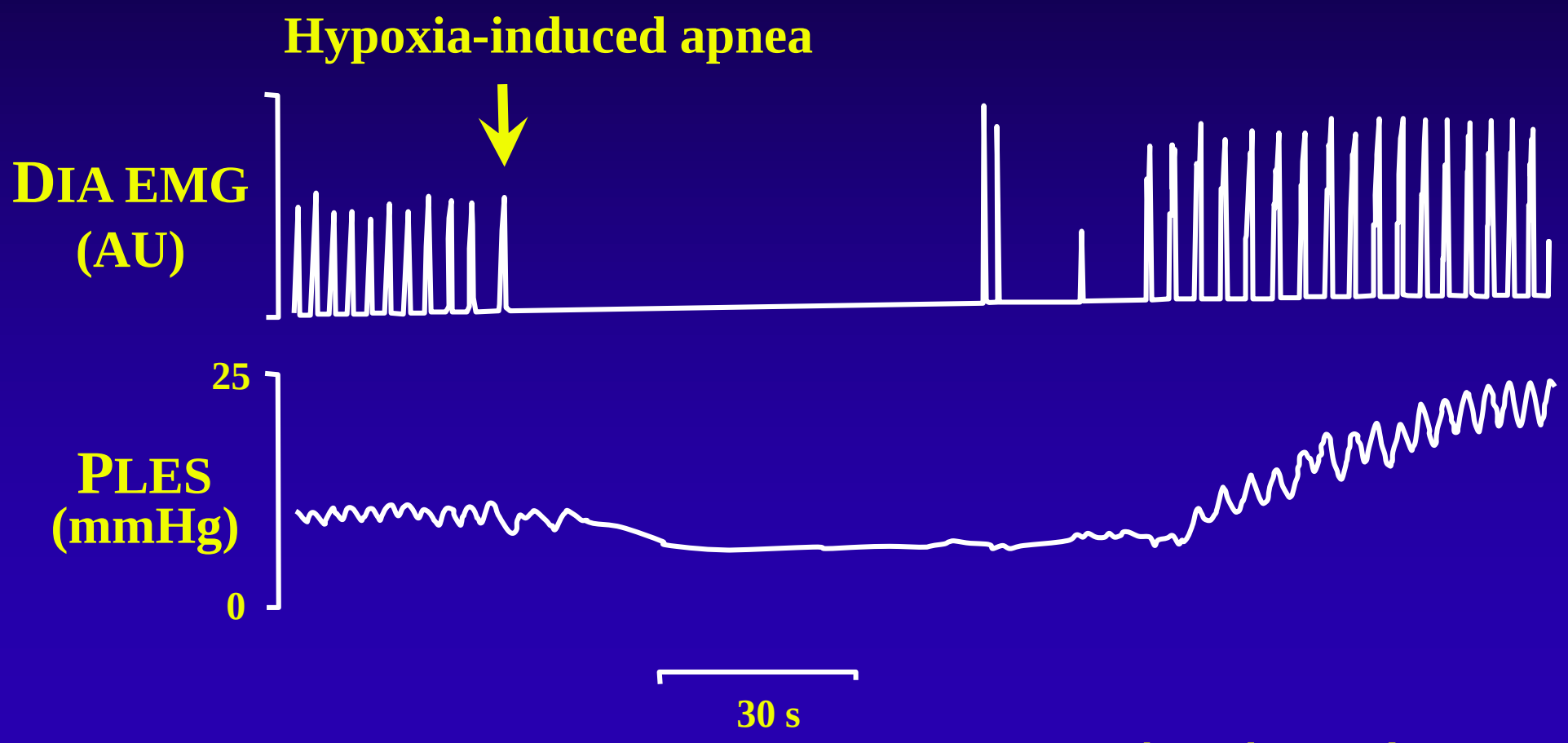
Bedside to Bench to Bedside

CO_2 Threshold of Respiratory Muscles



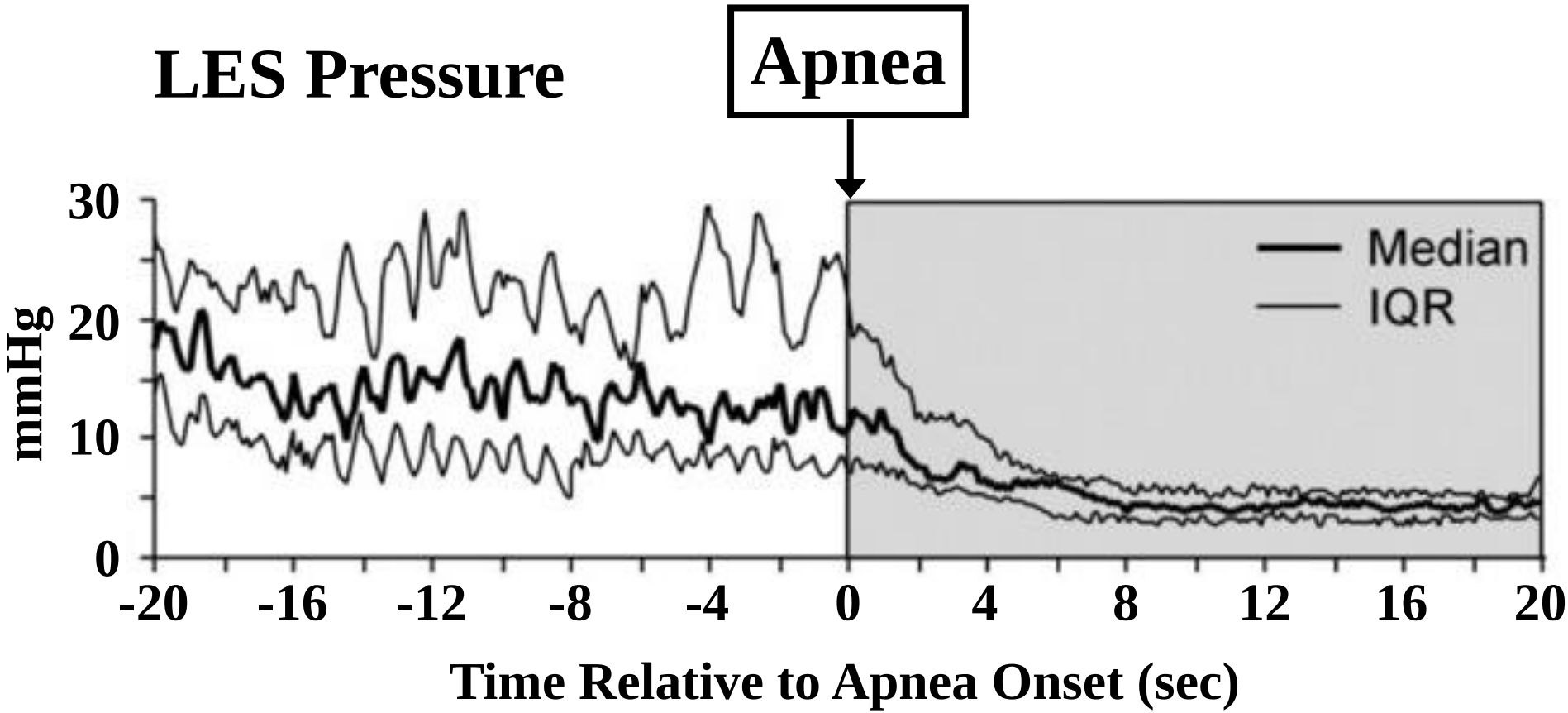
Carlo: J Appl Physiol 1988

Respiratory Control and LES Pressure



Kiatchoosakun, Pediatr Res 2002

LES Pressure Associated with Apnea Onset



Omari, J Pediatr 2009

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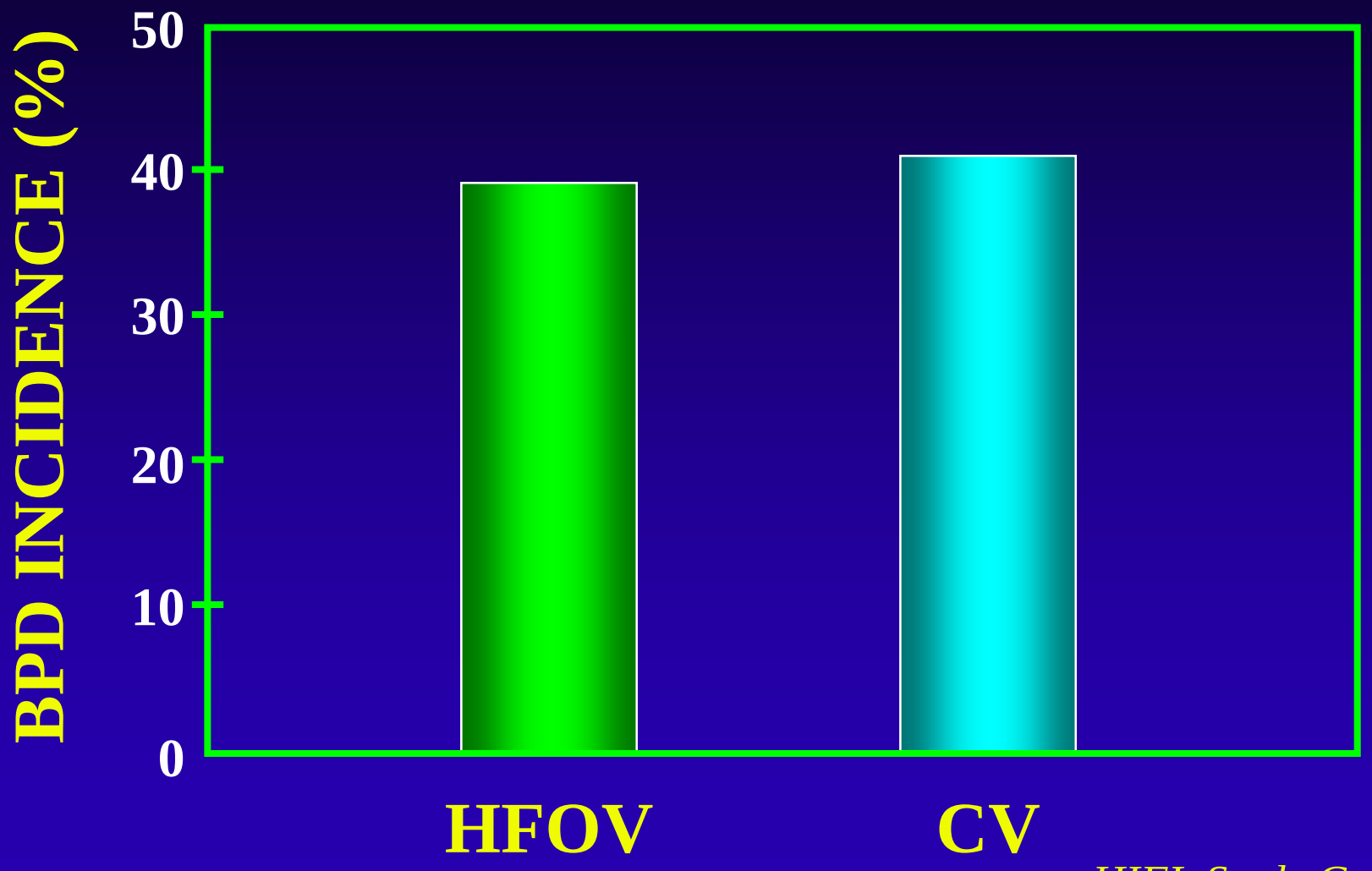
Lessons from Clinical Trial Opportunities

- HIFI Study, NEJM 1989
- CHIME Study, JAMA 2001
- NO CLD, NEJM 2006
- PreVent, 2016-

HFOV to Prevent BPD



HIFI Study Group, 1989

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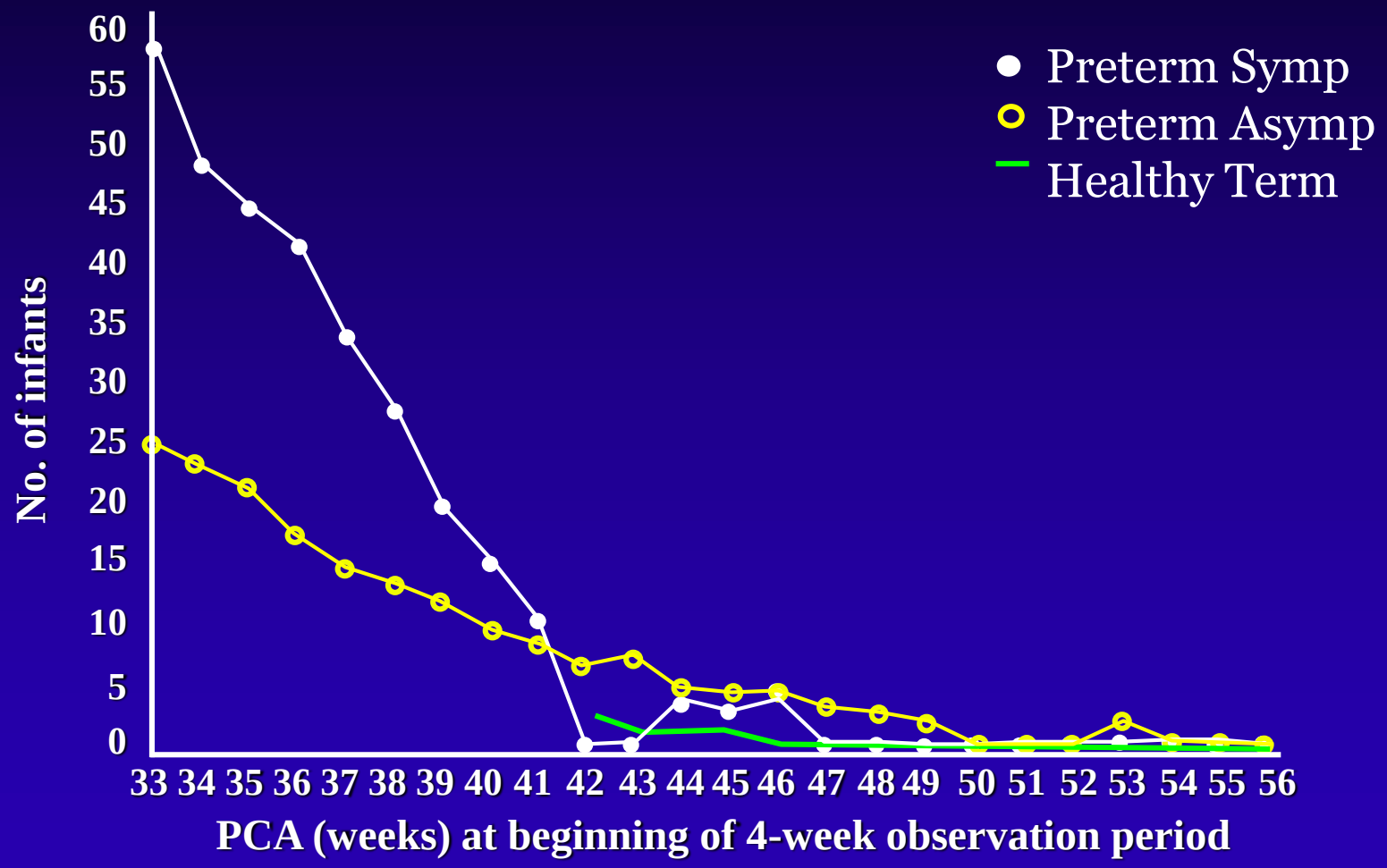
Infants with ≥ One Extreme Event per 20,000 Monitor Hours



CHIME Study: JAMA 2001

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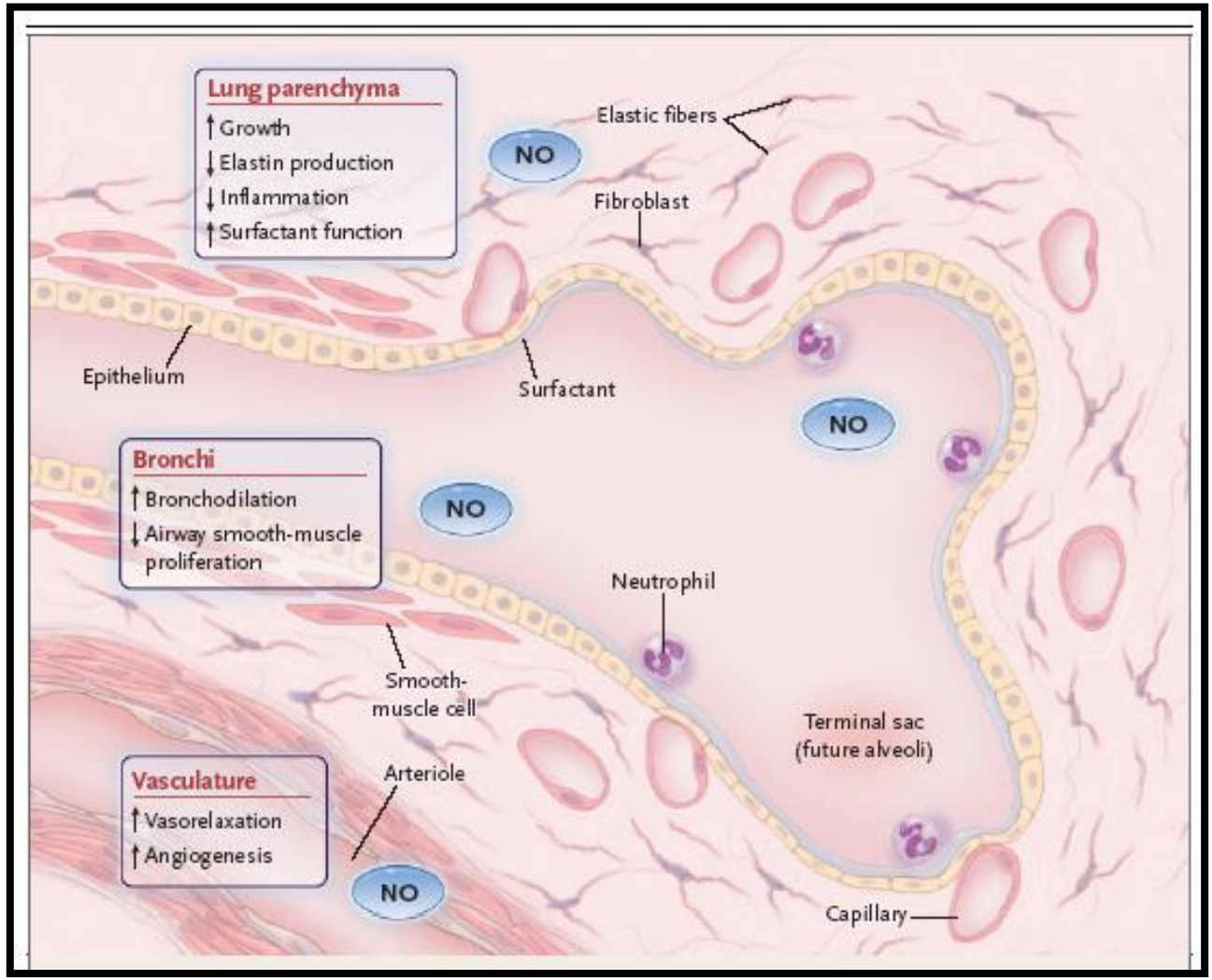
Proposed Effects of Nitric Oxide on the Development of the Respiratory System



Martin RJ: N Engl J Med 2005

NIH Consensus Development Conference: Inhaled Nitric Oxide for Premature Infants

- "Available evidence does not support use of iNO in routine care of premature infants who require respiratory support".
- "Future research should seek to understand the gap between benefits on lung development and function suggested by basic research and animal studies, and the results of clinical trials to date".

Pediatrics 2011

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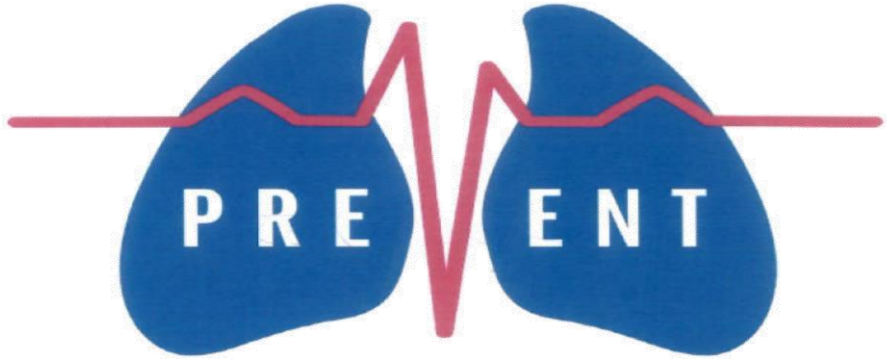
- NO CLD, NEJM 2006
- PreVent, 2016-

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



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Univ Miami • Washington Univ • UVA

So….
Does Apnea of Prematurity Still Matter?

- Serves as a biologic link between the lung and brain
- May contribute to pulmonary morbidity via need for increased respiratory support
- May contribute to neurodevelopmental morbidity via intermittent hypoxic episodes
- Prolongs hospitalization and cost