Can We Optimize Caffeine Therapy?

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CASE WESTERN RESERVE UNIVERSITY EST. 1826


Cafe
Tortoni

Caffeine Therapy

- **Where have we been?**
- Impact of the CAP Study
- How does caffeine work?
- What has happened?
- What to do now?

Apnoeic Attacks in the Newborn Treated with Aminophylline

"In 10 preterm babies with birthweights ranging from 860 to 2200 gm recurring apnoeic attacks ceased or became infrequent after administration of aminophylline 5 mg suppositories at 6-hourly intervals".

Kuzemko JA & Paala J: Dept of Paediatrics, Maternity Hospital, Peterborough, 1973


1974

Yale University ***New Haven, Connecticut 06510***

January 3, 1975

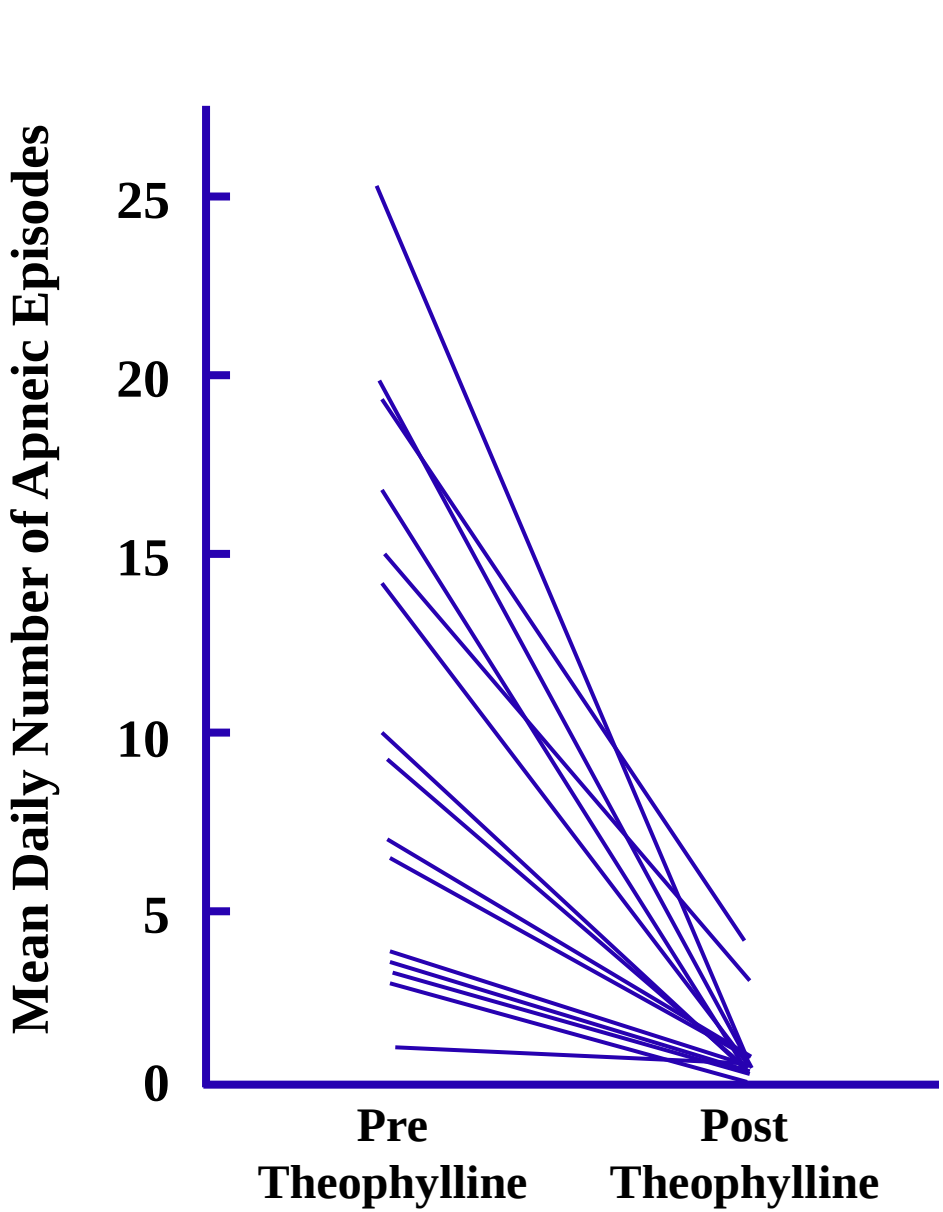
Dear Richard:

I will be happy to answer your questions concerning our apnea protocol. At the present time we are using patients as their own controls and carefully monitoring apnea lasting more than 20 seconds before and after therapy.

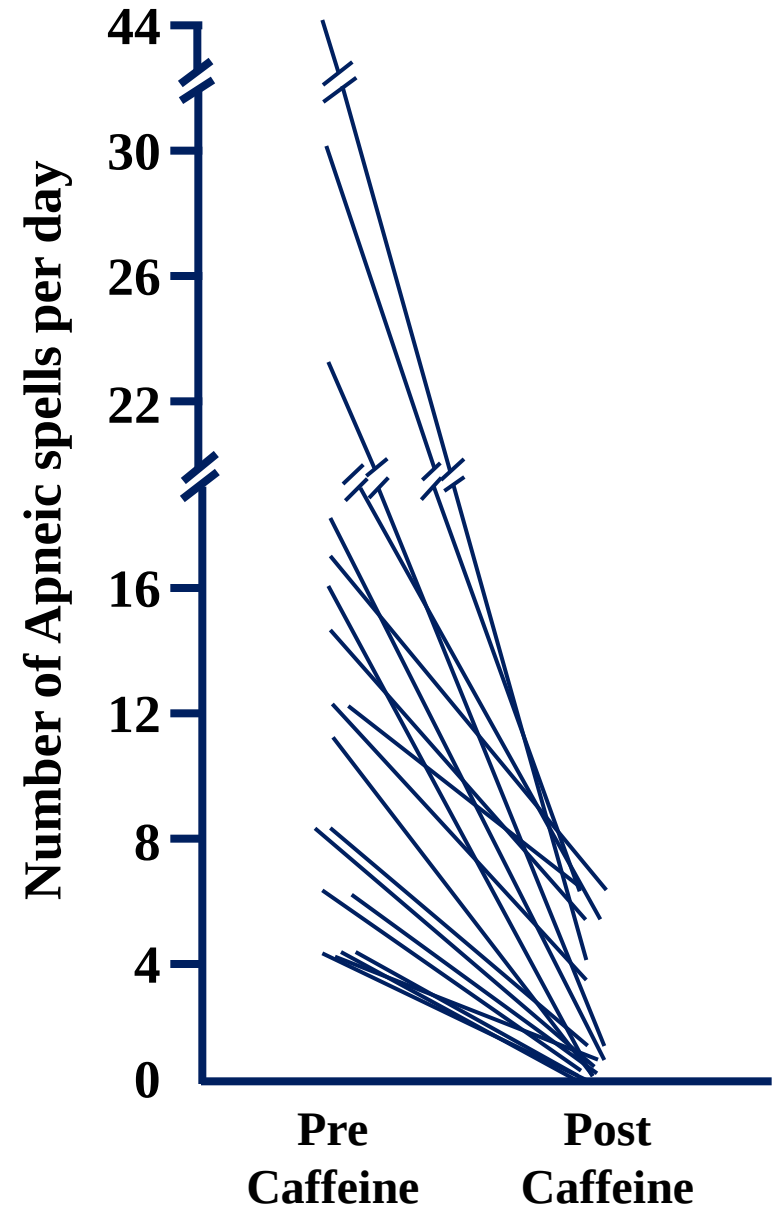
We have considered a double blind study, but that is of now difficult to embark upon as our initial results with theophylline have been quite effective.

Sincerely yours,

Joseph B. Warshaw, M.D.



Uauy, Pediatr 1975



Aranda, J Peds 1977

Caffeine Therapy

- Where have we been?
- **Impact of the CAP Study**
- How does caffeine work?
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Methylxanthine therapy in premature infants: Sound practice, disaster, or fruitless byway?

Schmidt B: J Pediatr 1999

CAP TRIAL

Schmidt B.

Effect of Caffeine Therapy for Apnea of Prematurity

	Caffeine Group (n=1006)	Placebo Group (n=1000)	
Postmenstrual age at last use of endotracheal tube			
Median	**29.1 weeks**	**30.0 weeks**	**<0.001**
Postmenstrual age at last use of supplemental oxygen			
Median	**33.6 weeks**	**35.1 weeks**	**<0.001**

Schmidt, NEJM 2006

Caffeine Therapy for Apnea Trial: Outcome at 18-21 Months

	Caffeine	Placebo	OR	p value
Death or disability	40%	46%	0.77	0.006
Cerebral palsy	4.4%	7.3%	0.58	0.009
MDI<85	34%	38%	0.80	0.035
Severe ROP	5.1%	7.9%	0.63	0.01

Schmidt B: NEJM 2007

Efficacy of Xanthine Therapy

"Infants receiving respiratory support derived more neurodevelopmental benefits from caffeine than infants not receiving support."

"Earlier discontinuation of any positive airway pressure explained 49% of the beneficial long term drug effect."

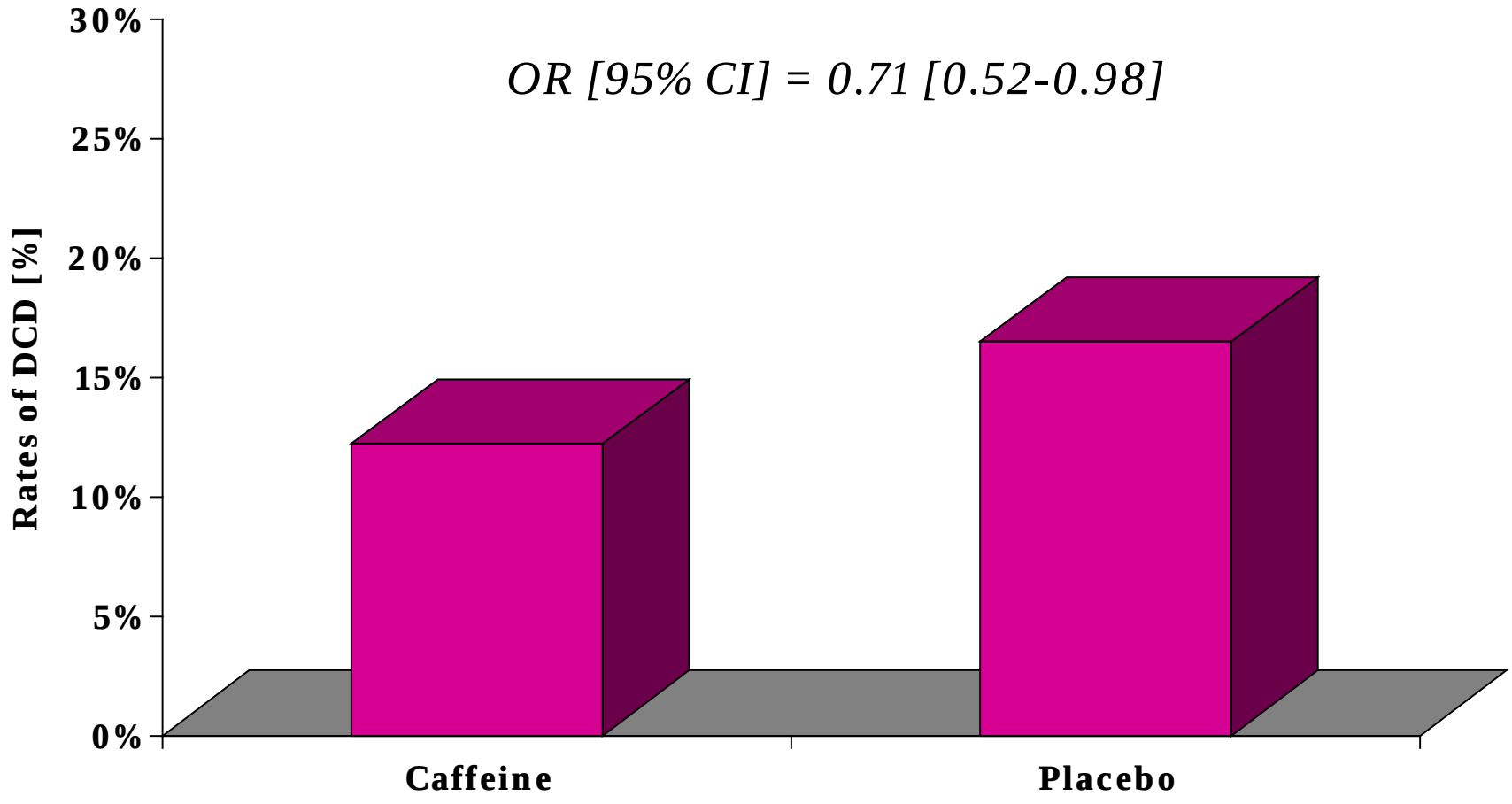
Davis PG, et al.: J Pediatr 2010

Survival Without Disability to Age 5 Years After Neonatal Caffeine Therapy for Apnea of Prematurity

"Neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children with very low birth weights who were assessed at 5 years."

Schmidt B: JAMA 2012

Developmental Coordination Disorder



Doyle LW, et al: J Pediatr 2014

Rates of Functional Impairment at 11 Years in the CAP Trial

	Caffeine	Placebo	p value
Poor academic performance	14.4%	13.2%	NS
Behavior problems	10.9%	8.3%	NS
Motor impairment	19.7%	27.5%	<0.01*

Schmidt: JAMA Pediatr, 2017

Caffeine Therapy

- Where have we been?
- Impact of the CAP Study
- **How does caffeine work?**
- What has happened?
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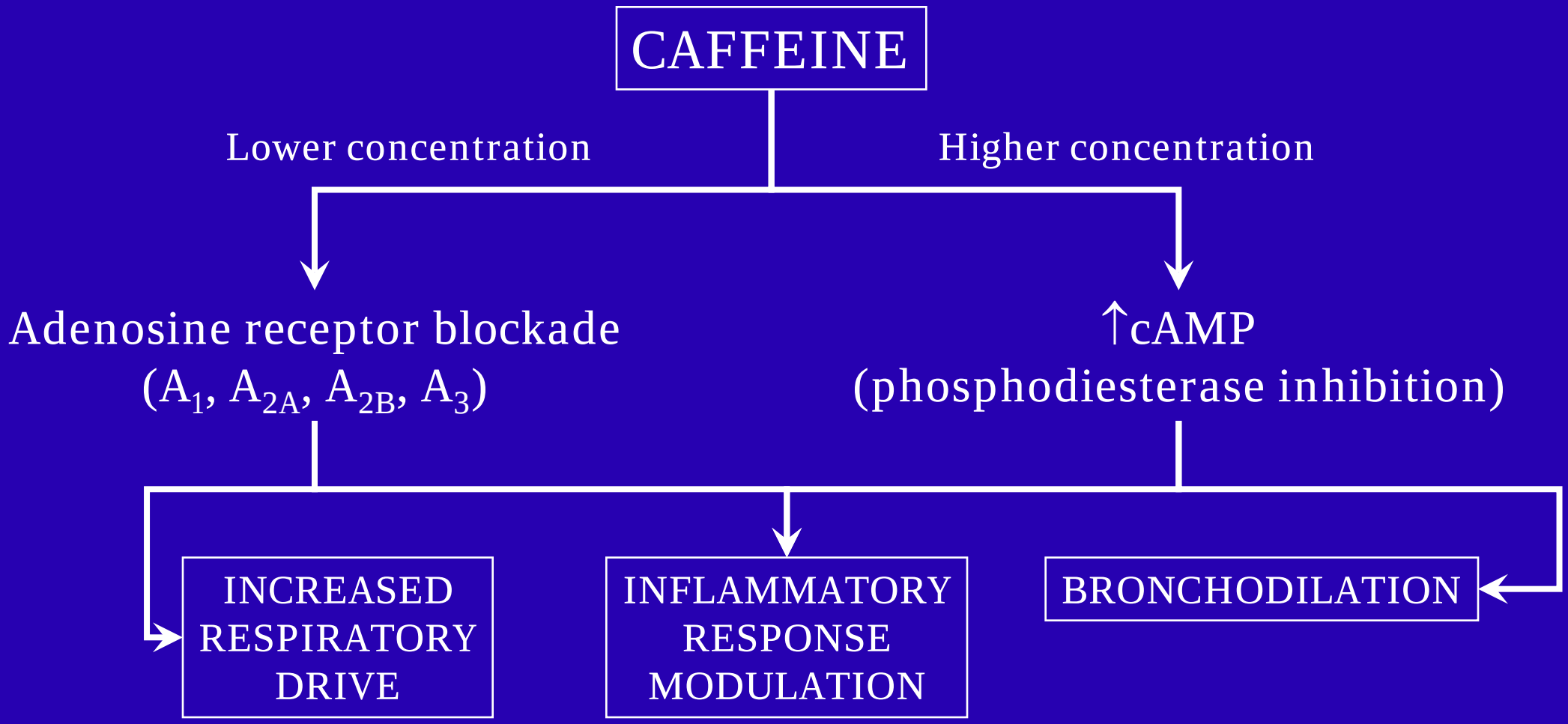
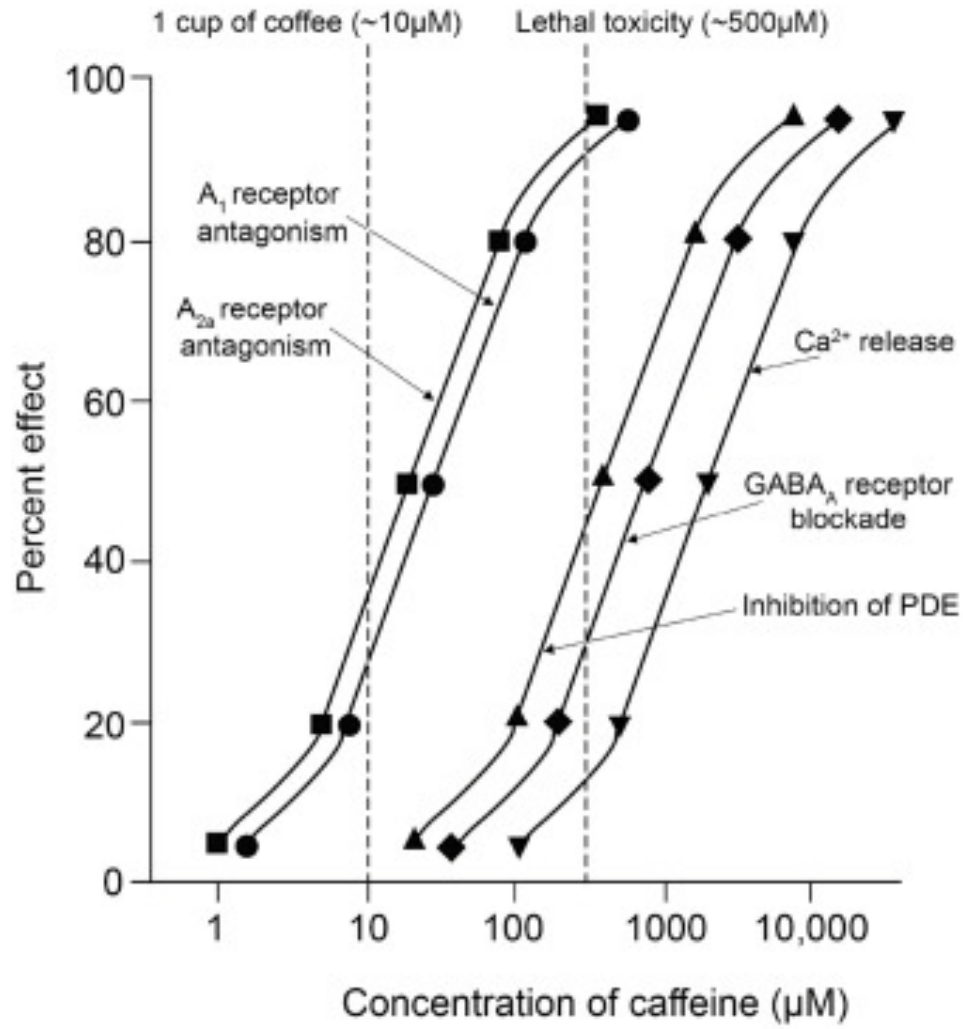
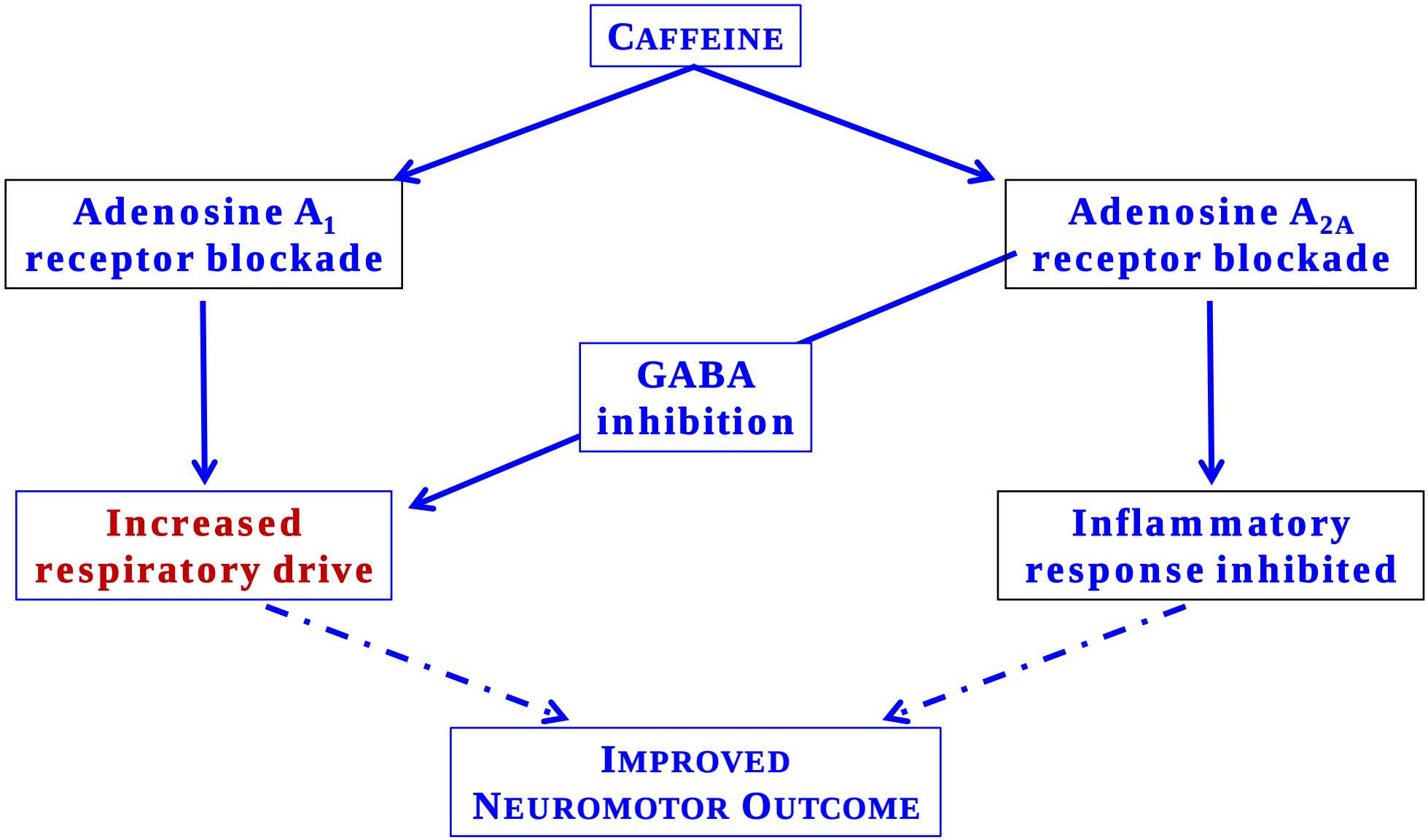
Proposed Beneficial Effects of Xanthine on BPD



Caffeine Concentration to Activate Molecular Targets



Atik A: NeuroToxicology 2016


CAFFEINE
Adenosine A_1 receptor blockade
Adenosine A_{2A} receptor blockade
GABA inhibition
Increased respiratory drive
Inflammatory response inhibited
IMPROVED NEUROMOTOR OUTCOME

Xanthines for Neonatal Apnea

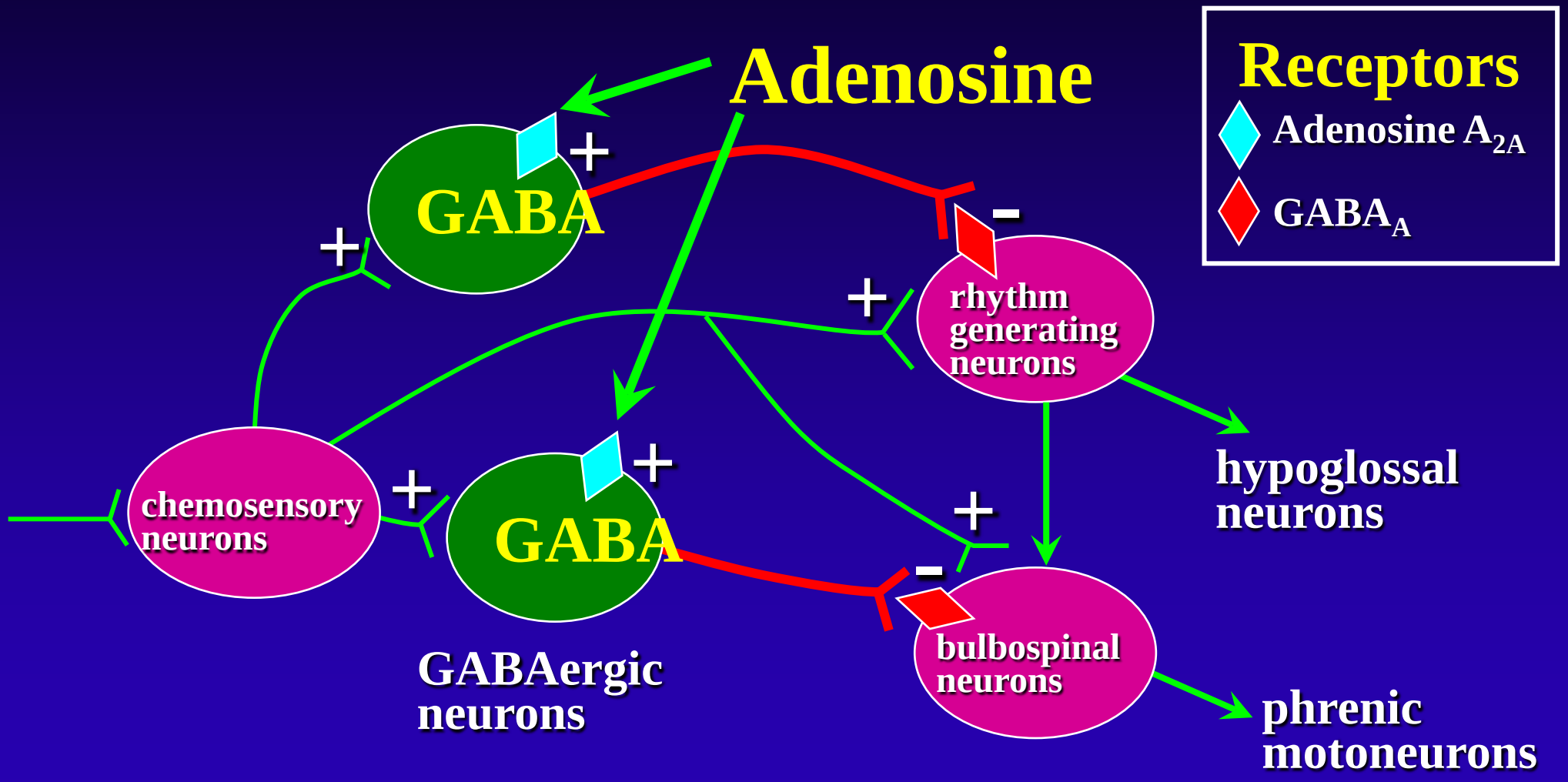
Physiologic

- Increased minute ventilation
- Shift of CO_2 response curve to left ± increased slope
- Improved pulmonary mechanics
- Decreased hypoxic ventilatory depression
- ? Greater efficiency of diaphragmatic contraction

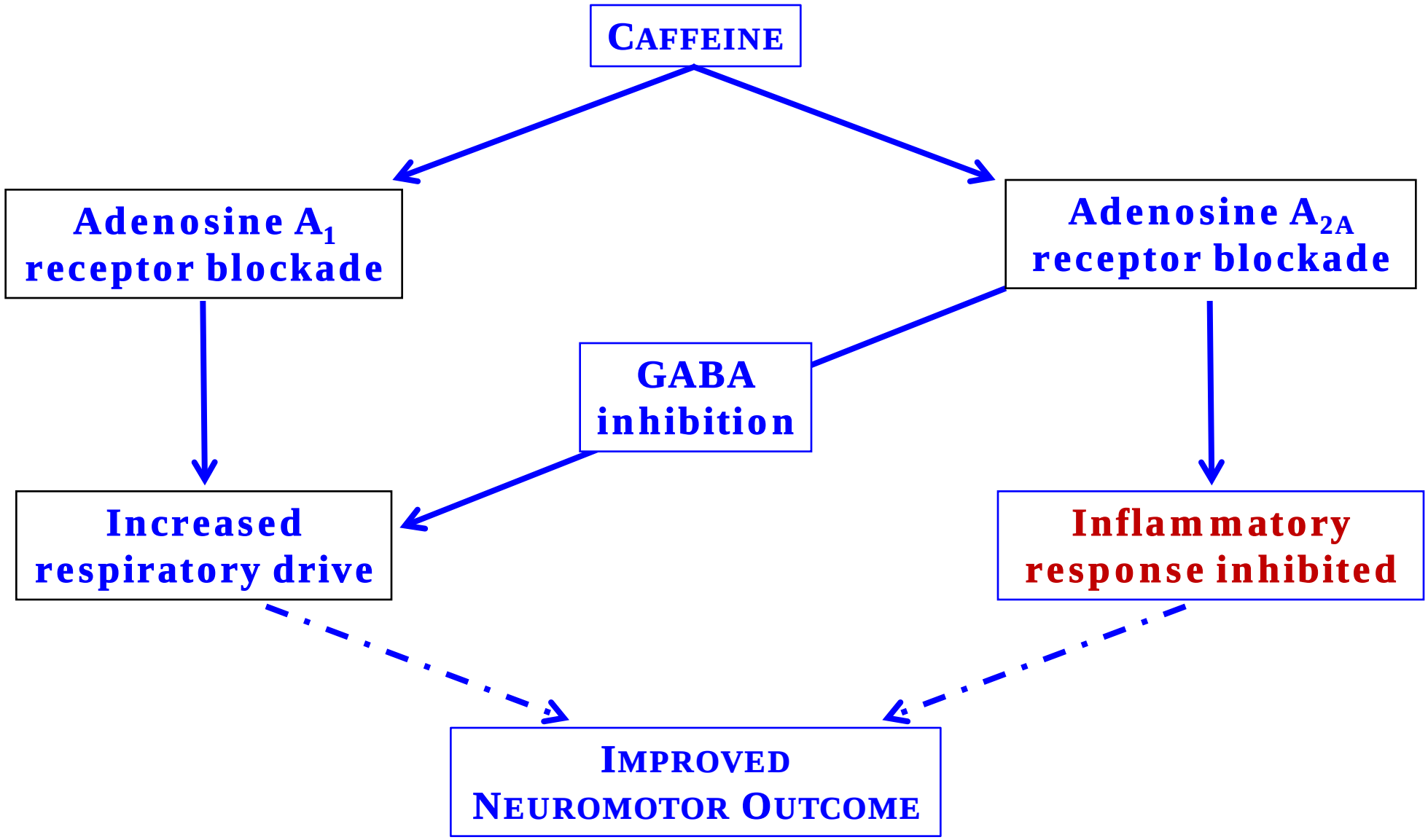
Biochemical

- Central adenosine receptor subtype antagonism
- ? Inhibition of phosphodiesterase

Proposed Model for GABA/Adenosine Interaction in Respiratory Regulation



Wilson: Resp Physiol Neurobiol 2004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Increased respiratory drive
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IMPROVED NEUROMOTOR OUTCOME

Background: Inconsistent Data!

Protective effects of adenosine A_{2A} receptor agonist in ventilator-induced lung injury in rats
Chen, et al: Crit Care Med 2009

Chronic or high dose acute caffeine treatment protects mice against oleic acid-induced acute lung injury via an adenosine A_{2A} receptor-independent mechanism
Li, et al: Eur J Pharmacol 2011

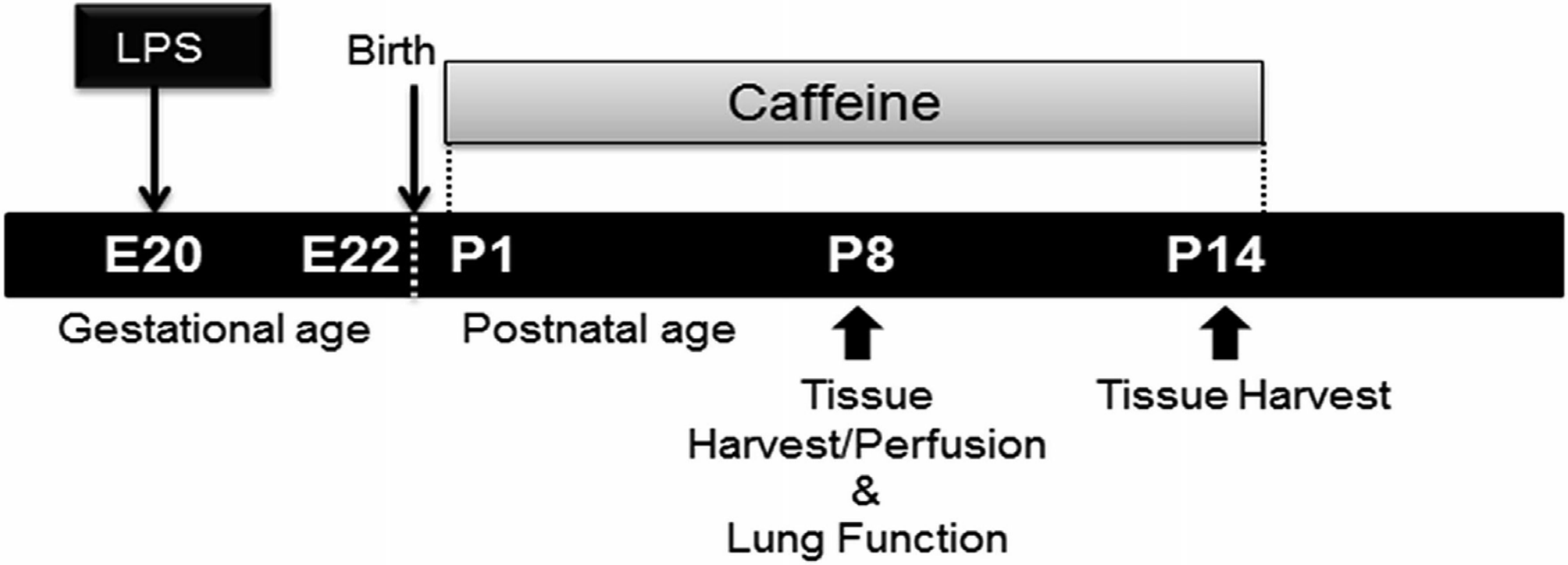
Correlation between serum caffeine levels and changes in cytokine profile in a cohort of preterm infants
Chavez-Valdez, et al: J Pediatr 2011

Prevention of Hyperoxia-mediated Pulmonary Inflammation in Neonatal Rats by Caffeine

"Treatment with caffeine at the beginning of hyperoxia blocked the upregulation of chemokines and proinflammatory cytokines and the influx of myeloid leukocytes seen with high oxygen".

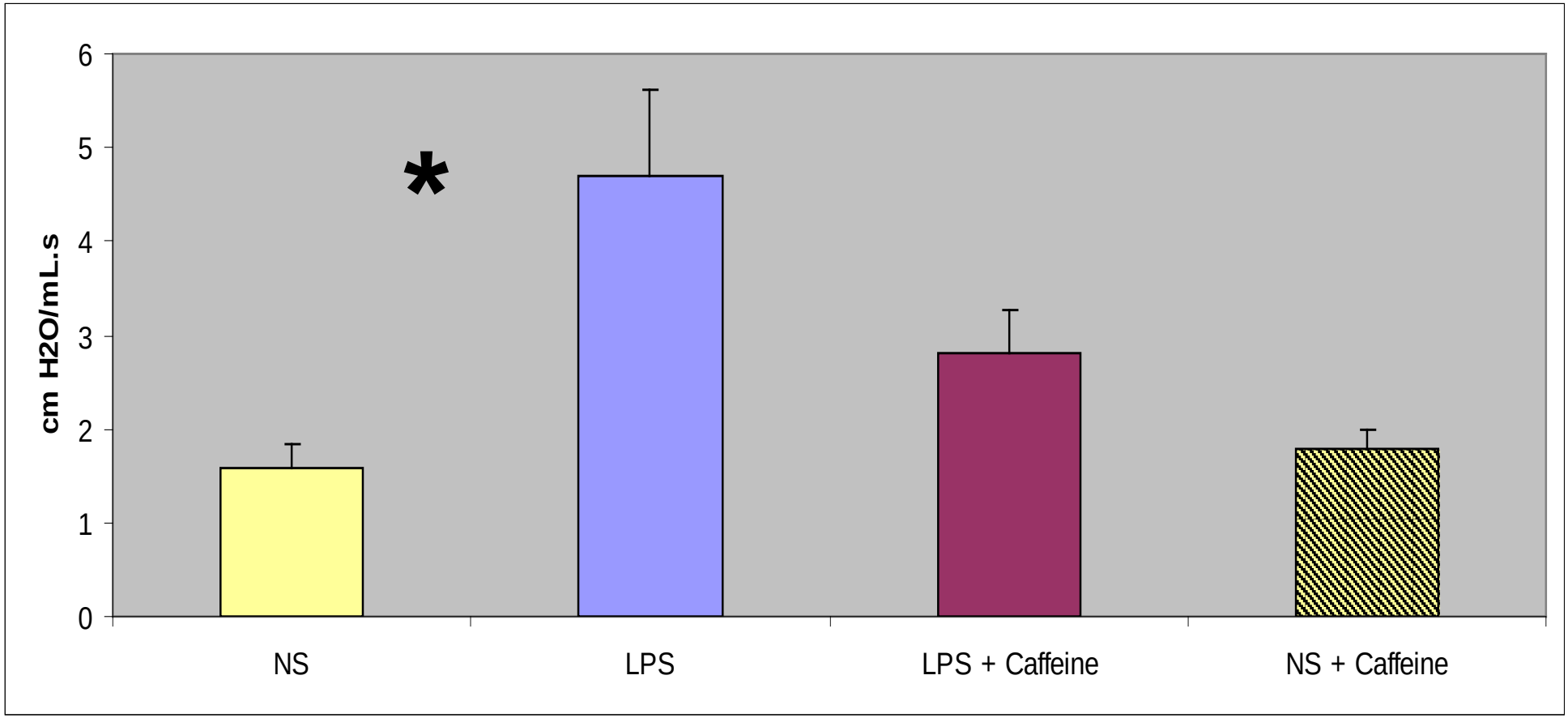
Weichelt U: Eur Respir J 2013

Methods



Experimental Protocol • Köroğlu OA: Neonatology 2014

Decrease in Respiratory System Resistance at Day 8 after Caffeine in LPS-Exposed Pups

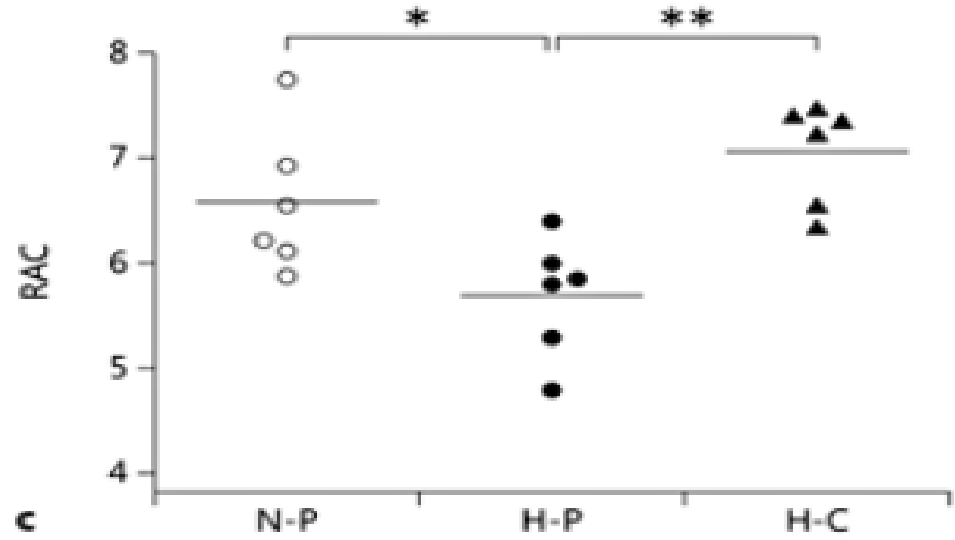


*p<.01 via one way ANOVA (post-hoc)

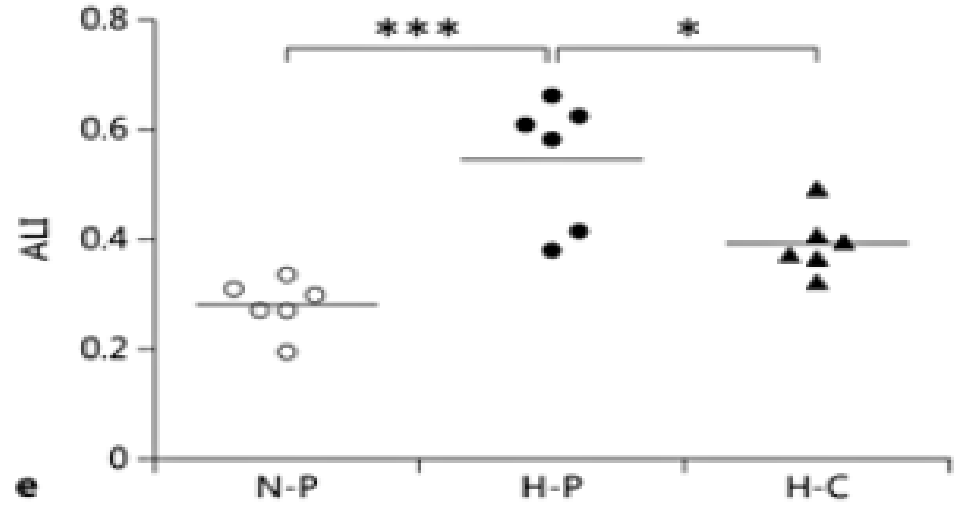
Köroğlu: Neonatology 2014

Caffeine Prevents Hyperoxia-induced Lung Damage in Preterm Rabbits

Radial alveolar counts



Acute lung inflammation scores



Nagatomo R: Neonatology 2016

CAN CAFFEINE BOOST YOUR BRAIN?

THE EVIDENCE

Multiple studies show that caffeine consumption may cut Alzheimer's risk.

THE THEORY

Caffeine may block inflammation linked to neurodegenerative diseases, a new University of Illinois study found.

Neuroprotection by Caffeine in Hyperoxia-Induced Neonatal Brain Injury

- Rat pups were pretreated with caffeine and exposed to 80% oxygen for 24-48 hours
- Caffeine...
  - reduced oxidative stress markers
  - promoted anti-oxidative responses
  - downregulated pro-inflammatory cytokines

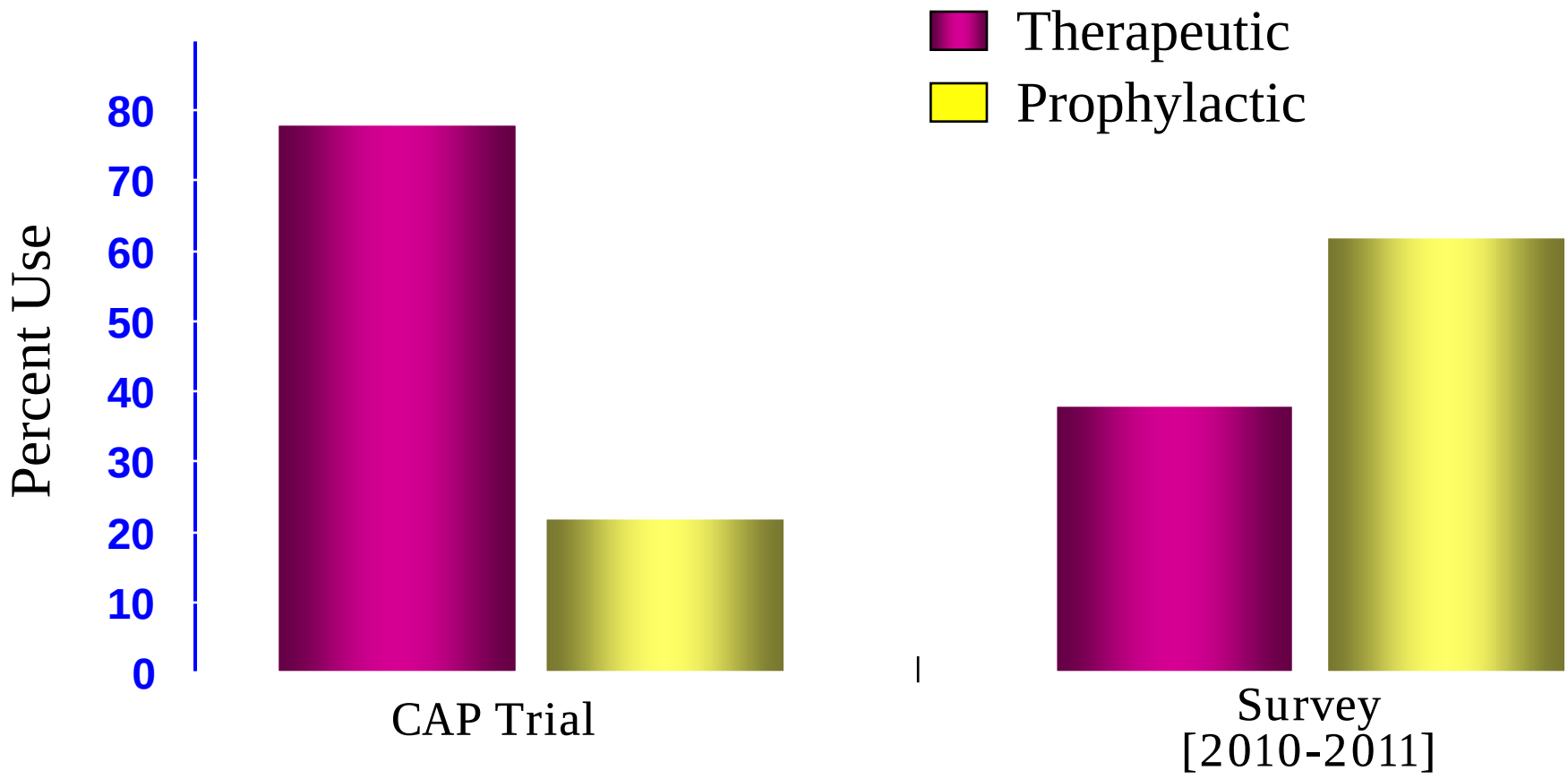
Endesfelder S et al: Int J Mol Sci 2017

Caffeine Therapy

- Where have we been?
- Impact of the CAP Study
- How does caffeine work?
- **What has happened?**
- What to do now?

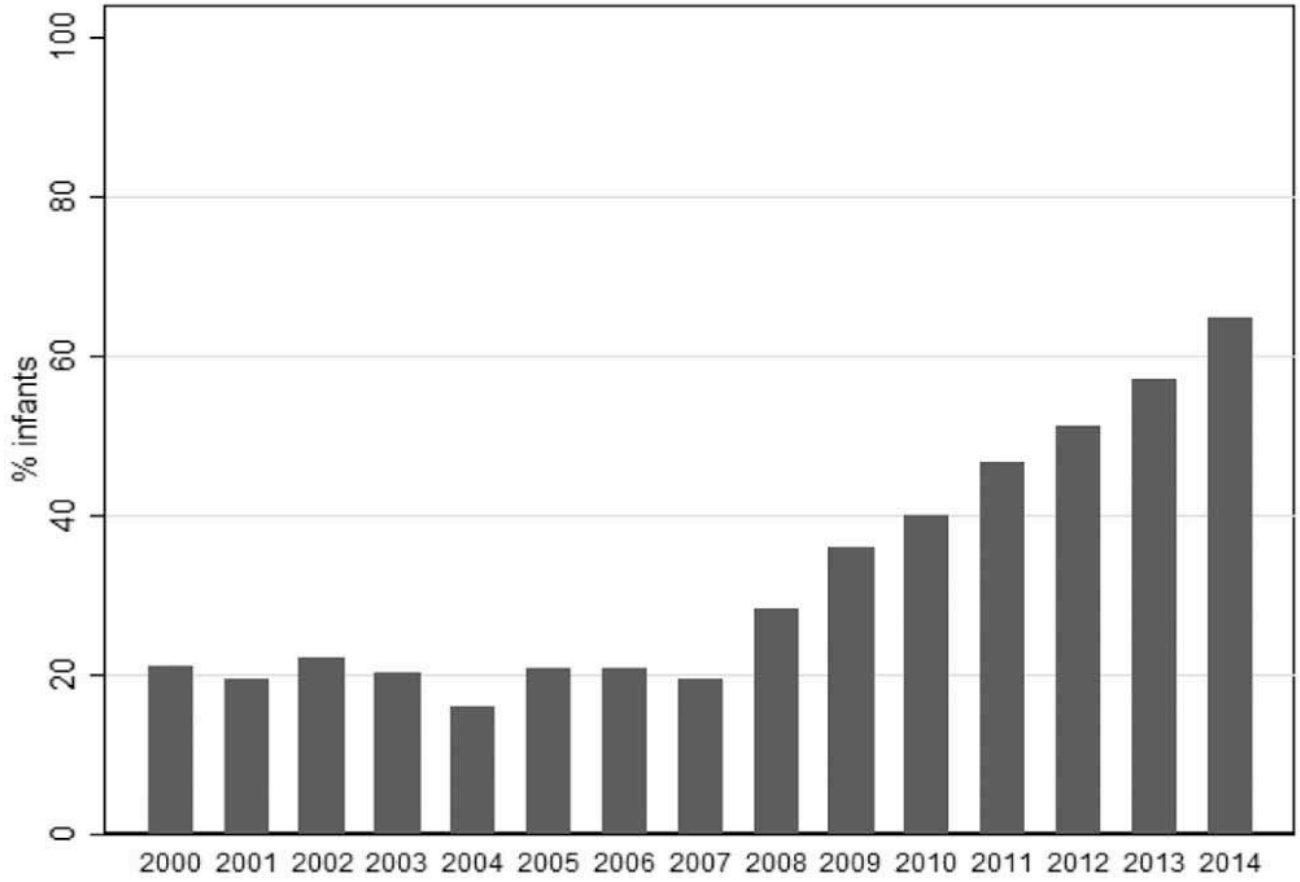
- ***When to start?***
- ***When to end?***
- ***How much?***

Indications for Caffeine Therapy



Abu Jawdeh: J Neonat Perinat Med 2013

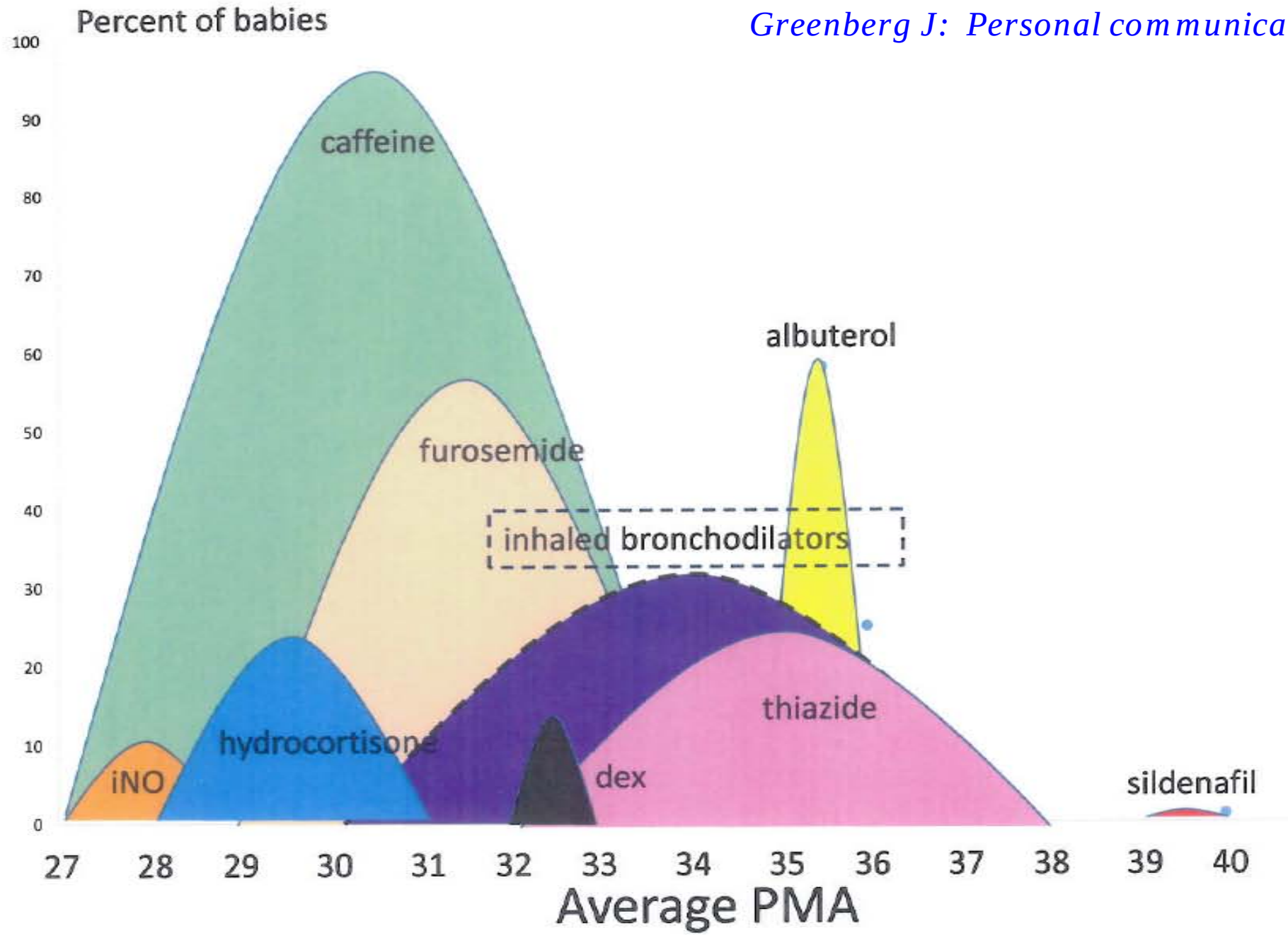
Early Caffeine Prophylaxis for VLBW: Pediatrix Database*



*Initiated on day of birth

Jobe AH: J Pediatr 2017

Greenberg J: Personal communication



Association of Early Caffeine and Outcome:*

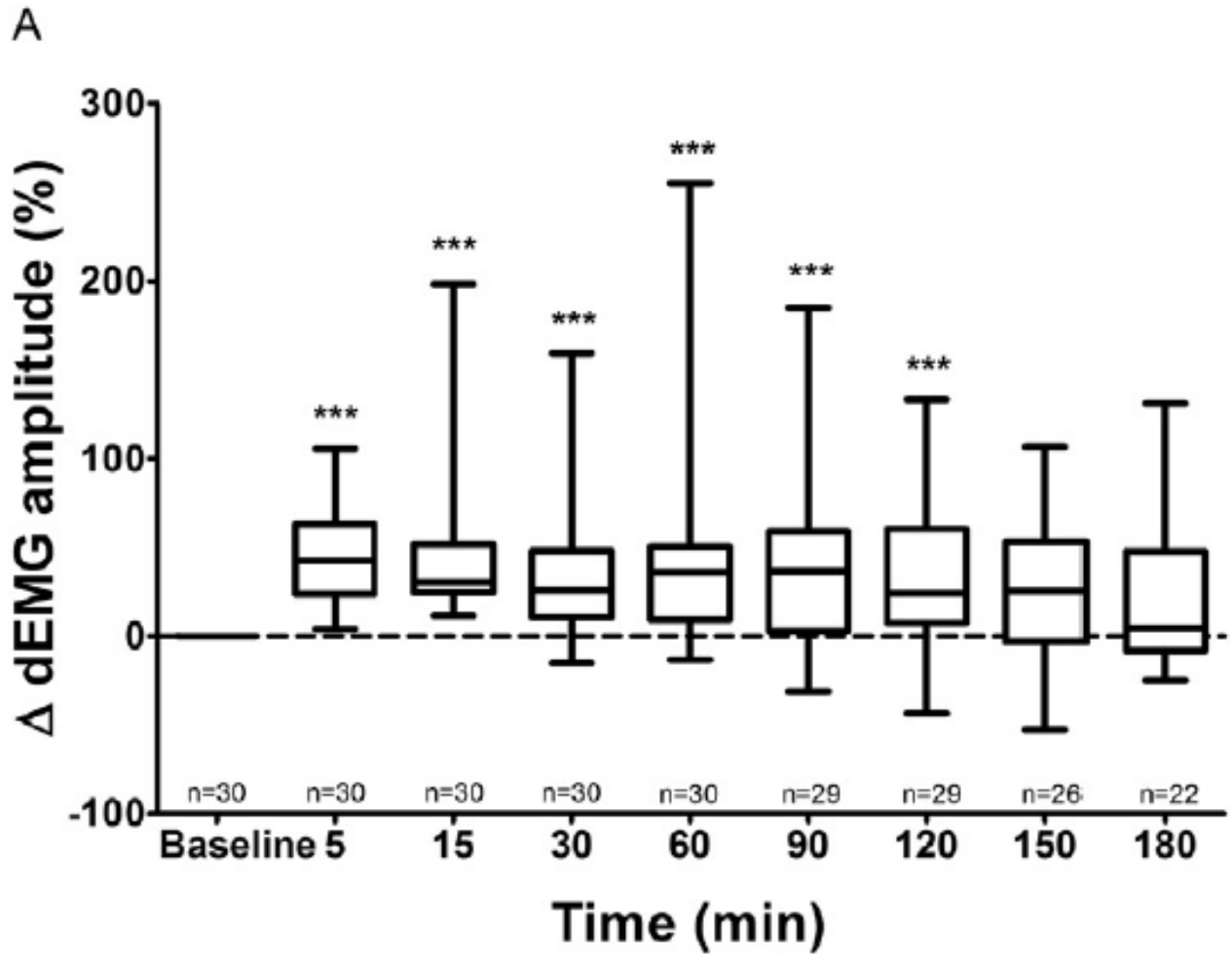
Retrospective Cohort Study

Variable	Caffeine Group, Median (IQR)		*P* Value
	Early (n = 3806)	Late (n = 1295)	
Discharged receiving oxygen, No. (%)	931 (24.5)	323 (24.9)	.73
Duration of oxygen requirement, d	9 (1-43)	8 (1-49)	.67
Duration of mechanical ventilation, d	2 (1-9)	4 (1-23)	<.01
Duration of noninvasive respiratory support, d	1 (1-5)	1 (1-5)	.02
Length of stay, d	52 (27-88)	49 (21-88)	.48
Discharged receiving caffeine, No. (%)	1386 (35.4)	475 (36.7)	.87

** Within the first two days*

Lodha A: JAMA Pediatr 2015

Rapid Response of Diaphragm EMG to Caffeine Bolus [10 mg/kg caffeine base]



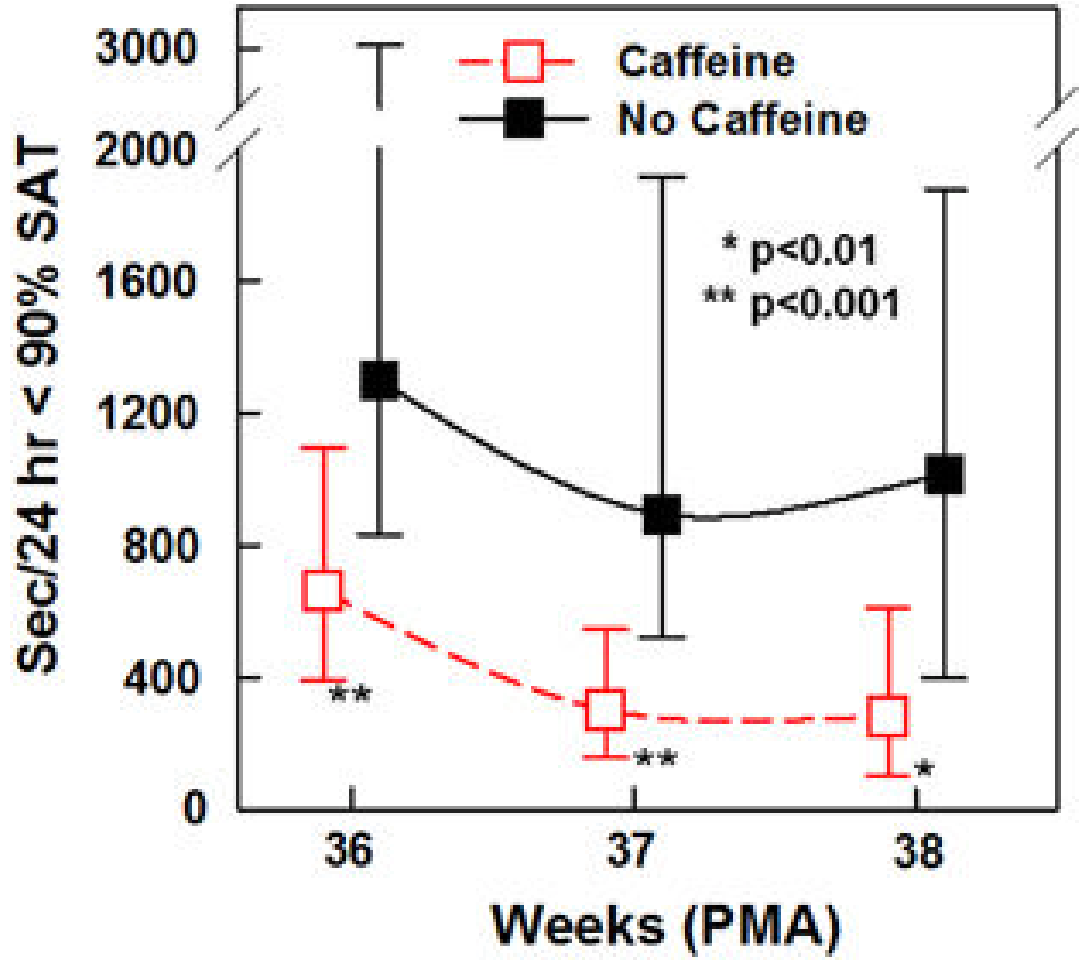
Kraaijenga JV: J Pediatr 2015

Caffeine to Improve Breathing Effort of Preterm Infants at Birth

	Caffeine DR group (13 patients) $N = 1{,}091$ breaths	Caffeine NICU group (10 patients) $N = 779$ breaths	*P* value
Minute volume (ml/kg)[a]	189 ± 74	162 ± 70	<0.05
Average inspired tidal volume (ml/kg)[b]	5.2 (3.9 to 6.4)	4.4 (3.0 to 5.6)	<0.001
Respiratory rate/min at 7–9 min after birth[a]	35 ± 10	33 ± 10	NS
Heart rate (b.p.m.)[b]	157 (141 to 170)	146 (135–160)	<0.001
Oxygen saturation (%) at 7–9 min after birth[b]	91 (87 to 94)	91 (88 to 94)	NS

Dekker J, et al.: Pediatr Res 2017

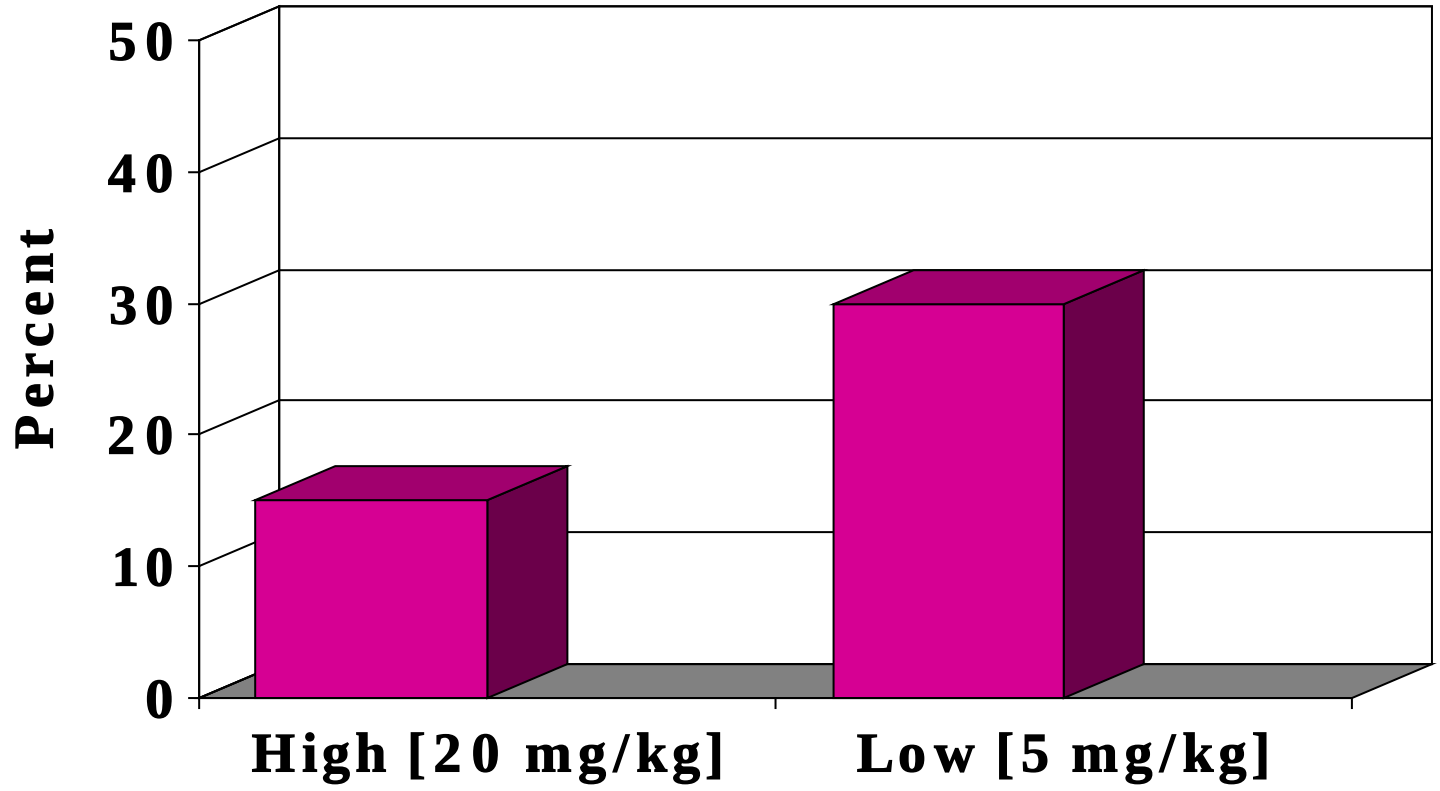
Caffeine Decreases Intermittent Hypoxia in Preterm Infants Nearing Term-equivalent Age



Dobson: J Perinatol, 2017

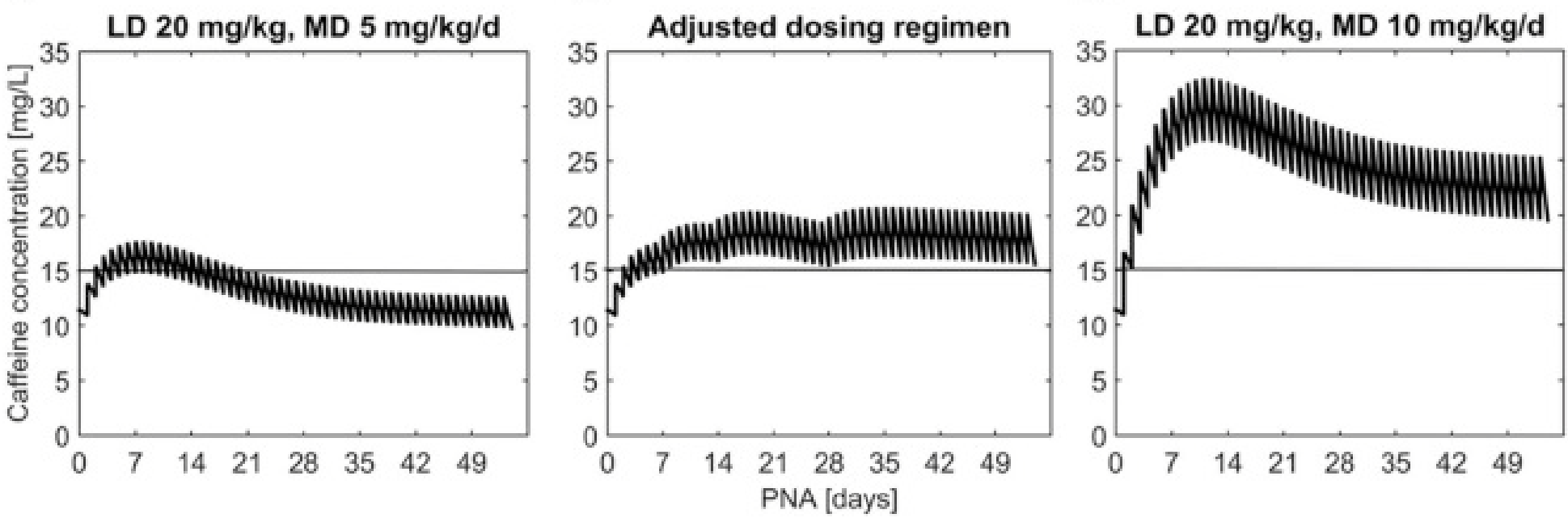
Extubation Failure after High vs Low Caffeine Citrate Maintenance Dosage

Randomized Controlled Trial



Steer P: Arch Dis Child Fetal Neonatal Ed 2004

Caffeine Citrate Dosing Adjustments to Assure Stable Caffeine Concentrations in Preterm Neonates



Koch G: J Pediatr 2017

Early Caffeine Prophylaxis and Risk of Initial CPAP Failure in VLBW Infants

[Data from 366 NICUs - 2000-2014]

	Early caffeine DOL 0	**Routine caffeine DOL 1-6**	**aOR**
	N = 4528	**N = 6605**	**(95% CI)**
CPAP failure	990 (22%)	1376 (21%)	1.05 (0.93, 1.18)
Invasive ventilation	683 (15%)	1029 (16%)	1.06 (0.92, 1.21)
Surfactant therapy	662 (15%)	919 (14%)	1.00 (0.88, 1.15)

Patel RM, et al.: J Pediatr 2017

Effect of Early Caffeine on Age of First Successful Extubation [23-30 wk GA]

Outcome	Early caffeine [n=41]	Control* [n=42]	p
Age at first successful extubation [days]	21 [10 to 41]	20 [9 to 43]	.703

data are median [IQR]

**placebo with caffeine load at extubation*

Amaro CM et al: J Pediatr 2018

Caffeine Therapy

- Where have we been?
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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