APNEA AND CONTROL OF BREATHING

CHRISTA MATRONE, M.D., M.ED.

DIOMEL DE LA CRUZ, M.D.

OBJECTIVES

- Define Apnea
- Review Causes and Appropriate Evaluation of Apnea in Neonates
- Review the Pathophysiology of Breathing Control and Apnea of Prematurity
- Review Management Options for Apnea of Prematurity
  - The Clinical Evidence for Caffeine
  - The Role of Gastroesophageal Reflux

DEFINITION OF APNEA

- Cessation of breathing for greater than 15 (or 20) seconds
  - Or if accompanied by desaturations or bradycardia
- Differentiate from periodic breathing
  - Regular cycles of respirations with intermittent pauses of >3 S
  - Not associated with other physiologic derangements
  - Benign and self-limiting

TYPES OF APNEA

CENTRAL

- Total cessation of inspiratory effort
- Absence of central respiratory drive

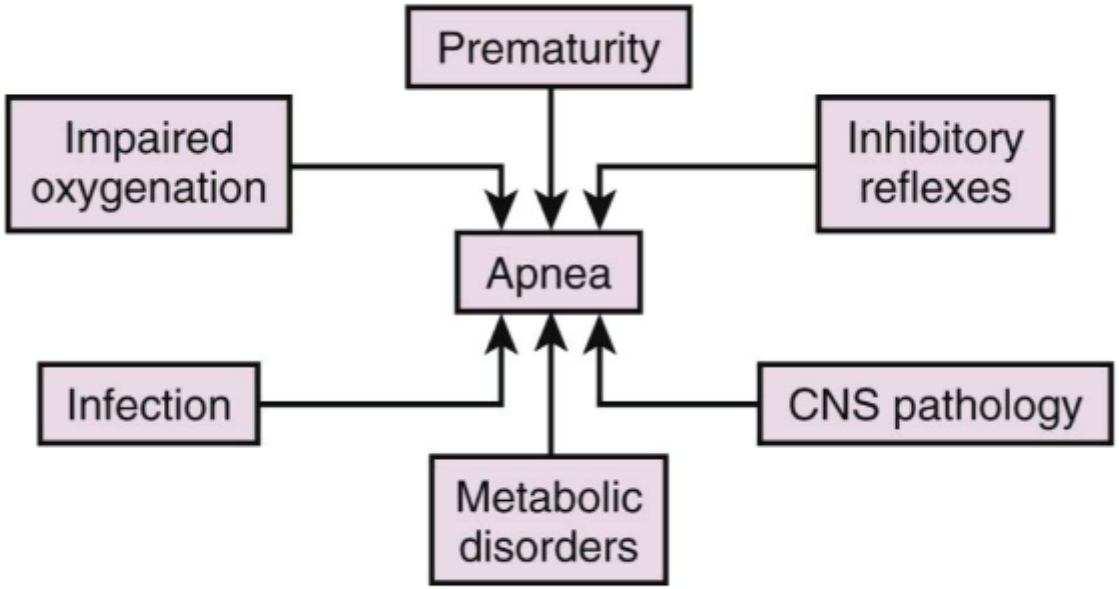
OBSTRUCTIVE

- Breathing against an obstructed airway
- Chest wall motion without nasal airflow

MIXED

- Obstructed respiratory effort after a central pause
- Accounts for majority of apnea in premature infants

APNEA IS A SYMPTOM, NOT A DIAGNOSIS



Martin RJ et al. Pathogenesis of apnea in preterm infants. *J Pediatr*. 1986; 109:733.

APNEA IN THE NEONATE: DIFFERENTIAL

Central Nervous System	Respiratory
• Intraventricular Hemorrhage • Seizure • Cerebral Infarct	• Airway Obstruction • Inadequate Ventilation / Fatigue • Hypoxia
Infection	**Gastrointestinal**
• Sepsis • Meningitis	• Necrotizing Enterocolitis • Gastroesophageal Reflux
Hematologic	**Drug Exposure**
• Anemia • Polycythemia	• Perinatal (Ex: Magnesium, Opioids) • Postnatal (Ex: Sedatives, PGE)
Cardiovascular	**Other**
• Patent Ductus Arteriosus	• Temperature instability • Metabolic derangements

APNEA IN THE NEONATE: EVALUATION

- Detailed History and Physical Examination
  - Gestational age, post-natal age, and birth history
  - Other new signs or symptoms
  - Careful attention to neurologic, cardiorespiratory, and abdominal exam

APNEA IN THE NEONATE: EVALUATION

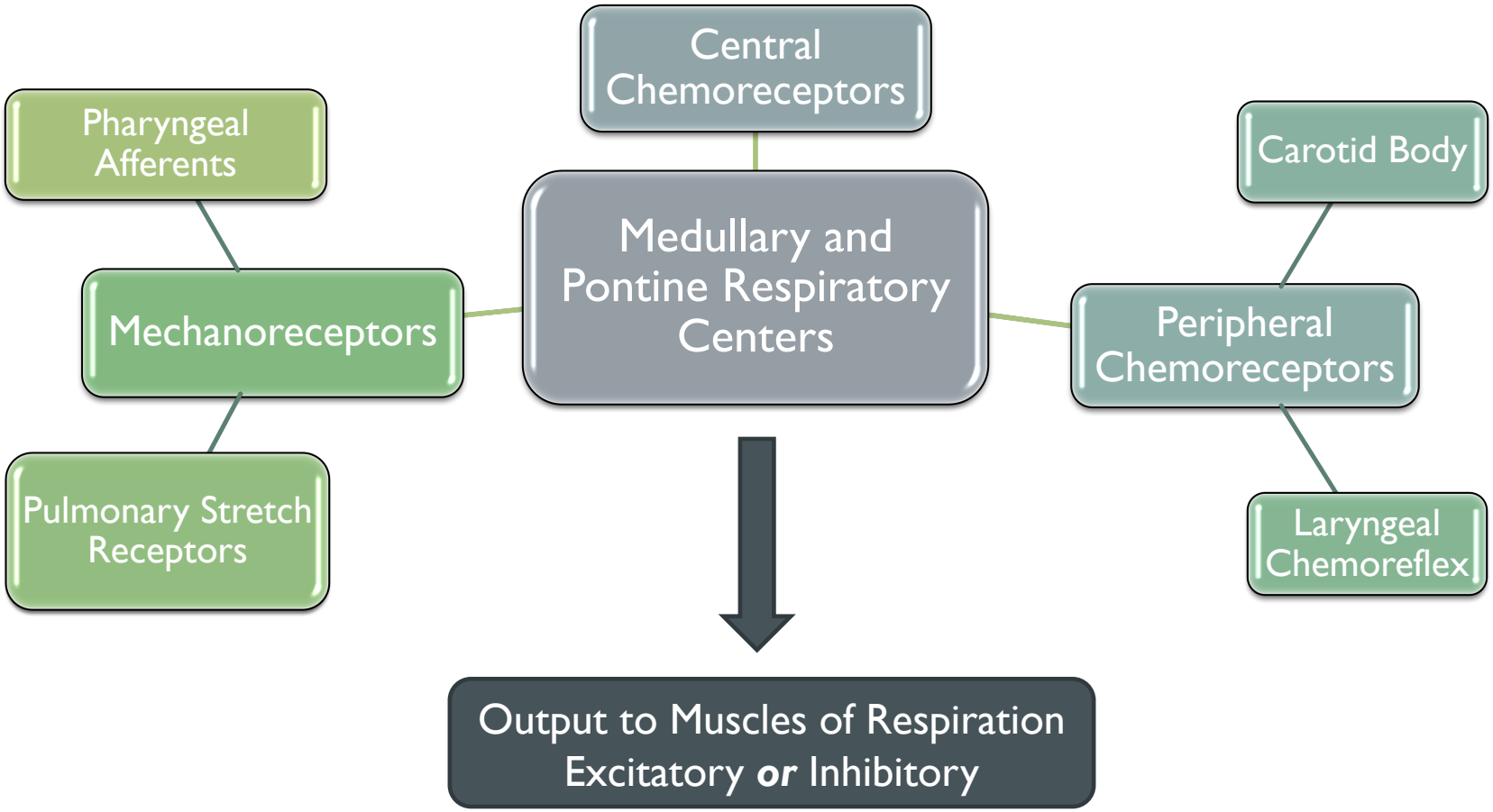
- Laboratory Studies
  - CBC/diff and CRP
  - Cultures, consideration of LP
  - Electrolytes including magnesium
  - Blood gas and lactate

- Radiologic Studies
  - Head ultrasound vs. MRI
  - Chest and/or abdominal films
  - Cardiac studies (EKG, echo)

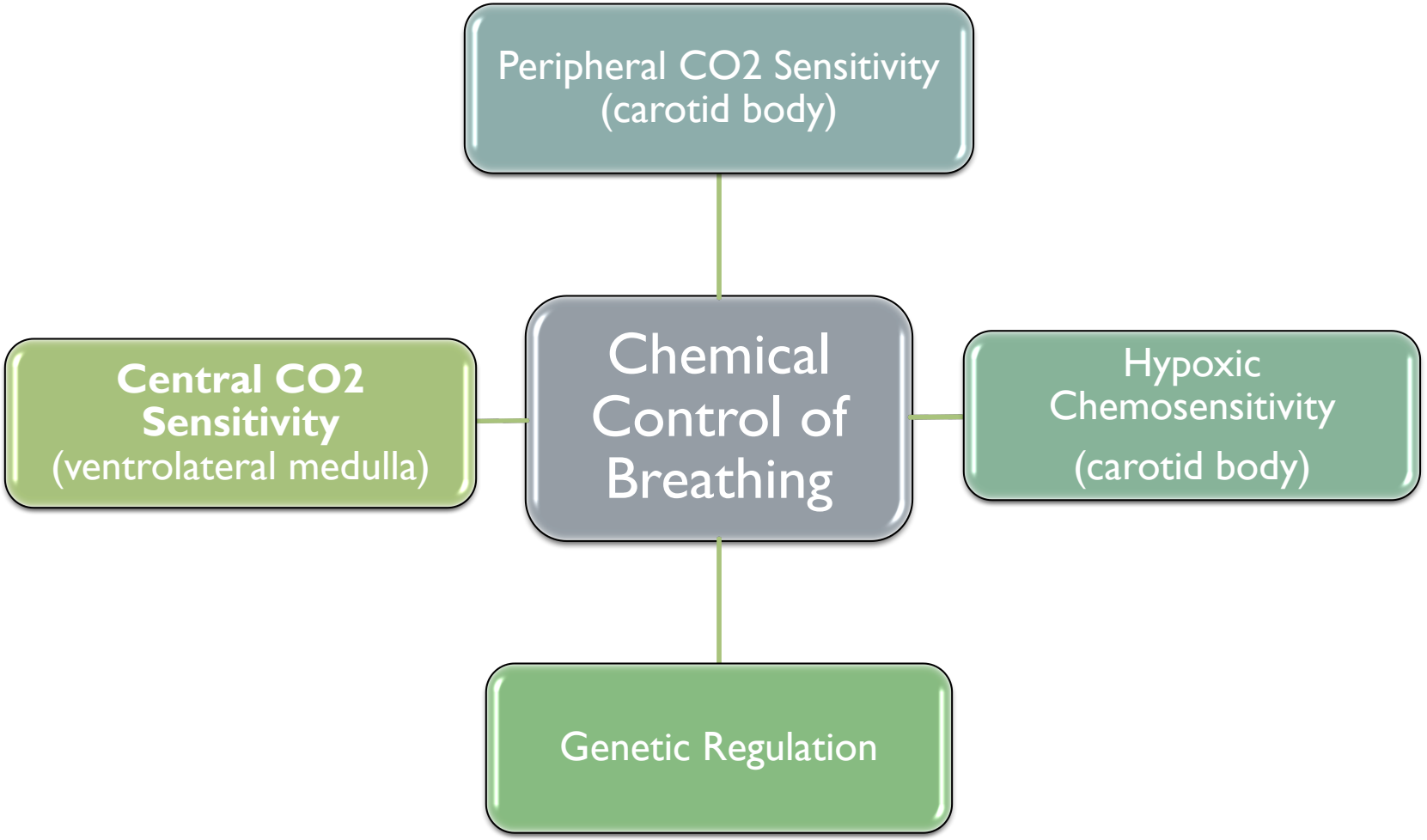
APNEA OF PREMATURITY

- Apnea of Prematurity (AOP) is a **diagnosis of exclusion**
- Peak onset is at 5-7 days of post-natal age
- The likelihood of AOP increases with decreasing gestational age and weight
- The pathophysiology of AOP is multifactorial
  - Understanding is extrapolated from basic science and animal models

RESPIRATORY HOMEOSTASIS

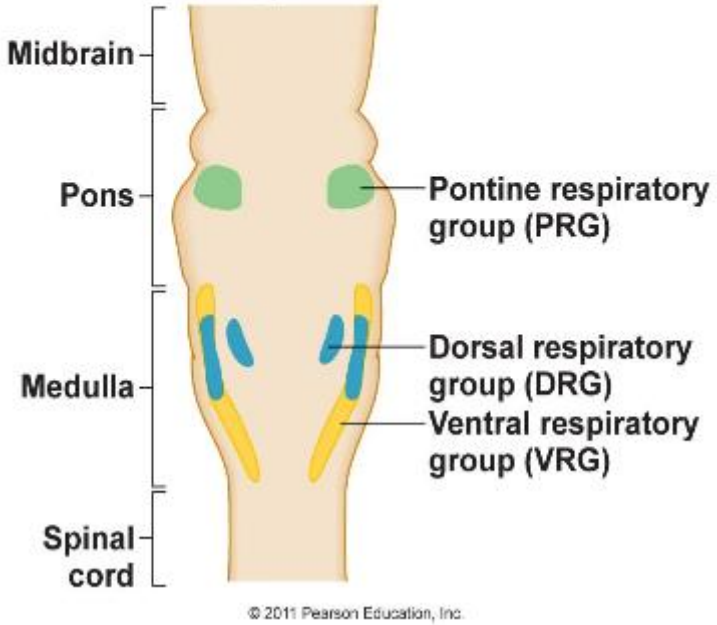


CHEMICAL CONTROL OF BREATHING



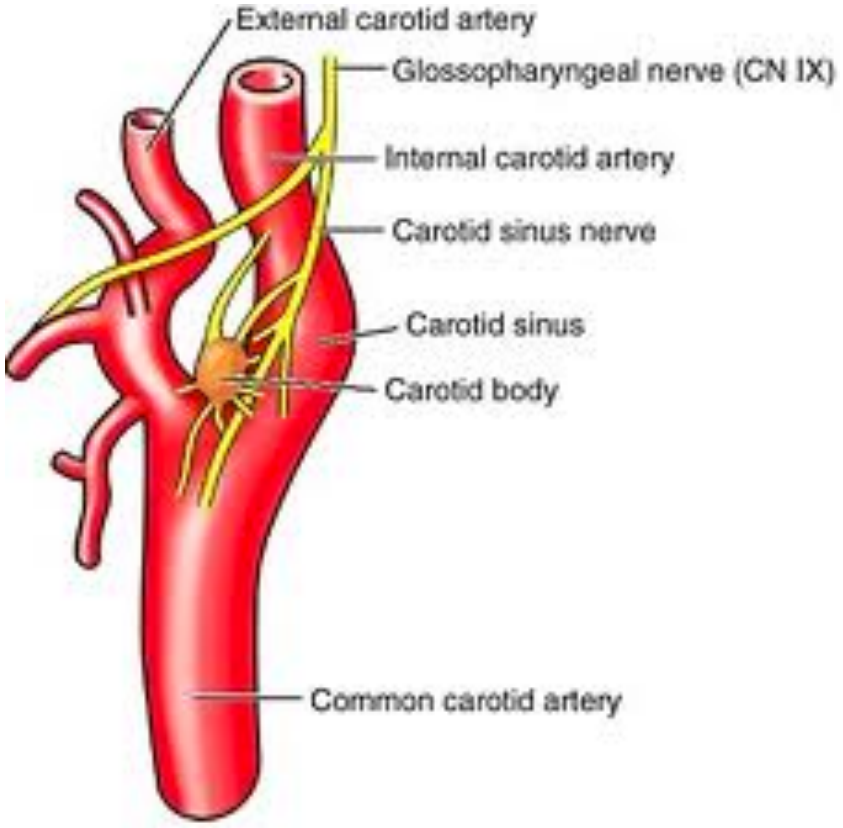
CENTRAL CHEMORECEPTORS

- Central Chemoreceptors
  - Located on ventral medulla
  - Detects changes in CSF pH
  - Sensitive to CO2 and H+
  - Maintain CO2 and pH in narrow physiologic range

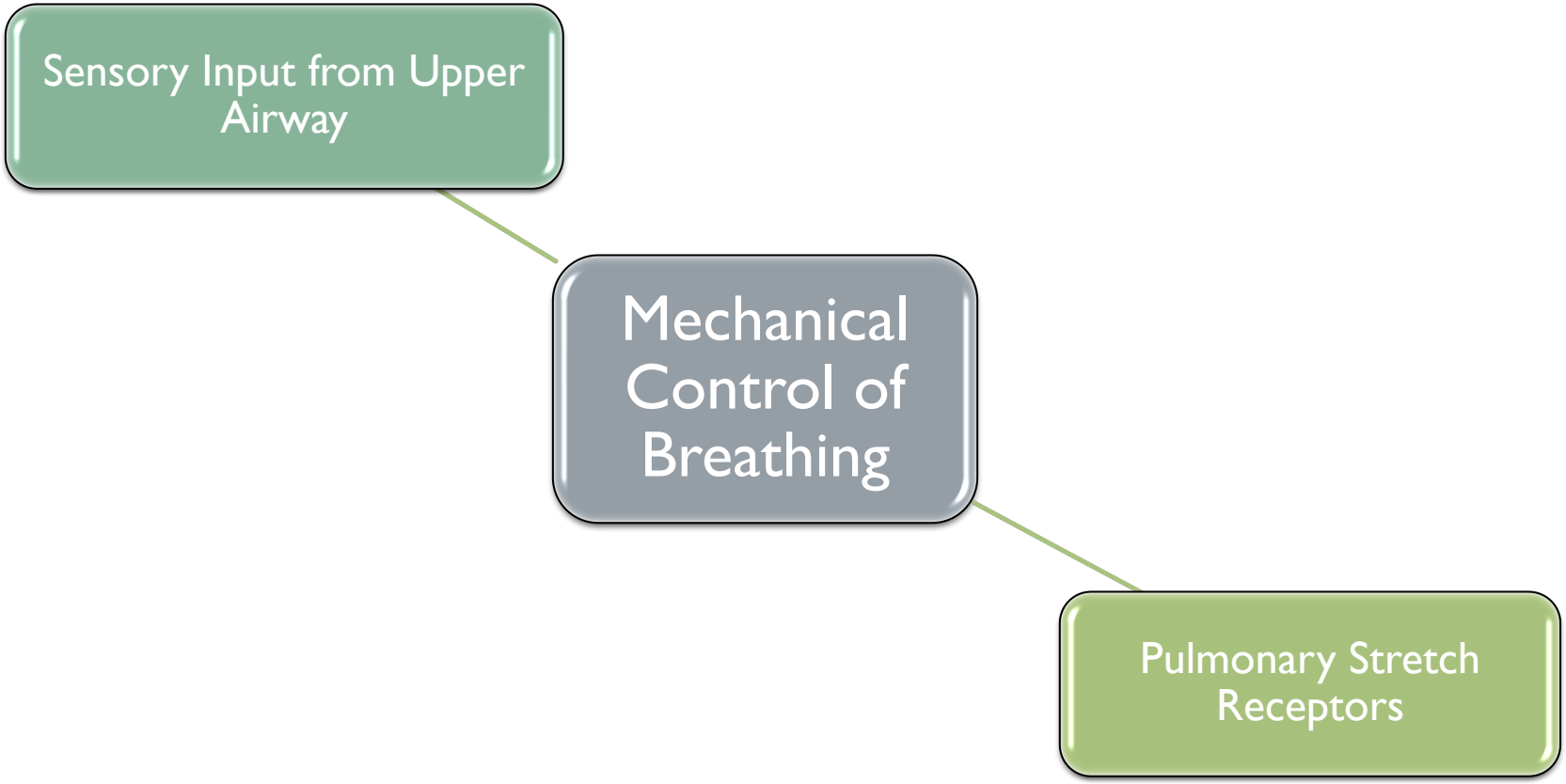


THE CAROTID BODY

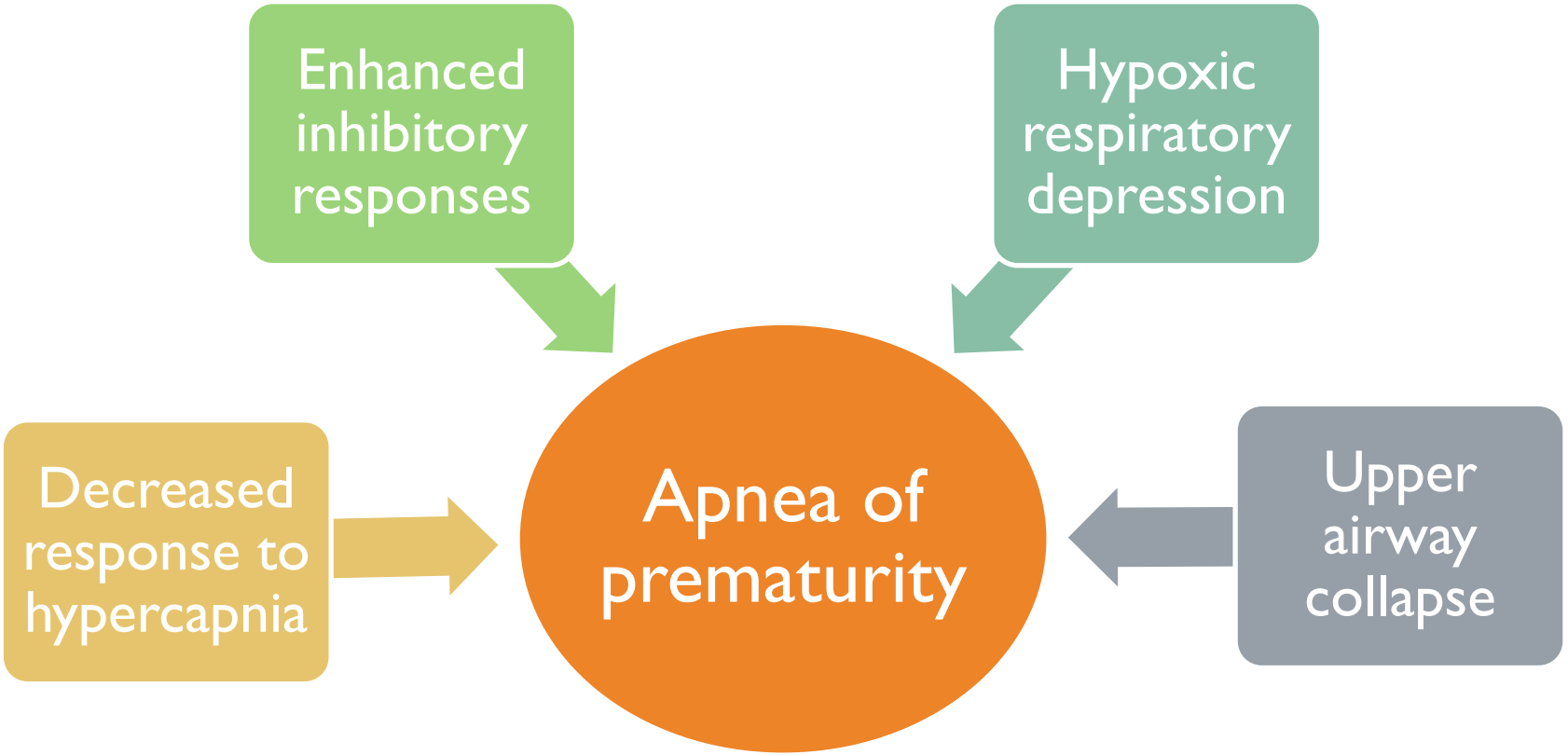
- Carotid Body
  - Primary peripheral chemoreceptor
  - Sensitive primarily to hypoxia
  - Can also detect changes in CO2, pH, temperature
  - Hypoxia triggers increase in minute ventilation



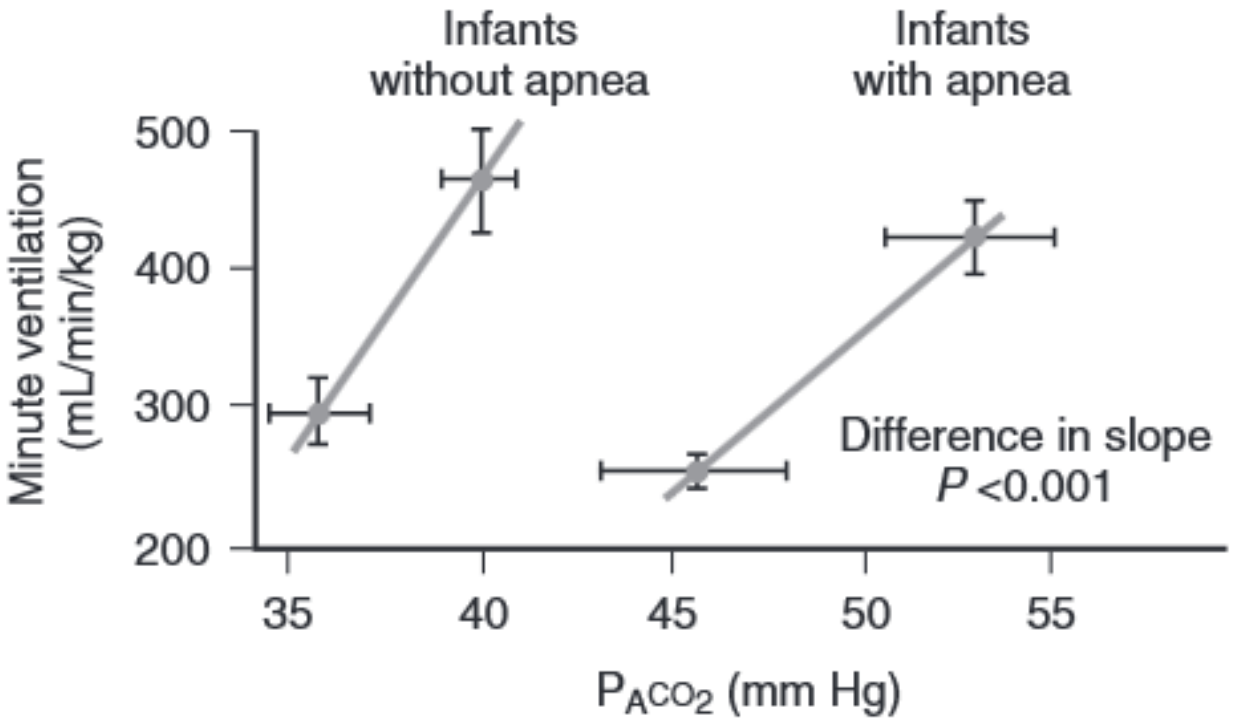
MECHANICAL CONTROL OF BREATHING



DYSREGULATION IN THE NEONATE



RESPONSE TO HYPERCAPNIA



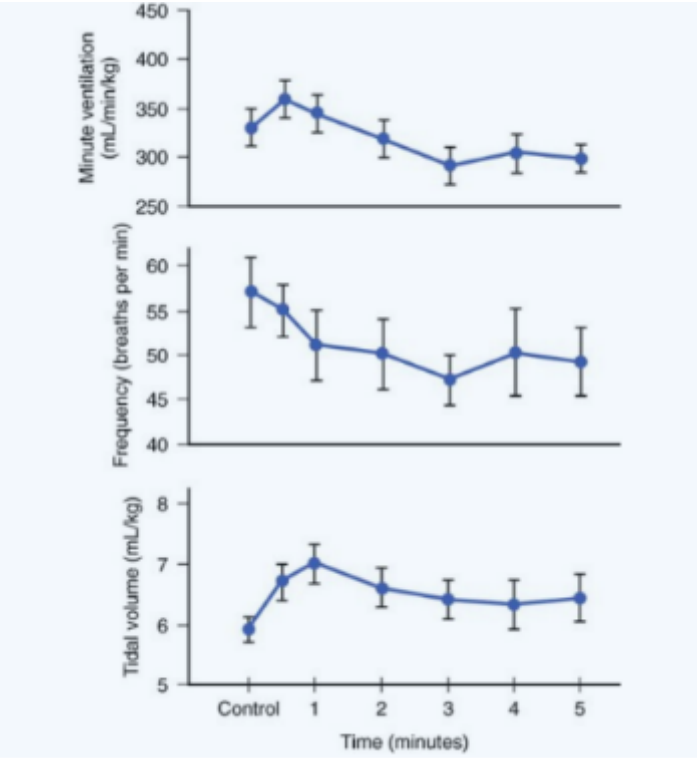
Gerhardt T, et al. Apnea of prematurity: I. Lung function and regulation of breathing. *Pediatrics*. 1984; 74:58.

RESPONSE TO HYPOXIA

- Abnormal biphasic response to hypoxia
  - Initial increase in ventilation followed by a decline
  - Likely represents depression of central respiratory center due to hypoxia

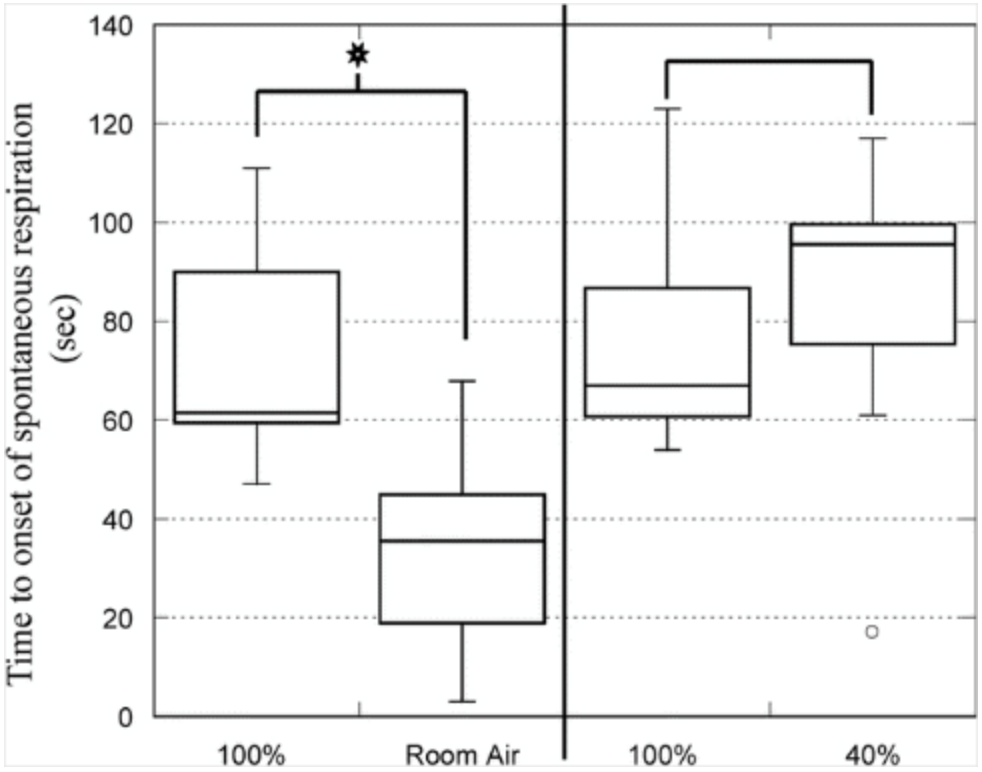
- Theoretical role of 'Diving Reflex' in bradycardia
  - In diving mammals, results in bradycardia during episodes of hypoxia
  - 'Diving Reflex' persistent in humans until around 6 months of age

VENTILATORY RESPONSE TO 15% FIO2 HYPOXIA IN PRETERM INFANTS



Martin RJ, et al. Persistence of the biphasic ventilator responses to hypoxia in preterm infants. *J Pediatr.* 1998;132:960.

INITIATION OF BREATHING AFTER RESUSCITATION OF RAT PUPS



Bookatz GB et al. Effect of Supplemental Oxygen on Reinitiation of Breathing after Neonatal Resuscitation in Rat Pups. *Pediatric Research.* 2007; 61: 698–702.

IMMATURITY OF THE CNS

- Immaturity of pre-term brain present in histologic samples
  - Fewer synaptic connections
  - Paucity of myelin
  - Less dendritic arborization
- Auditory evoked responses impaired in preterm infants with AOP

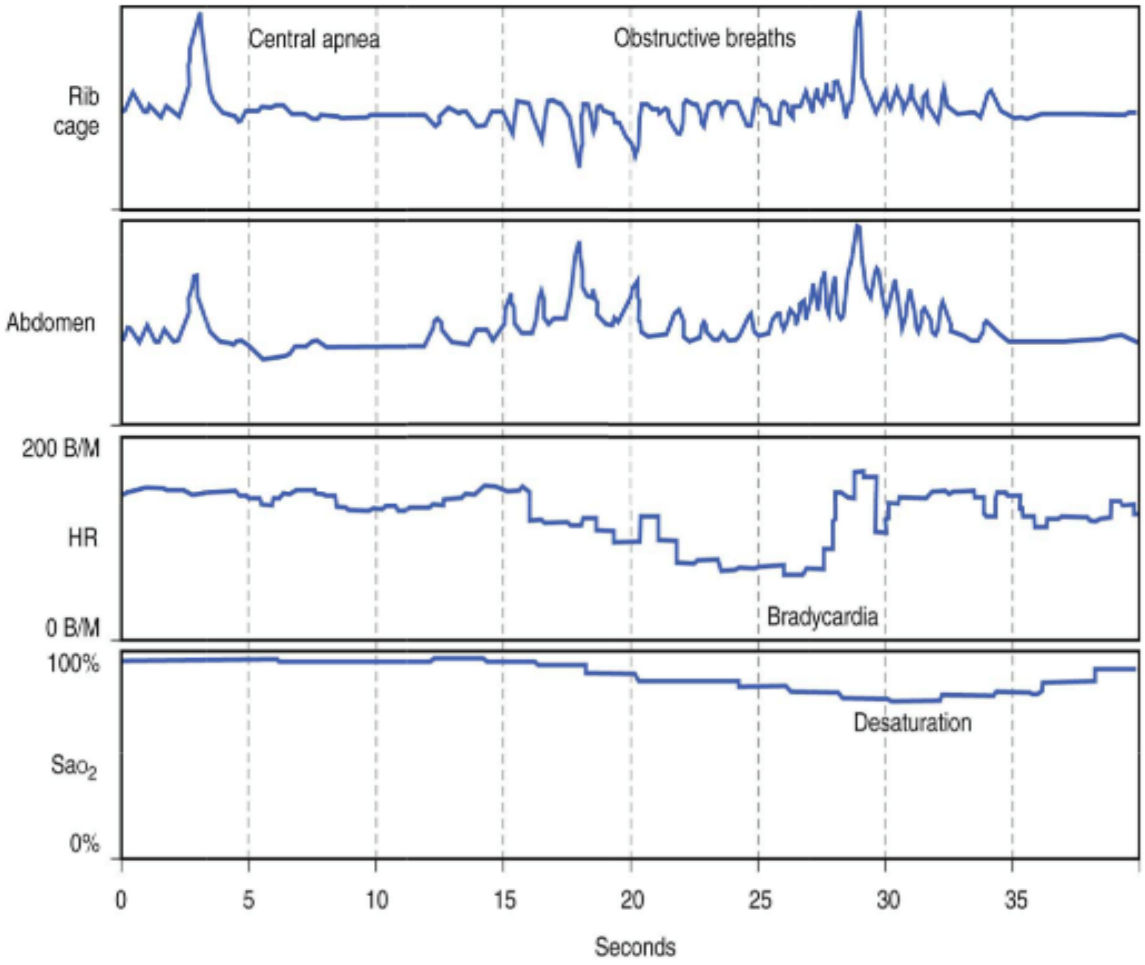
INHIBITORY NEUROTRANSMITTERS

- Increased presence and activity of inhibitory neural pathways and neurotransmitters
- GABA
  - Major inhibitory neurotransmitter
  - Increased number of GABA-A receptors in early post-natal life
    - Implicated in hypoxic ventilatory depression
- Adenosine
  - Depresses neural function and respiration
  - Indirect evidence for role in AOP from animal studies
  - Methylxanthines are competitive antagonists at the adenosine receptor

UPPER AIRWAY COLLAPSE

- Upper airway obstruction is a prominent component of AOP
  - Delay in activation of tone-maintaining airway musculature during hypercapneic episodes
  - Theoretical 'overactive' vagal inhibition of airway dilator muscles

UPPER AIRWAY COLLAPSE



MANAGEMENT OF AOP - METHYLXANTHINES

- Mainstay of therapy for AOP since the 1970s
  - Studies showed decrease in apnea frequency when on theophylline and caffeine
- Competitive antagonist at adenosine receptors
- Initial concerns about safety
  - Increased metabolic demand and impact on growth
  - Adenosine as a neuroprotective agent in hypoxia

MANAGEMENT OF AOP – THE CAP TRIAL

- The CAP Trial
  - Large, multi-center RCT comparing caffeine to placebo
  - Originally designed to evaluate safety
  - Published follow-up at discharge, 18 months, and 5 years

- Initial results at hospital discharge
  - Decreased GA at last extubation and cessation of PPV
  - Decreased rates of BPD
  - Slower weight gain in 3 weeks after therapy initiated

Schmidt B et al. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20):2112-21.

MANAGEMENT OF AOP – THE CAP TRIAL

Table 2. Primary Outcome of Death or Neurodevelopmental Disability.

Outcome	Caffeine Group	Placebo Group	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value	Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)*
	no./total no. (%)					
Composite						
Death or disability	377/937 (40.2)	431/932 (46.2)	0.78	0.77 (0.64–0.93)	0.008	0.79 (0.65–0.96)
Components						
Death before 18 mo†	62/974 (6.4)	63/970 (6.5)	0.98	0.97 (0.67–1.40)	0.87	0.99 (0.65–1.50)
Cerebral palsy‡	40/909 (4.4)	66/901 (7.3)	0.58	0.58 (0.39–0.87)	0.009	0.59 (0.39–0.89)
Cognitive delay‡§	293/867 (33.8)	329/858 (38.3)	0.82	0.81 (0.66–0.99)	0.04	0.83 (0.67–1.02)
Severe hearing loss‡¶	17/909 (1.9)	22/905 (2.4)	0.77	0.77 (0.40–1.45)	0.41	0.81 (0.43–1.55)
Bilateral blindness‡	6/911 (0.7)	8/905 (0.9)	0.74	0.74 (0.26–2.15)	0.58	0.79 (0.27–2.31)

Schmidt B et al. Long-Term Effects of Caffeine Therapy for Apnea of Prematurity. *N Engl J Med.* 2007; 357:1893-1902

MANAGEMENT OF AOP – THE CAP TRIAL

Table 2. Primary Outcome of Death or Disability

Outcome	Caffeine Group, No./Total (%)	Placebo Group, No./Total (%)	Unadjusted OR (95% CI)	OR Adjusted for Center (95% CI)	*P* Value	OR Adjusted for Center and Patient Characteristics (95% CI)[a]
Composite						
Death or disability	176/833 (21.1)	200/807 (24.8)	0.81 (0.65-1.02)	0.82 (0.65-1.03)	.09	0.86 (0.67-1.09)
Components						
Death before 5 y[b]	59/867 (6.8)	58/837 (6.9)	0.98 (0.67-1.43)	0.98 (0.70-1.43)	.92	1.03 (0.69-1.52)
Motor impairment[c,d]	13/803 (1.6)	21/773 (2.7)	0.59 (0.29-1.18)	0.59 (0.29-1.18)[e]	.20	0.63 (0.31-1.28)[e]
Cognitive impairment[c,f]	38/768 (4.9)	38/750 (5.1)	0.98 (0.62-1.55)	0.97 (0.61-1.55)	.89	1.11 (0.68-1.80)
Behavior problem[c,g]	42/773 (5.4)	53/748 (7.1)	0.75 (0.50-1.14)	0.75 (0.49-1.15)	.18	0.78 (0.51-1.20)
Poor general health[c]	32/805 (4.0)	33/775 (4.3)	0.93 (0.57-1.51)	0.92 (0.56-1.52)	.75	0.95 (0.57-1.58)
Severe hearing loss[c]	22/798 (2.8)	25/773 (3.2)	0.85 (0.47-1.52)	0.85 (0.47-1.52)[e]	.58	0.91 (0.51-1.64)[e]
Bilateral blindness[c]	7/792 (0.9)	7/763 (0.9)	0.96 (0.34-2.75)	0.96 (0.34-2.75)[e]	.94	1.04 (0.35-3.02)[e]

Schmidt B et al. Survival Without Disability to Age 5 Years After Neonatal Caffeine Therapy for Apnea of Prematurity. *JAMA.* 2012;307(3):275-282.

MANAGEMENT OF AOP – THE CAP TRIAL

Table 3. Secondary Outcomes of Motor and Cognitive Impairment

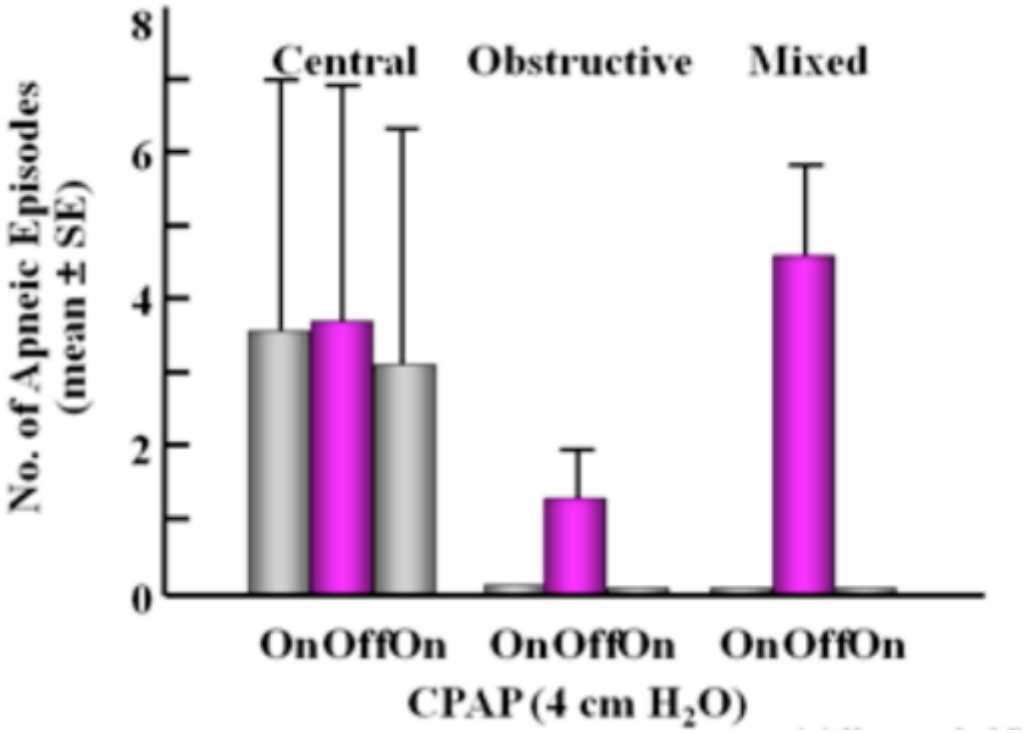
Outcome Variable	Caffeine Group, No./Total (%)	Placebo Group, No./Total (%)	Unadjusted OR (95% CI)	OR Adjusted for Center (95%CI)	*P* Value	OR Adjusted for Center and Patient Characteristics (95% CI)
Gross motor function GMFCS level[a]						
Normal	728/803 (90.7)	666/773 (86.2)				
1	56/803 (7.0)	78/773 (10.1)	0.66 (0.46-0.94)	0.64 (0.47-0.88)[b]	.006	0.66 (0.48-0.91)[b]
2	6/803 (0.7)	8/773 (1.0)	0.69 (0.24-1.99)			
3	5/803 (0.6)	5/773 (0.6)	0.91 (0.26-3.17)			
4	4/803 (0.5)	10/773 (1.3)	0.37 (0.11-1.17)			
5	4/803 (0.5)	6/773 (0.8)	0.61 (0.17-2.17)			
Full scale IQ <85	137/764 (17.9)	144/742 (19.4)	0.91 (0.70-1.18)	0.90 (0.69-1.17)	.44	0.96 (0.73-1.26)

Schmidt B et al. Survival Without Disability to Age 5 Years After Neonatal Caffeine Therapy for Apnea of Prematurity. *JAMA*. 2012;307(3):275-282.

MANAGEMENT OF AOP - CPAP

- Provides distending pressure in airway
  - May prevent upper airway collapse and obstruction
- Improves oxygenation
  - May blunt hypoxic ventilatory depression

MANAGEMENT OF AOP - CPAP

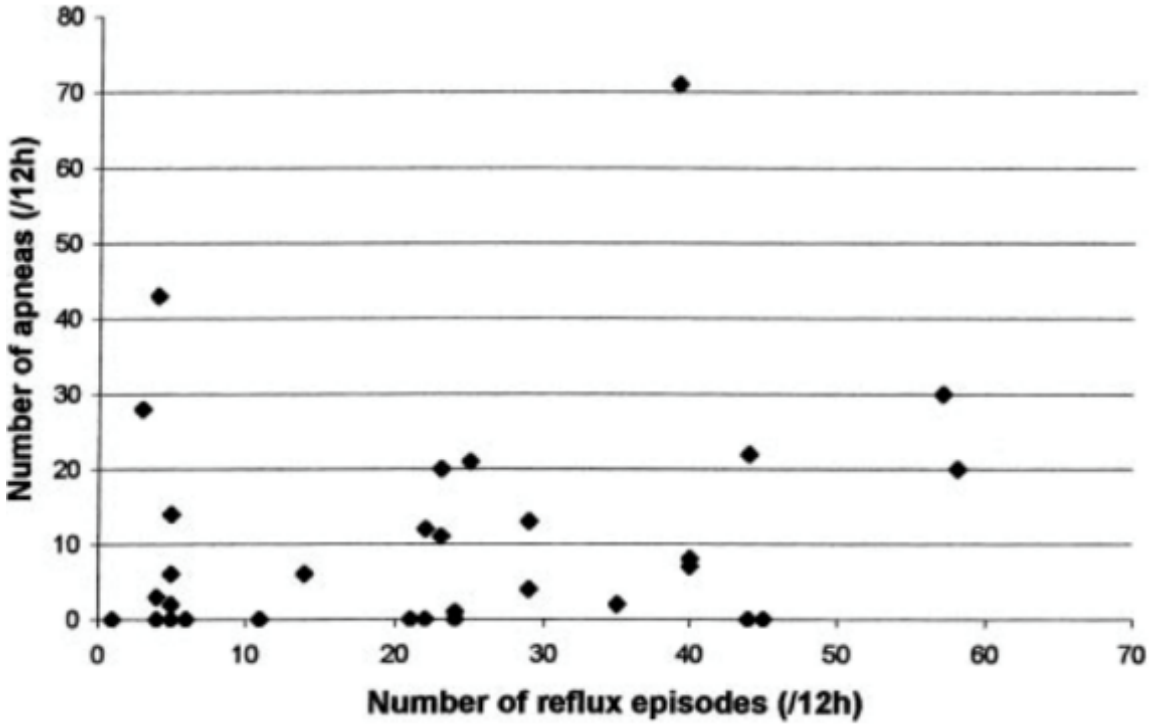


Miller MJ et al. Continuous positive airway pressure selectively reduces obstructive apnea in preterm infants. *The Journal of Pediatrics*. 1985; 106 (1): 91 – 94.

APNEA AND GASTROESOPHAGEAL REFLUX THE CONTINUED CONTROVERSY

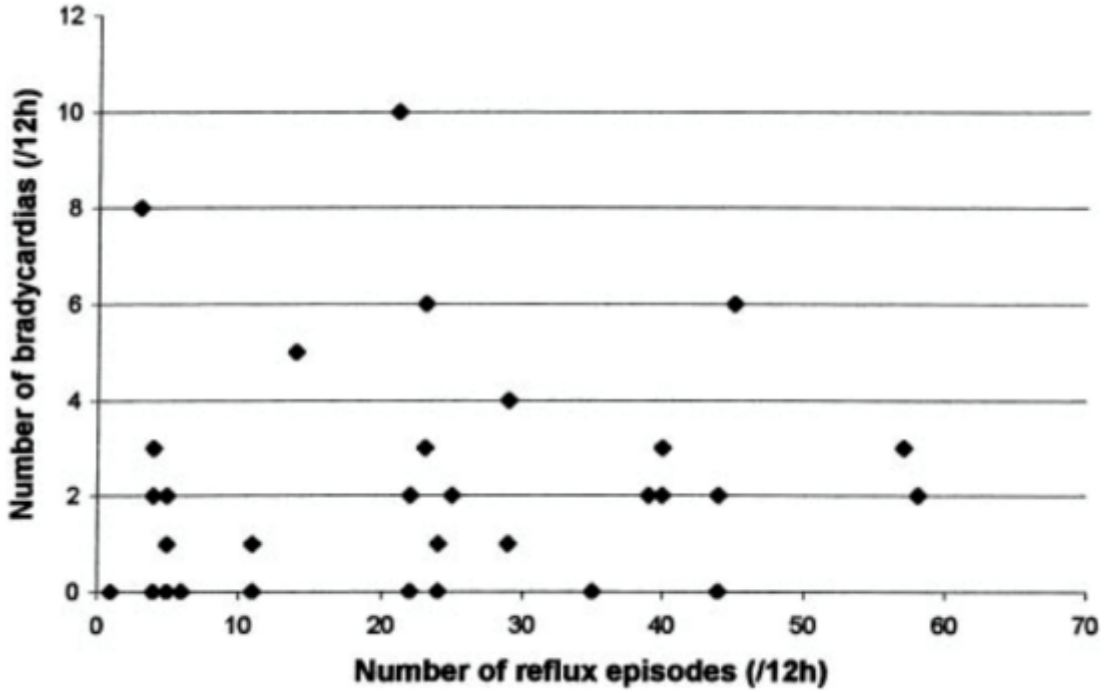
- Postulated link between apnea GER in pre-term infant
  - Rate of GER is high in pre-term infants
  - Physiologic mechanism via laryngeal chemoreflex
- Many studies over decades with inconsistent results

APNEA AND GER
THE CONTINUED CONTROVERSY



Barrington J et al. Apnea at Discharge and Gastro-Esophageal Reflux in the Preterm Infant. *Journal of Perinatology.* 2002; 22:8 – 11.

APNEA AND GER IN PRETERM INFANTS



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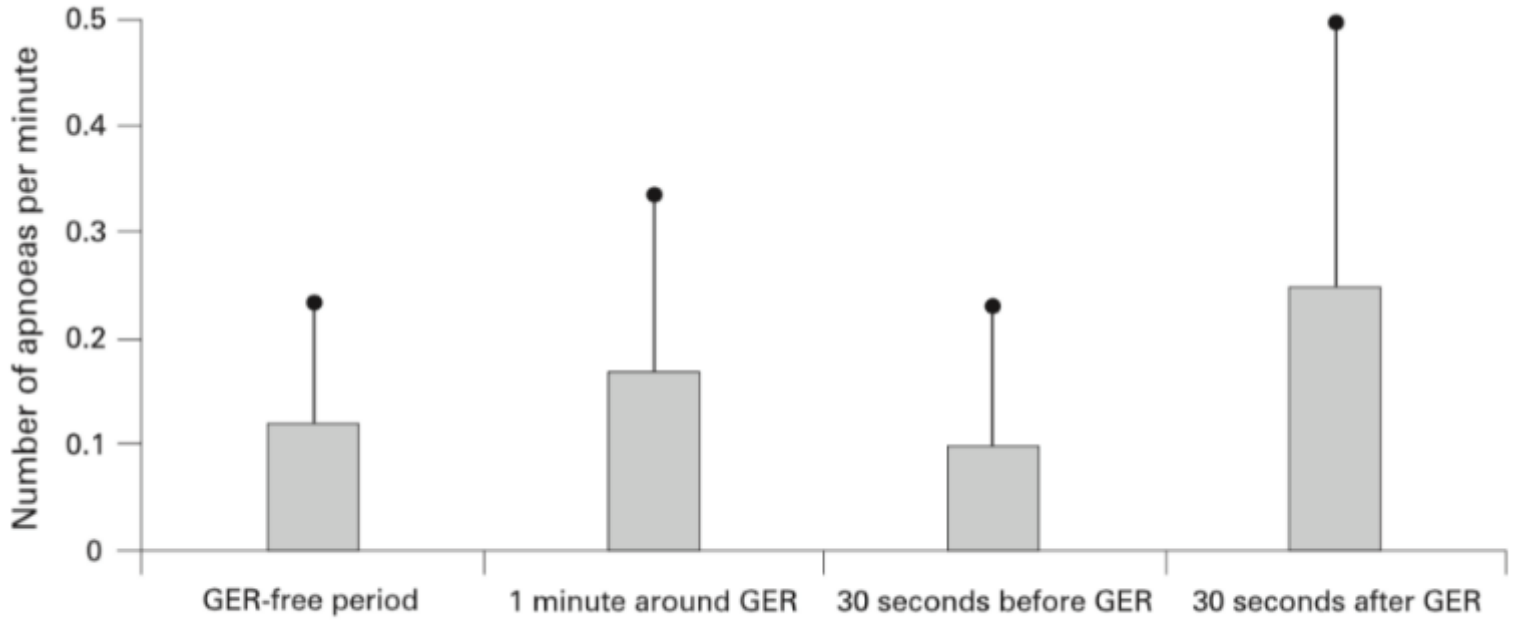
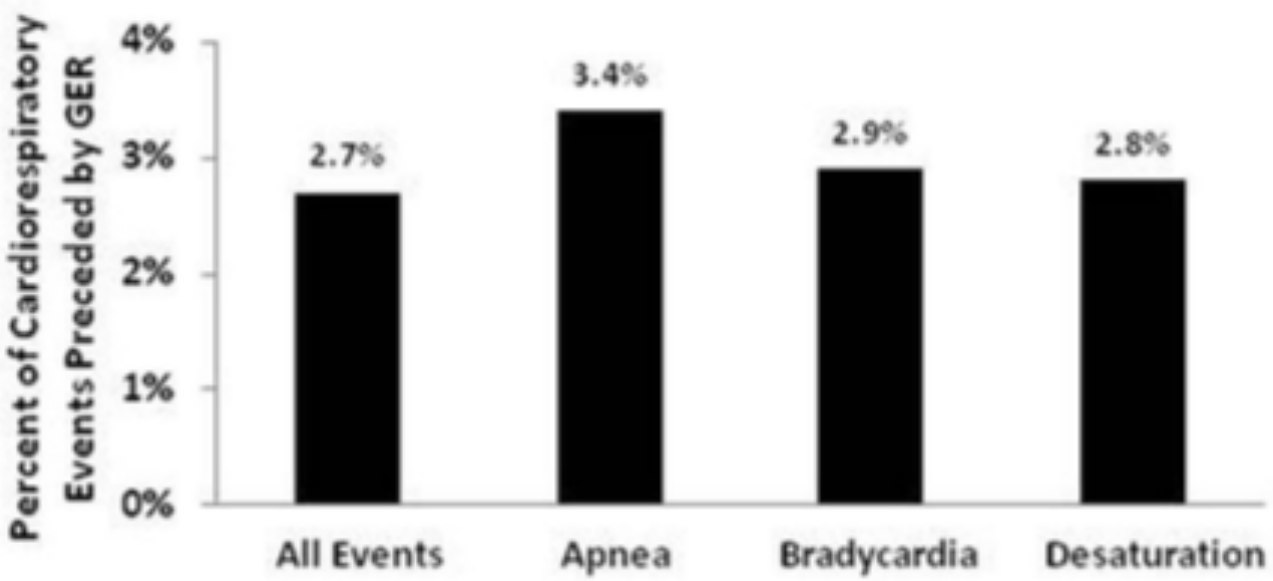
APNEA AND GER IN PRETERM INFANTS



GER-free period versus 1 minute around GER: p = 0.03; 30 seconds before GER versus 30 seconds after GER: p = 0.01
GER-free period versus 30 seconds before GER: not significant; GER-free period versus 30 seconds after GER: p = 0.02

Corvaglia L et al. Gastro-Oesophageal Reflux Increases the Number of Apnoeas in Very Preterm Infants. *Arch Dis Child Fetal Neonatal Ed. 2008;* 94 (3): F188-F192.

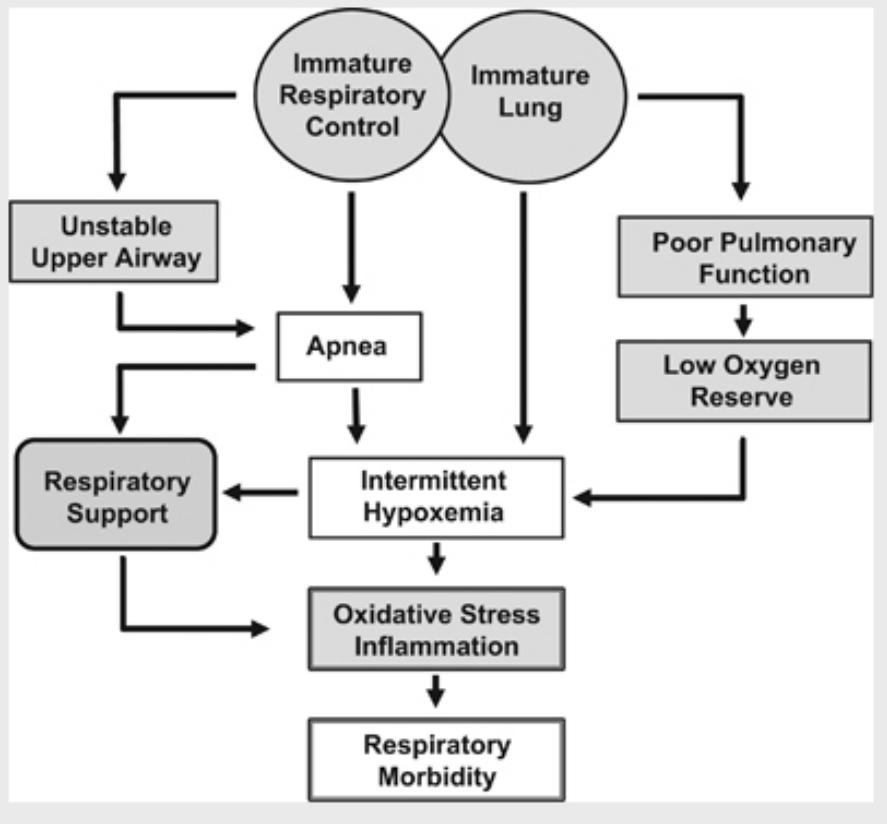
APNEA AND GER IN PRETERM INFANTS



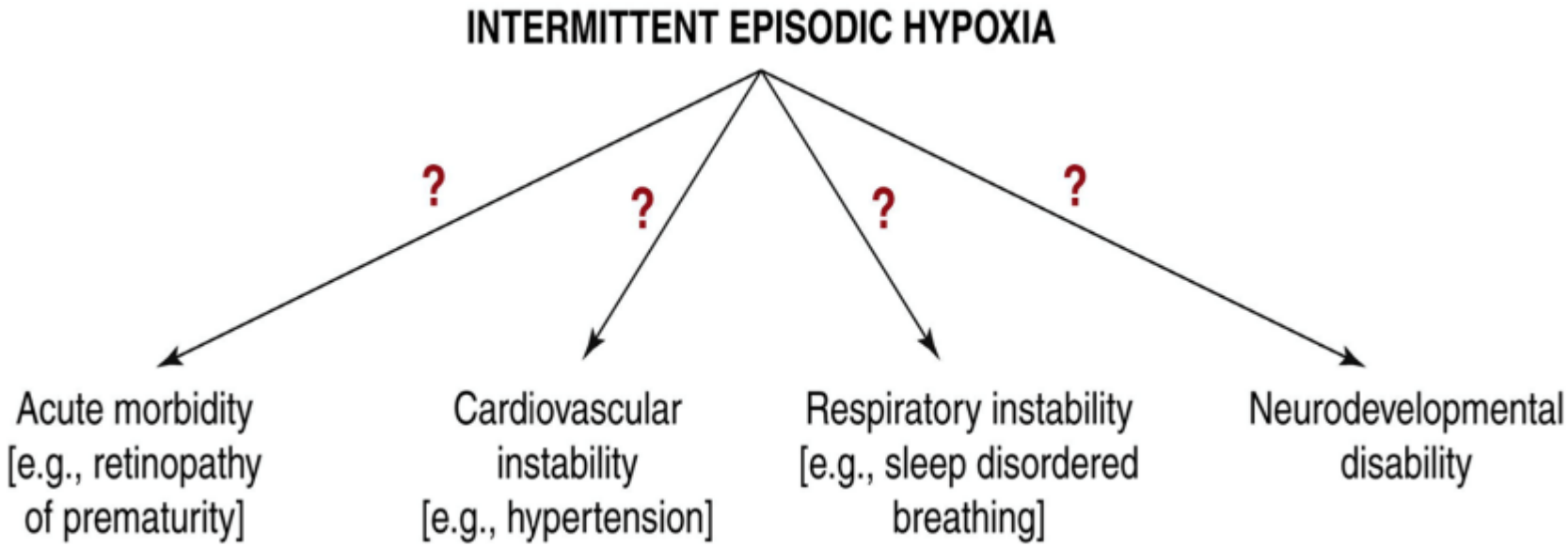
Di Fiore J et al. Characterization of Cardiorespiratory Events following Gastroesophageal Reflux (GER) in Preterm Infants. *J Perinatol.* 2010 October ; 30(10): 683-687

LONG-TERM OUTCOMES OF AOP

- Long-term risks of AOP are unclear
  - Difficult to separate from other comorbid problems
  - Particularly confounded by BPD/CLD

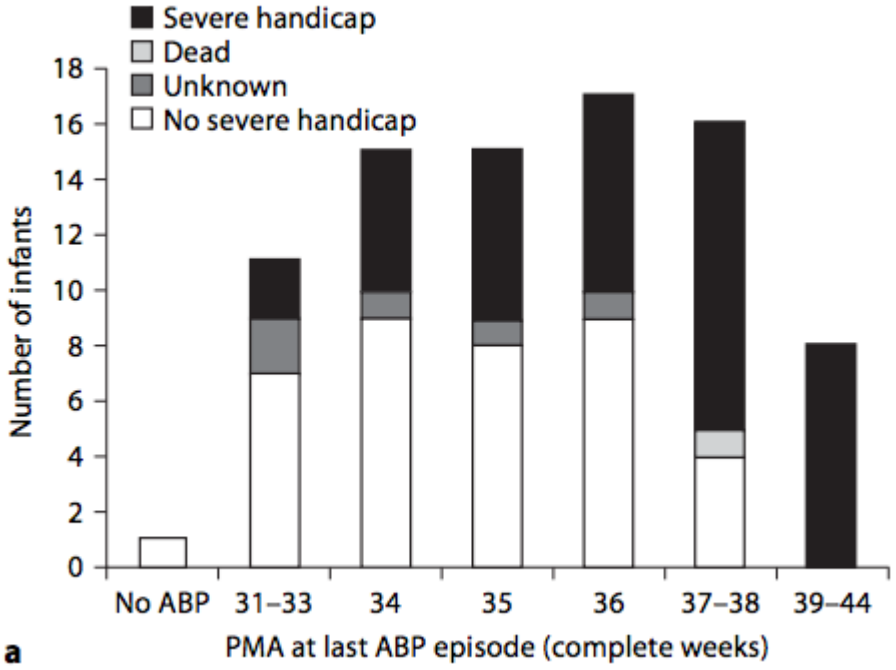


LONG-TERM OUTCOMES OF AOP



AOP AND NEURODEVELOPMENT

- Prolonged AOP is correlated with more severe neurodevelopmental handicaps



Pillekamp F et al. Factors Influencing Apnea and Bradycardia of Prematurity – Implications for Neurodevelopment. *Neonatology*. 2007;91:155-161

AOP AND RECEPTIVE LANGUAGE

- 2014 retrospective chart review of ELBW babies with AOP
  - Followed at 8 and 20 months
  - Frequency of AOP was related to worse language scores at 8 months
  - Severity of AOP related to worse language at 20 months CA

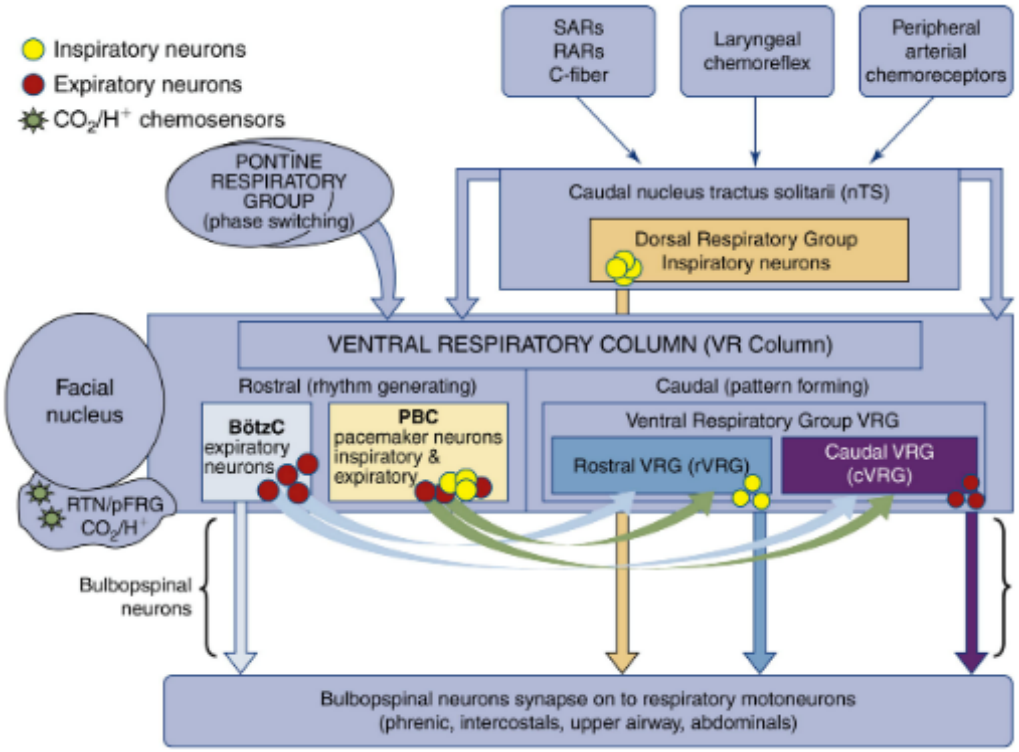
Greene J et al. Cardiorespiratory events in extremely low birth weight infants: neurodevelopmental outcome at 1 and 2 years. *Journal of Perinatology.* 2014; 34:562–565

SUMMARY

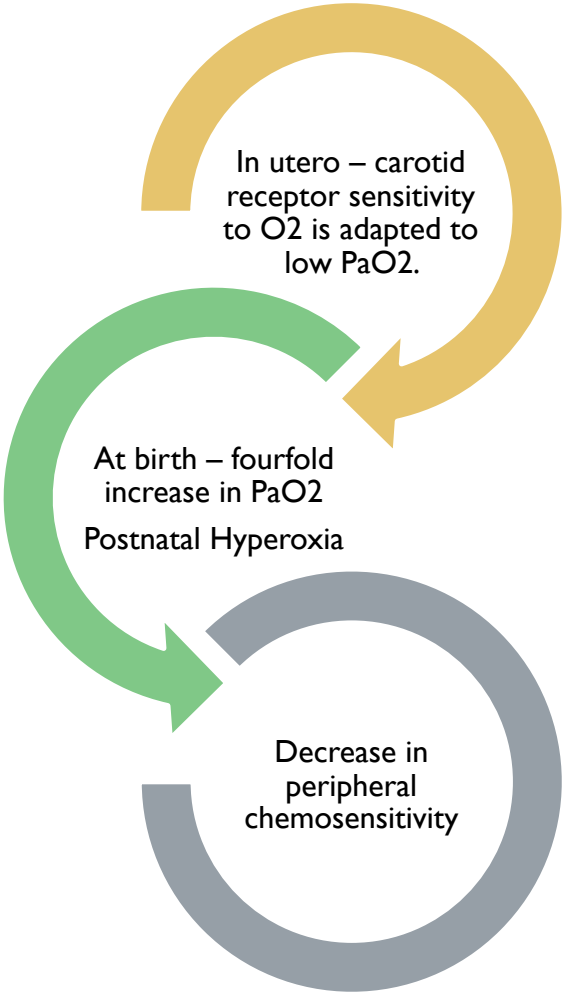
- Apnea is a symptom, not a diagnosis
  - New onset apnea requires thoughtful evaluation
- Respiratory control relies on complex interplay of central and peripheral receptors and reflexes
  - Abnormal in the neonate
- Caffeine and CPAP are both effective therapies for AOP
  - Caffeine improves neurodevelopmental outcomes
- The link between AOP and GER remains controversial
  - Most studies suggest no benefit to reflux and promotility medications

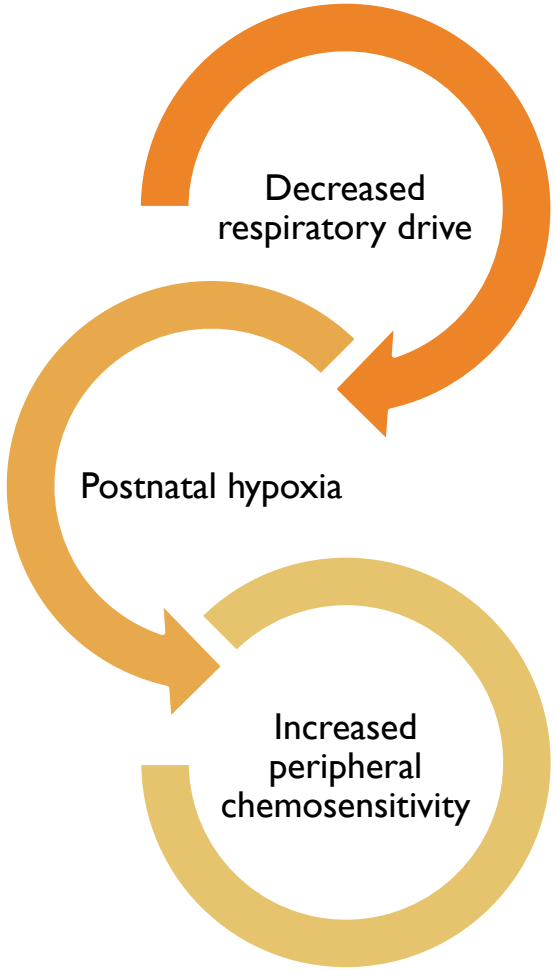
THANK YOU. QUESTIONS?

RESPIRATORY CENTER NEUROANATOMY

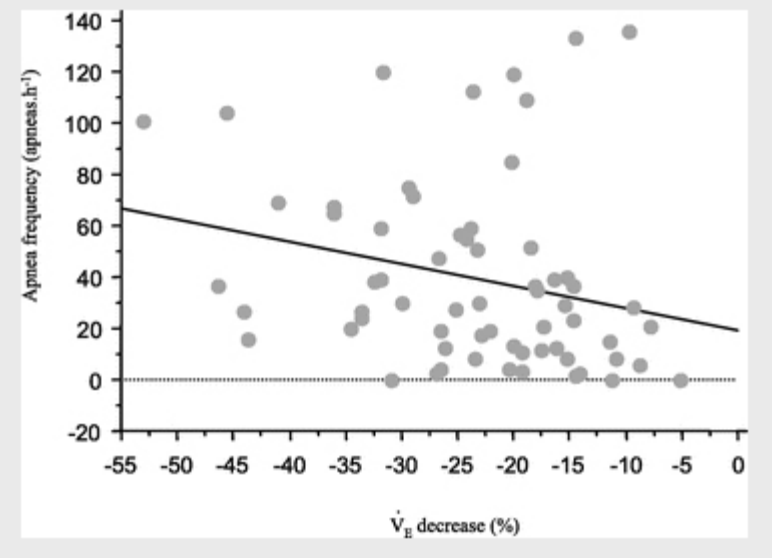


PERIPHERAL CHEMORECEPTORS





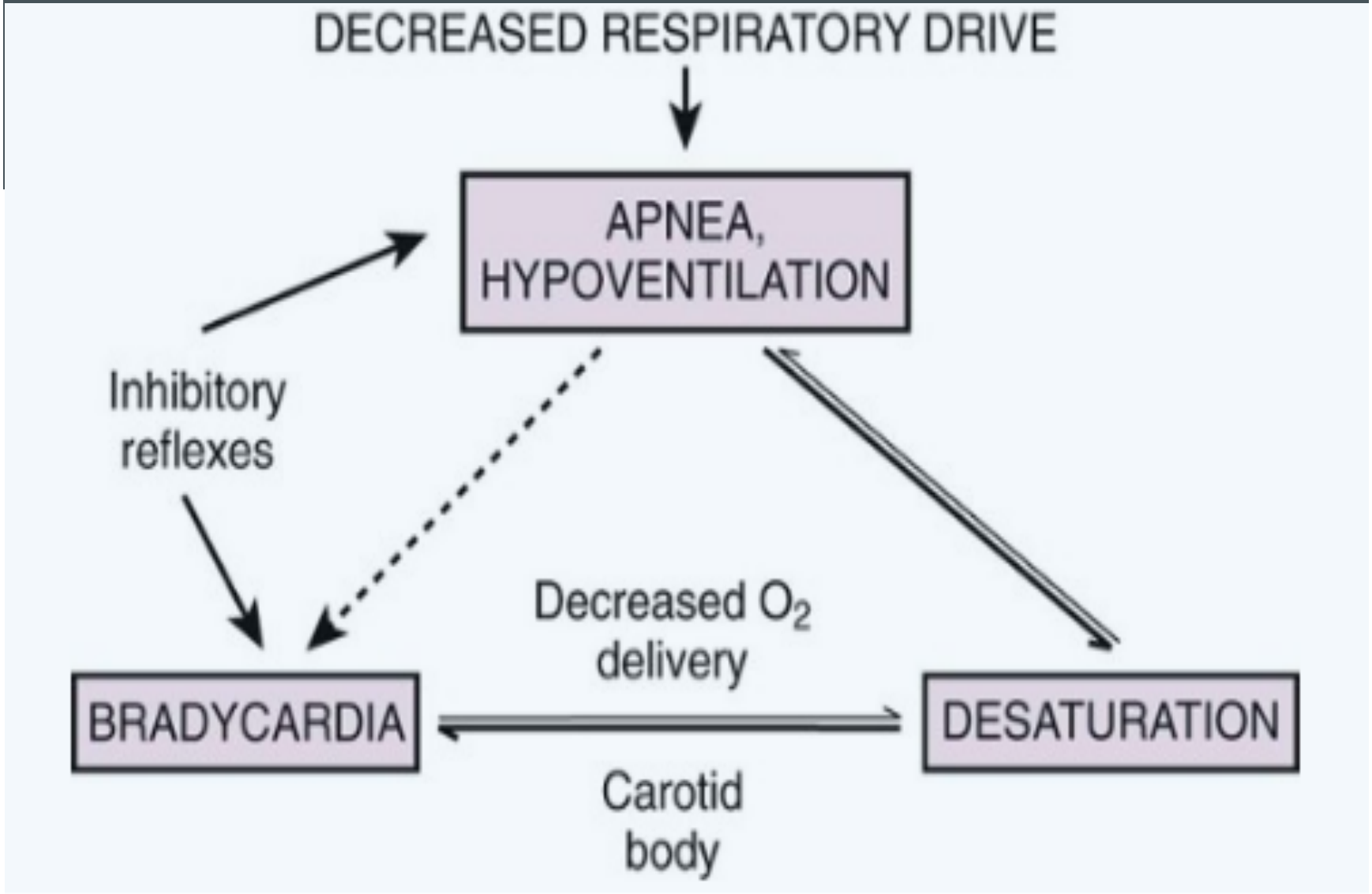
APNEA AND RESPONSE TO HYPEROXIC TEST



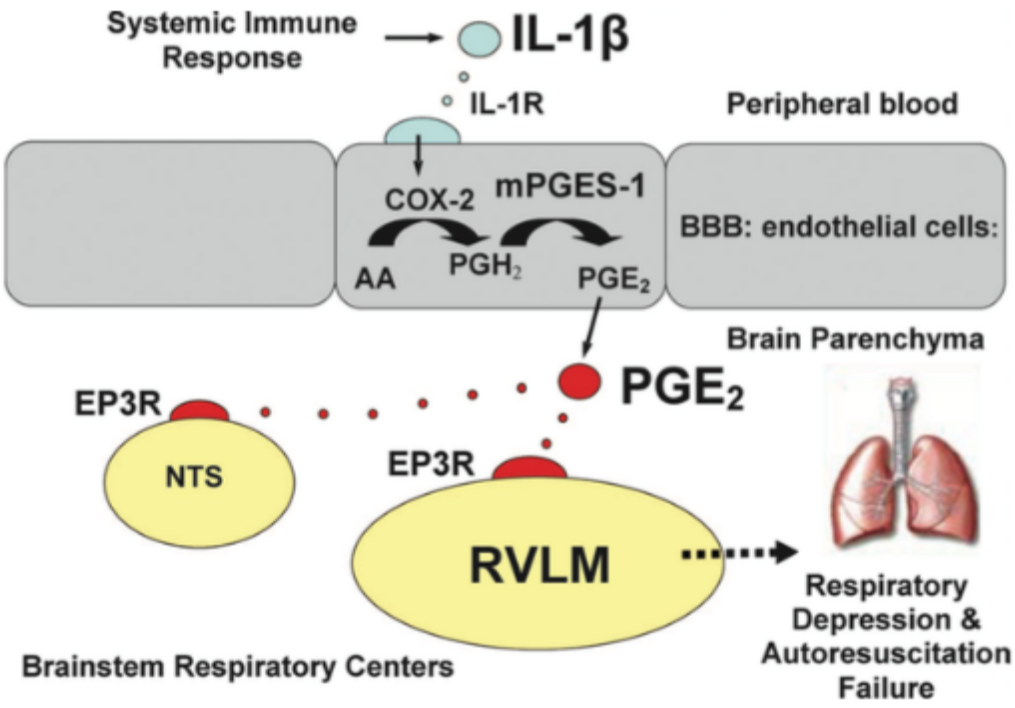
Cardot, Pediatric Res 2007

PATHOGENESIS

Central Mechanisms	Peripheral Reflex Pathways	Others
Decreased central chemosensitivity	Decreased carotid body activity	Genetic predisposition
Hypoxic ventilatory depression	Increased carotid body activity	Sepsis and cytokines
Upregulated inhibitory neurotransmitters, e.g., GABA, adenosine	Laryngeal chemoreflex Excessive bradycardic response to hypoxia	Bilirubin

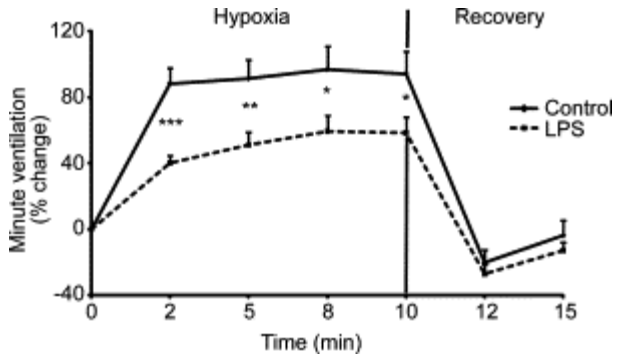

DECREASED RESPIRATORY DRIVE
APNEA, HYPOVENTILATION
Inhibitory reflexes
Decreased O_2 delivery
BRADYCARDIA
DESATURATION
Carotid body

SEPSIS

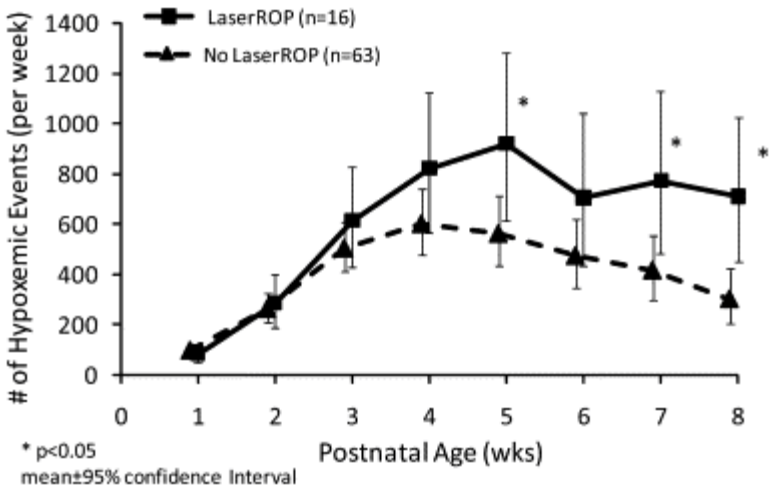


Hofstetter, PNAS 2007

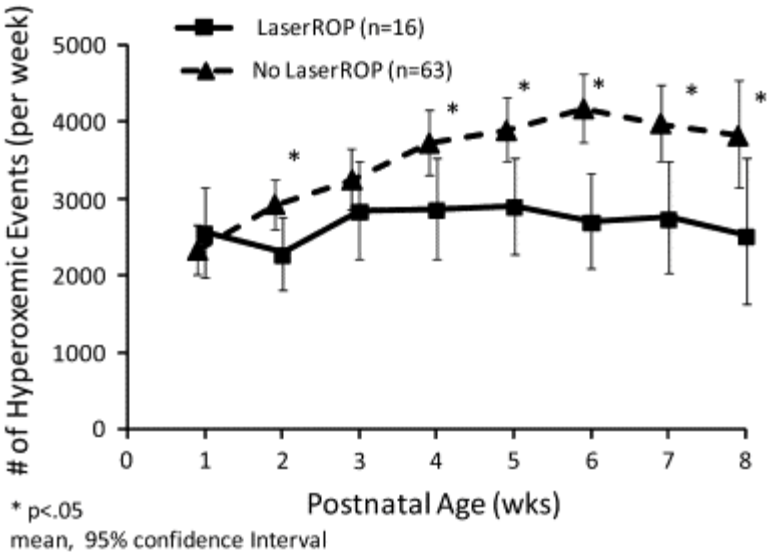
EFFECT OF LPS ON MINUTE VENTILATION DURING EXPOSURE TO 10%FIO2 IN RATS



Balan, Resp Physiology and Neurobiology, 2011



Di Fiore, J of Pediatrics, 2010



Di Fiore, J of Pediatrics, 2010

MANAGEMENT OF AOP – THE CAP TRIAL

Table 3. Other Outcomes.

Outcome Variable	Caffeine Group	Placebo Group	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value
Retinopathy of prematurity — no./total no. (%)					
All stages*	382/966 (39.5)	417/955 (43.7)	0.84	0.83 (0.69 to 1.01)	0.06
Severe retinopathy†	49/965 (5.1)	75/955 (7.9)	0.63	0.61 (0.42 to 0.89)	0.01
Cerebral palsy with a GMFCS level of 3 to 5 — no./total no. (%)‡§	12/905 (1.3)	19/898 (2.1)	0.62	0.62 (0.30 to 1.29)	0.20
Seizure disorder — no./total no. (%)‡	13/907 (1.4)	12/903 (1.3)	1.08	1.08 (0.49 to 2.38)	0.85
			Unadjusted Mean Difference	Mean Difference Adjusted for Center (95% CI)	
Height percentile¶					
Mean	40.7	40.5	0.19	0.21 (–2.48 to 2.90)	0.88
Median (interquartile range)	38.5 (14.5 to 64.9)	36.8 (14.6 to 64.0)			
Weight percentile‖					
Mean	27.9	28.5	–0.60	–0.59 (–3.22 to 2.05)	0.66
Median (interquartile range)	16.8 (3.9 to 46.1)	16.8 (3.7 to 48.5)			
Head circumference percentile**					
Mean	54.3	52.1	2.16	2.28 (–0.63 to 5.18)	0.12
Median (interquartile range)	56.4 (27.0 to 83.8)	51.1 (25.0 to 81.8)			

Schmidt B et al. Long-Term Effects of Caffeine Therapy for Apnea of Prematurity. *N Engl J Med.* 2007; 357:1893-1902