Thoughtful Approach to Non-Invasive Ventilation

- What, When, & Why

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Conflict of Interest Disclosures

- **Faculty: Bradley Yoder, MD**
- **Relationships w/in past 10 years:**
  - **Research Support:**
    - **NHLBI, NICHD**
    - **Drager, Vapotherm, INO Therapeutics**
  - **Speakers Bureau:**
    - **Fisher & Paykel (unpaid, except travel support)**

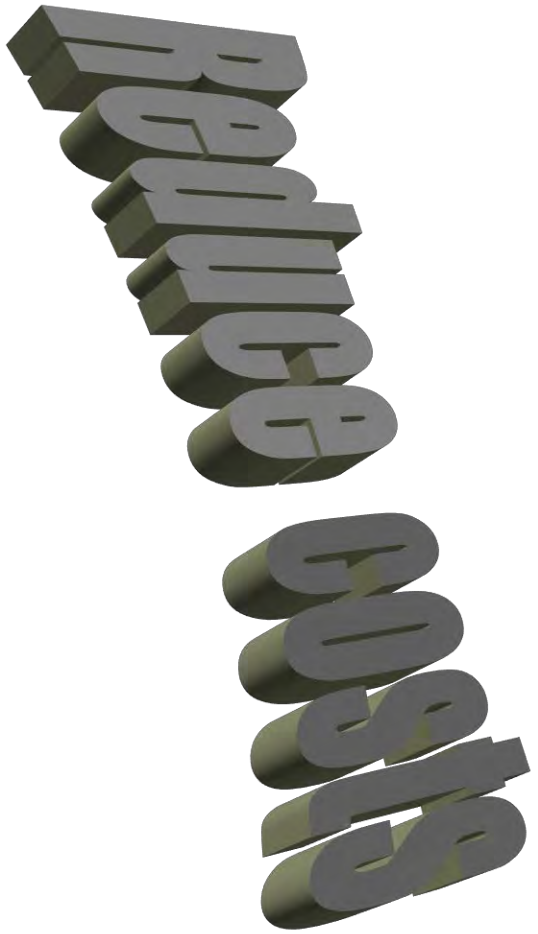
Objectives

- Discuss similarities and differences in the most common NIV modes of respiratory support
- Identify key differences in different interfaces for non-invasive respiratory support
- Recognize limited trial evidence identifying best NIV approaches on long-term function

Non-invasive ventilation….
….in 45 minutes!!

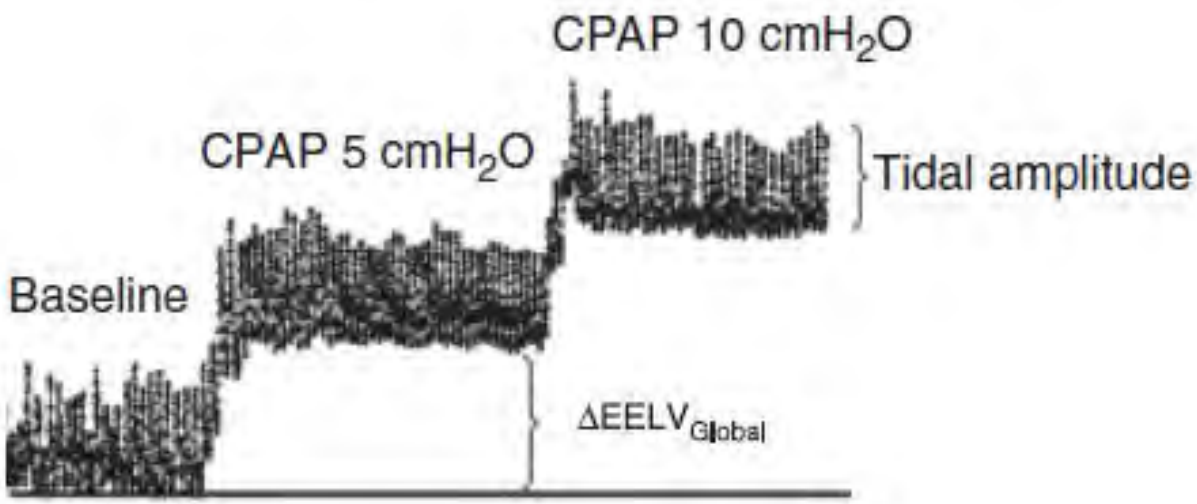
Rationale/Goals of Non-Invasive Ventilation

- Minimize apnea
- Improve oxygenation
- Improve ventilation
- Reduce work of breathing
- Minimize lung injury

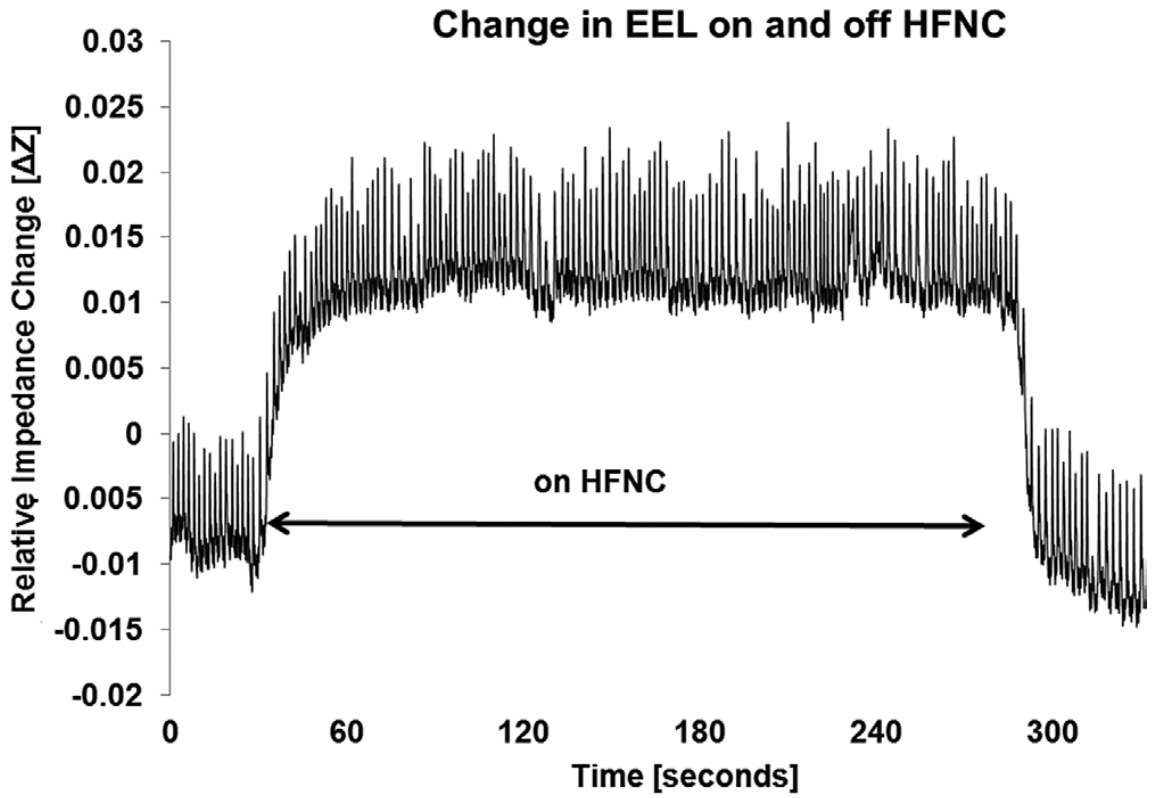


All NIV modes can increase end-expiratory lung volume (EELV) → improve O2

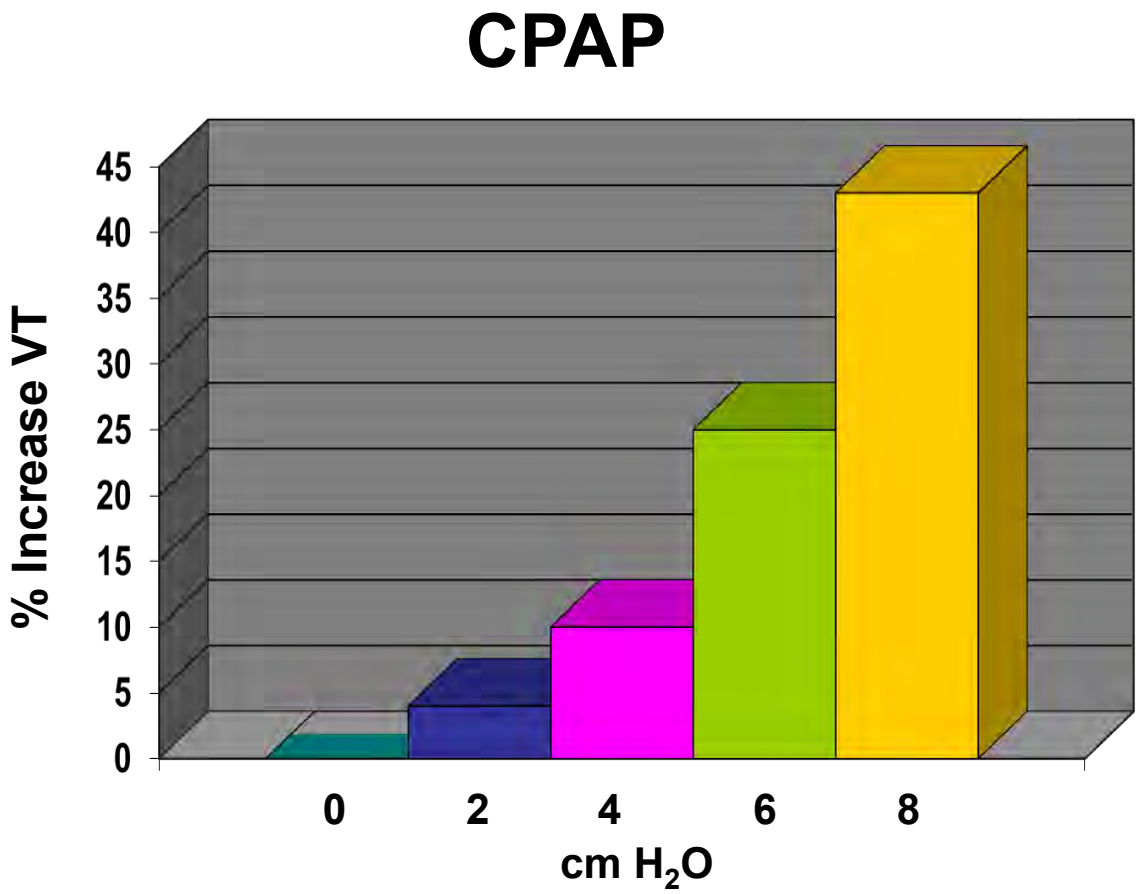
Change in EEL on nCPAP

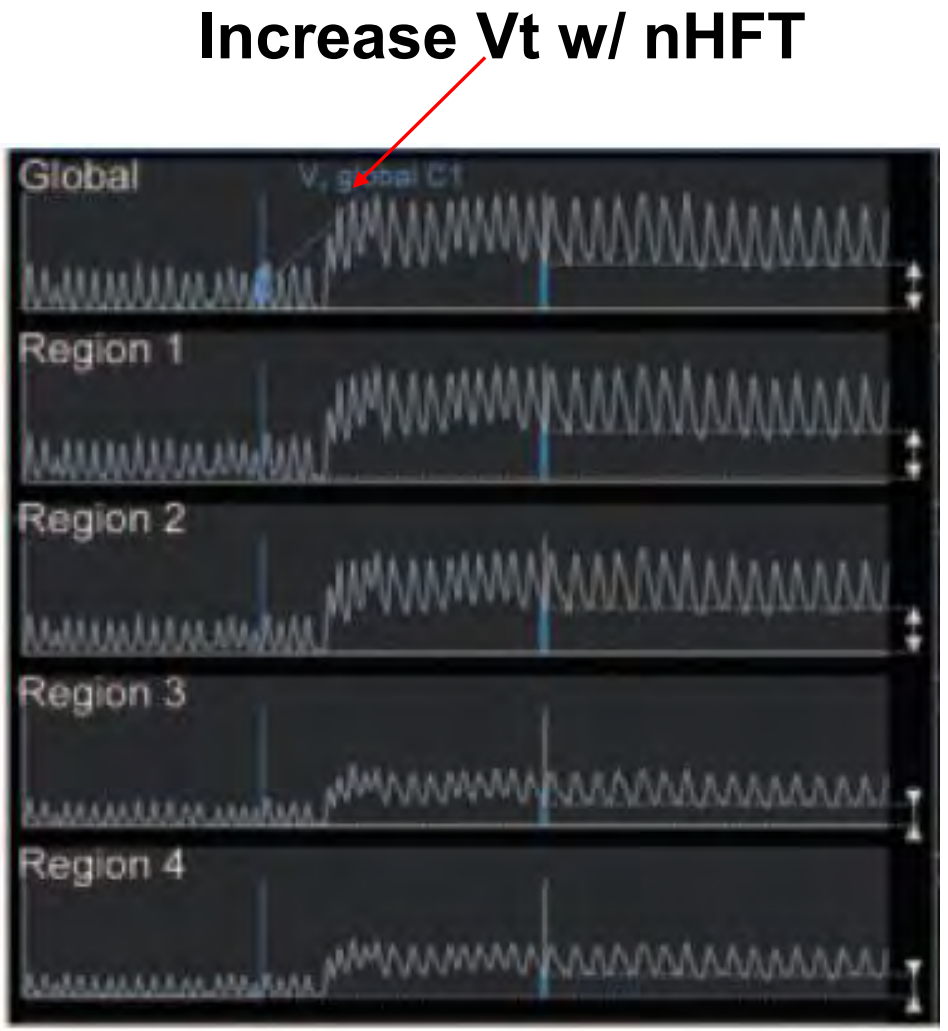


Change in EEL on & off nHFT



All NIV modes can improve ventilation





All NIV Modes can minimize lung injury

(we think)

Prevent/Remove endotracheal tube

- Decrease volu-trauma
- Decrease atelectotrauma
- Reduce risk for nosocomial infection
- Minimize inflammation

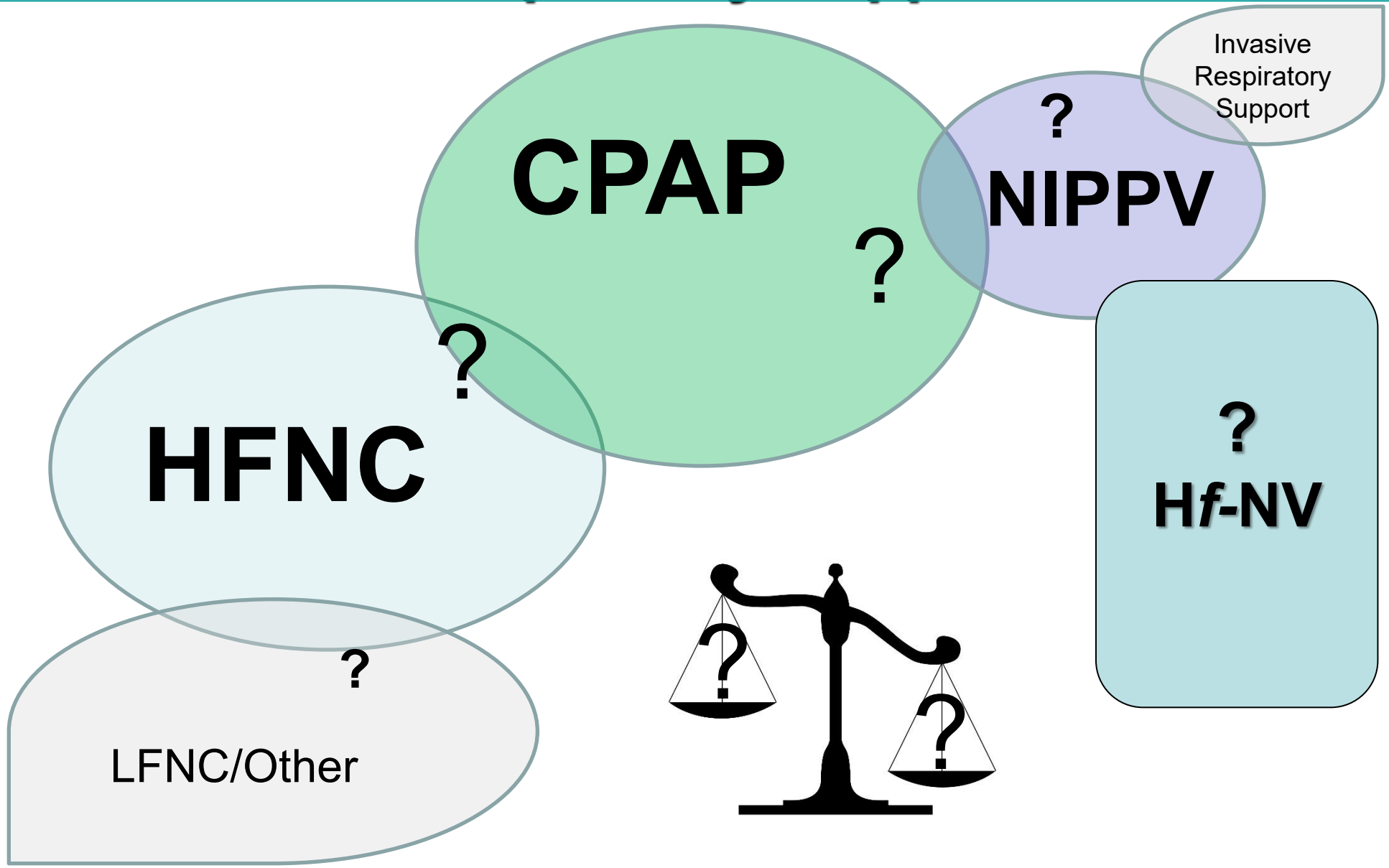
Non-Invasive Ventilation

- Are all modes equivalent?
- Are all devices similar within each mode?
- What effect does the interface have?

Non-Invasive Ventilation

- What pressure is optimal?
- Is gestational age important?
- How long should NIV be employed?

What Devices & Modes are Available for Non-invasive Respiratory Support in the NICU



Argyle

RAM Nasal Cannula

Hudson Prongs

HFNC cannula

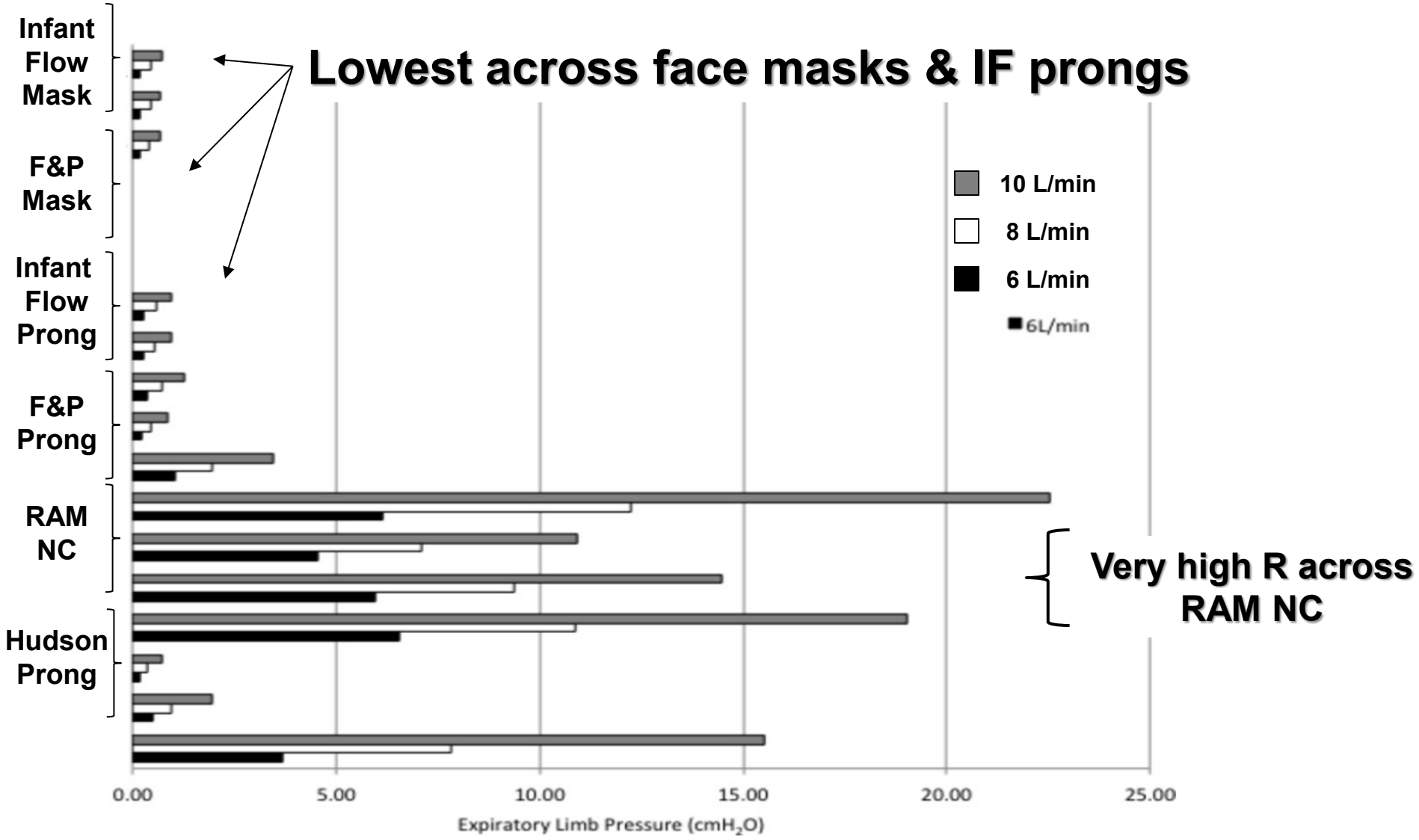
The *interface* – as or more important than the driver ?

Biomedica

Mask

NeoTech Duotube

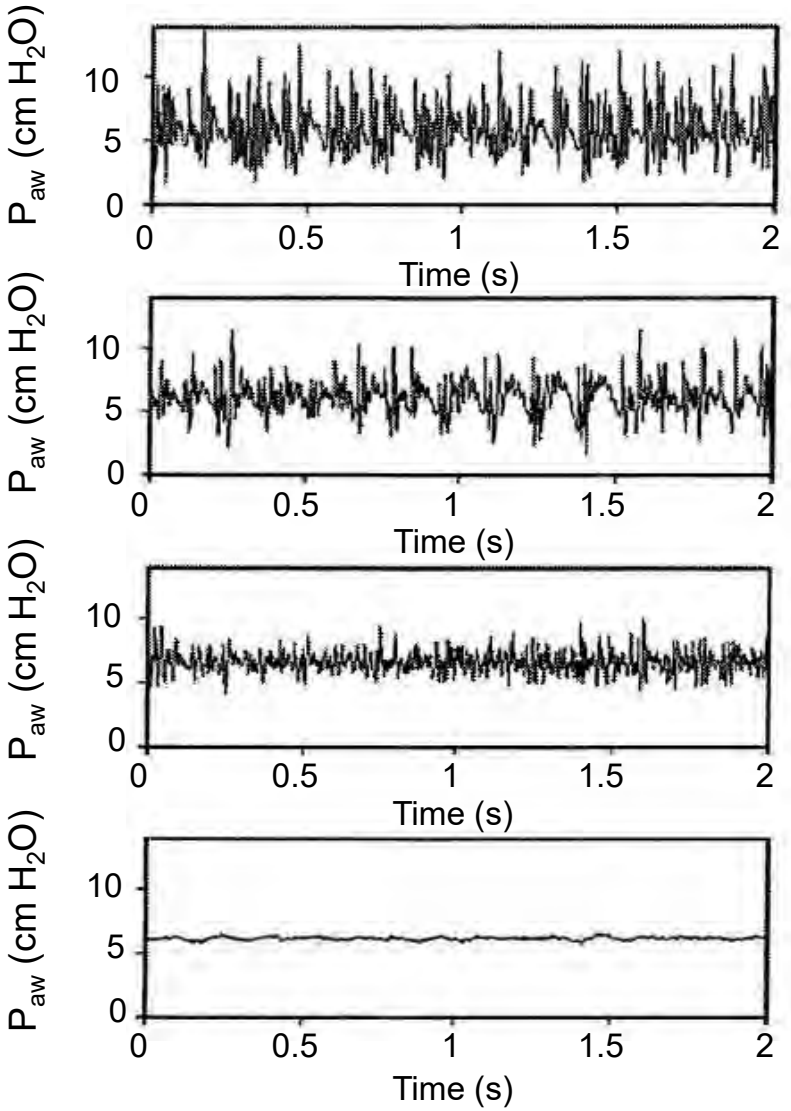
Large differences in resistance across different nasal interfaces



Green EA et al, ADCFNE 2019

All “bubbles” may not be the same!

RAM NC also significantly dampens “bubble” effect



Homemade

Fisher & Paykel

Airway Development

Babi Plus

Poli JA et al, Resp Care 2014

Meta-analysis suggests nasal mask may be more effective than bi-nasal prongs for preventing CPAP failure

Outcome	Mask	Prongs	RR (95%CI)	Total #	GRADE Quality
CPAP failure	17.8%	28.8%	**0.63** (0.45-0.88)	459	Low
Mod/Severe nasal trauma	10.1%	26.3%	**0.41** (0.24-0.72)	275	Low

….but with no difference in BPD

Jasani B et al, Pediatr Pulmonol 2018

There are various

levels of “Gentleness”

“Is Gentler Better”?

Nasal High Flow Therapy

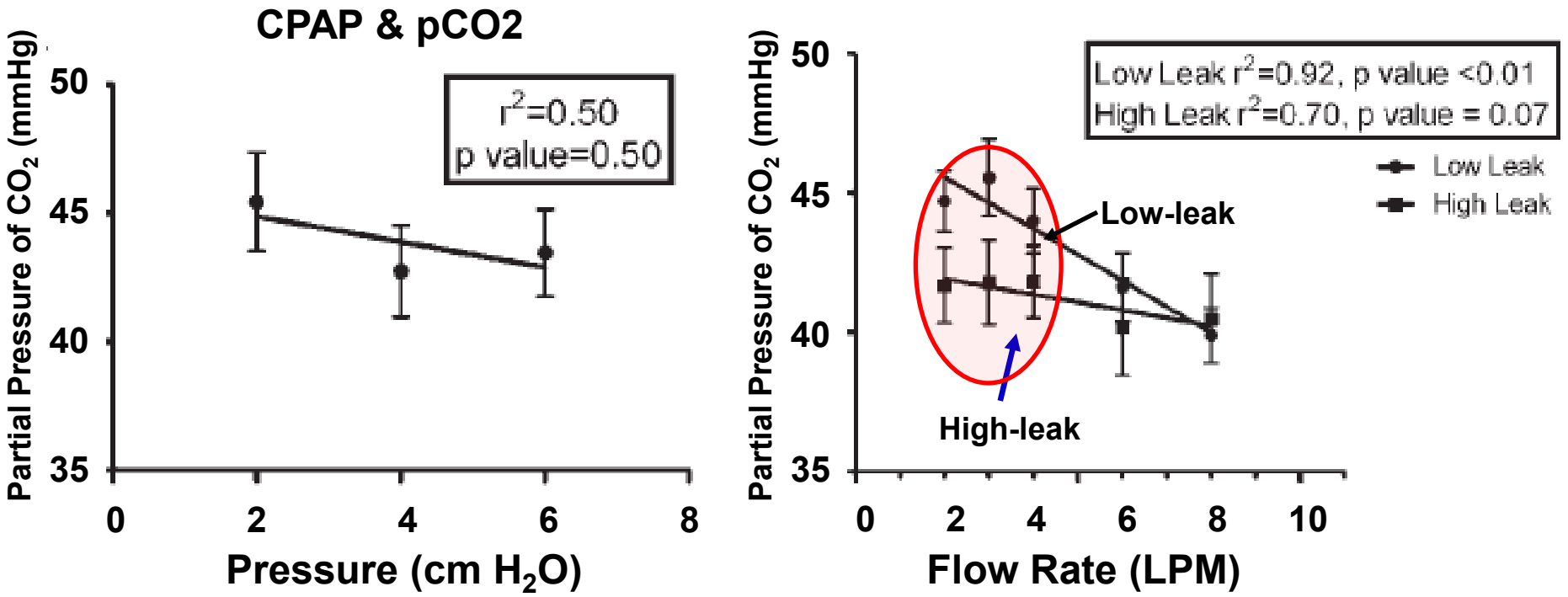
It's probably the gentlest…
…but is it as good or better than other modes?

nHFT - Mechanisms of Action

Mechanism	Process	References
Gas conditioning	**Maintain epithelial integrity** **Improved airway mechanics** **Reduce metabolic work**	Greenspan, JPeds 1991 Williams, CCM 1996 Waugh, Resp Care 2004 Schiffmann, RCCNA 2006 Chidekel, Pulm Med 2012
↑ Flow	**↑ Dead space gas washout** **↓ Inspiratory resistance** **Augment tidal volume** **Off-load diaphragm activity**	Dewan, Chest 1994 Frizzola, Peds Pulm 2011 Rubin, Peds CCM 2014 Pham, Peds Pulm 2014 Sivieri, Peds Pulm 2017,2018 Liew, ADCFNE 2019
↑ Pressure	**Dependent on:** **Flow** **Leak** **Weight** **Increases EELV**	Saslow, J Perinatol 2006 Kubicka, Peds 2008 Wilkinson, J Perinatol 2008 Frizzola, Peds Pulm 2011 Collins, J Paeds Child 2013 Hough, Peds CCM 2014 Liew, ADCFNE 2019 Hough, Peds Pulm 2020

V_{DS} Washout Effect during nHFT

Frizzola M et al, Peds Res 2011

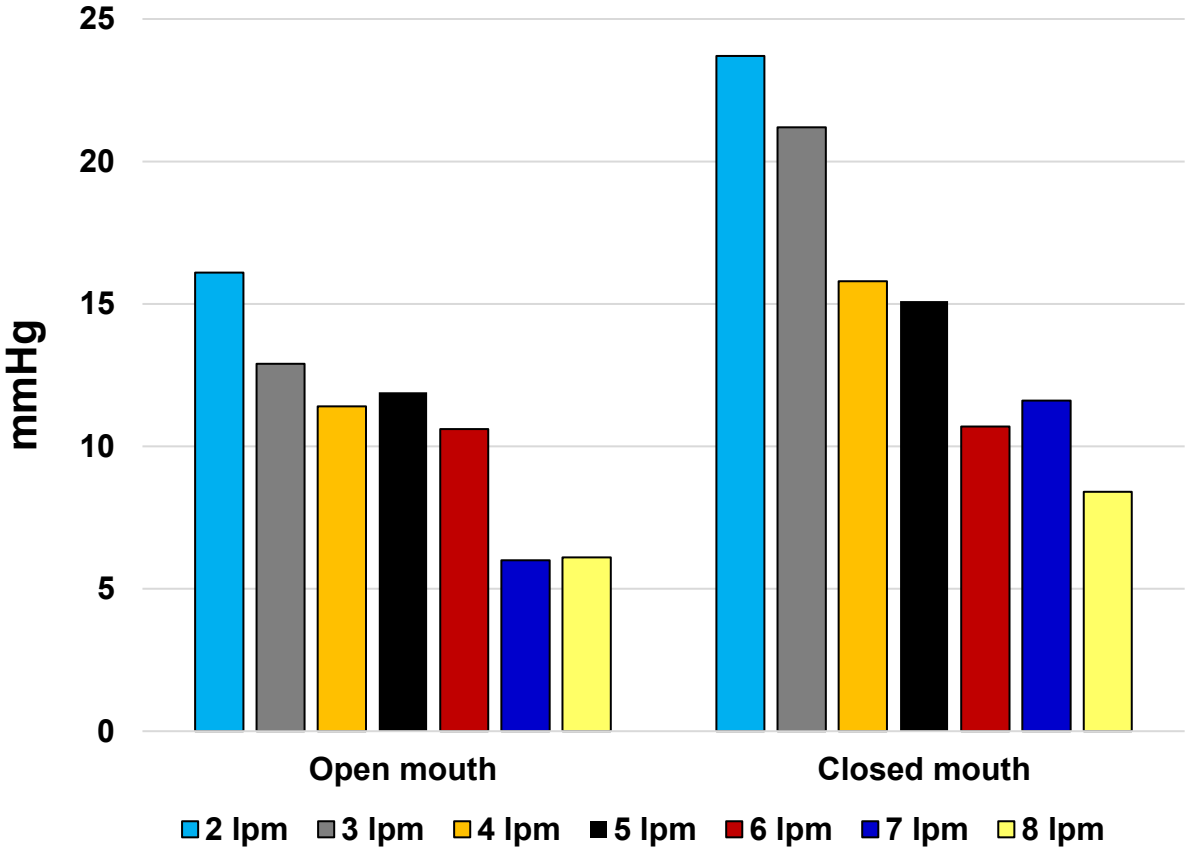


Increased "leak" is accompanied by ↓ paCO2….

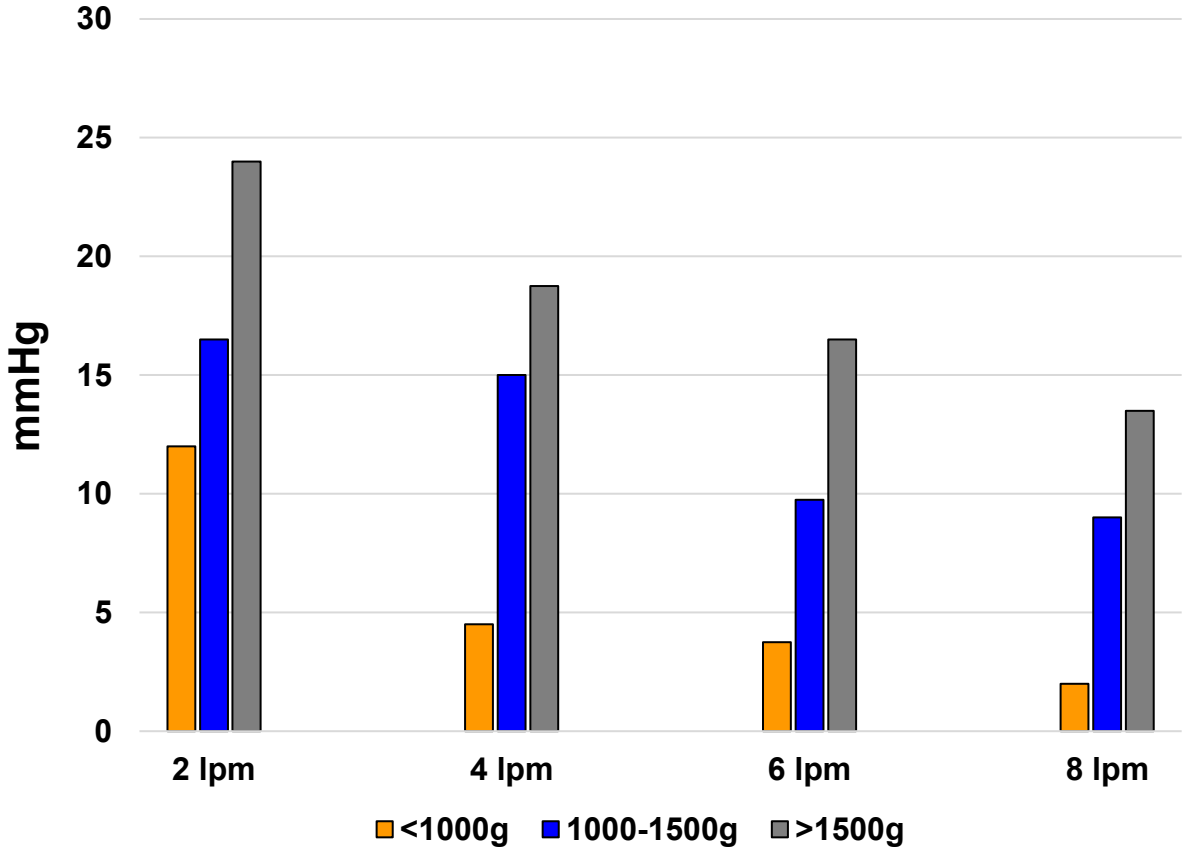
….despite similar minute ventilation

Dead Space Gas Washout

npEECO2 ↓ with ↑ flow & ↑ leak (open vs closed mouth)



At any specific flow npEECO2 ↓ as weight ↓

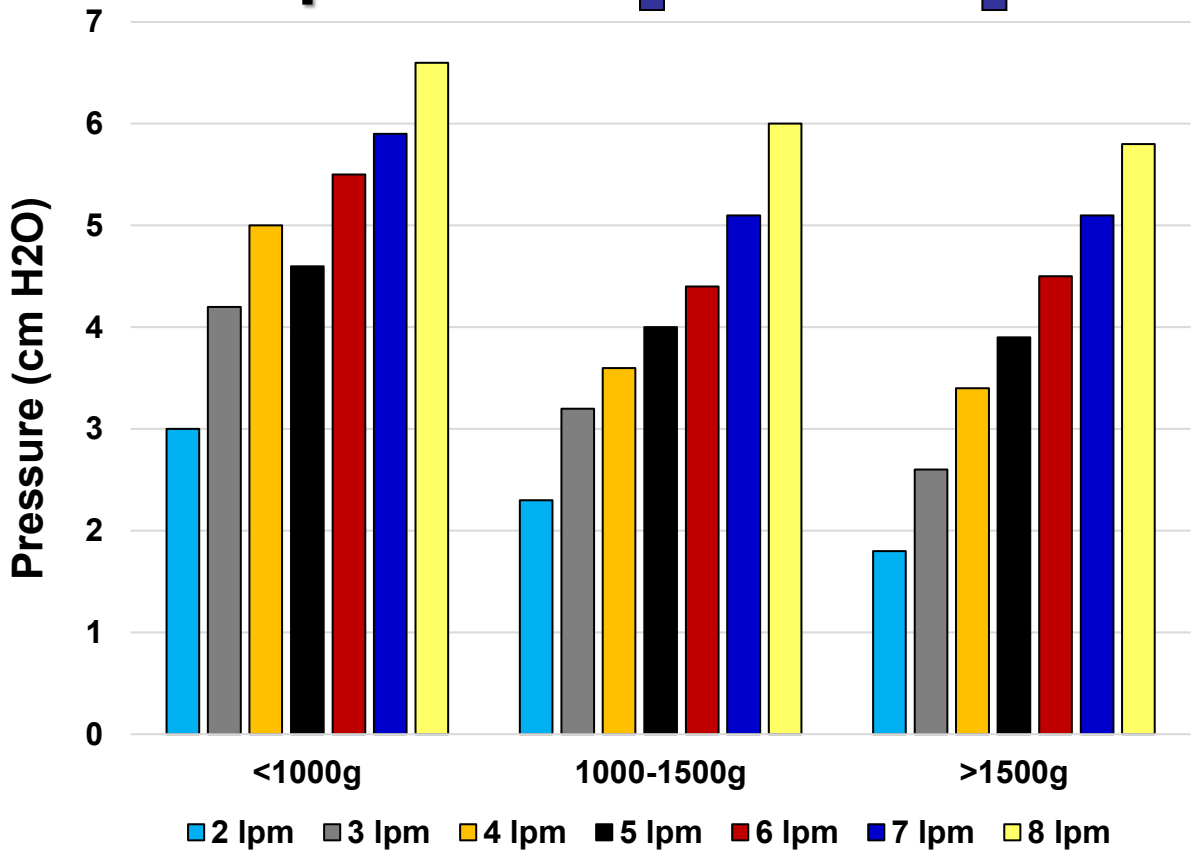


Liew Z et al ADCFNE 2019

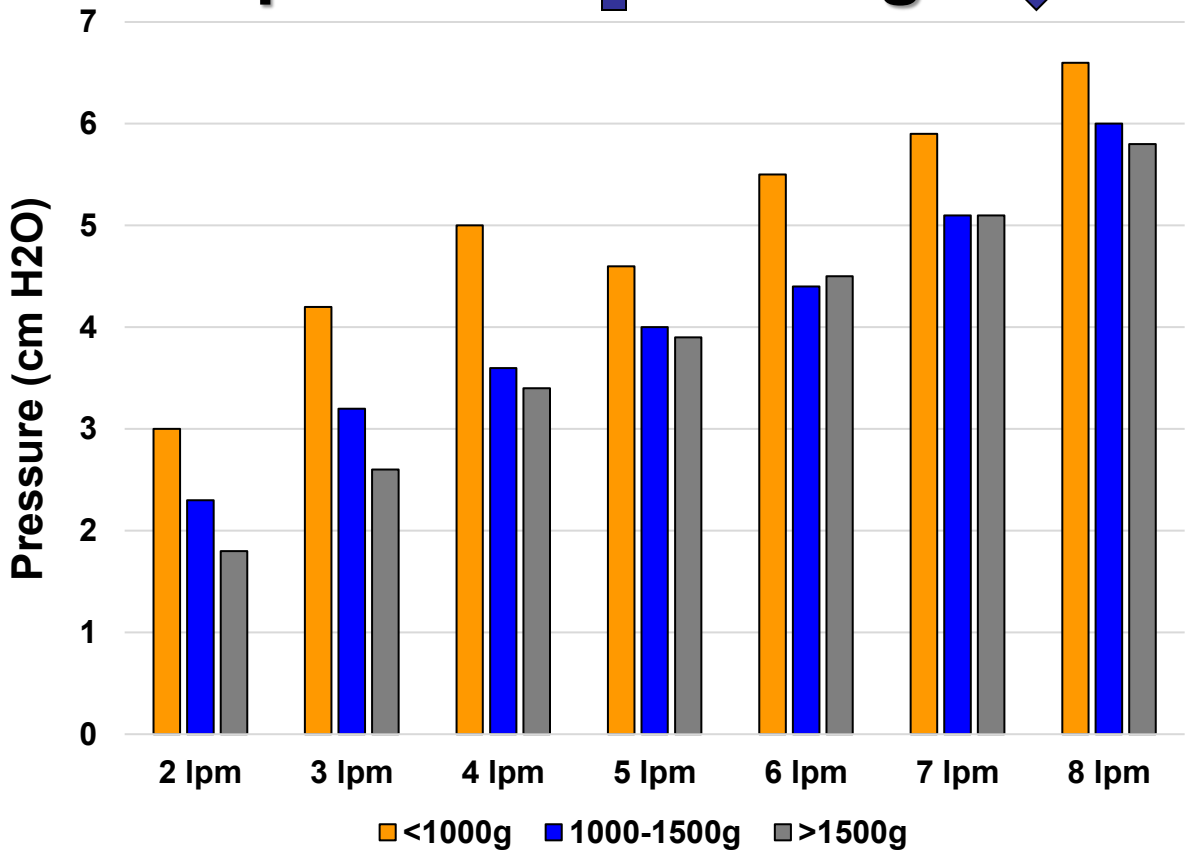
npEECO2 = nasopharyngeal end-expiratory pCO2

Nasopharyngeal Pressure during nHFT

For any specific weight pressure ↑ as flow ↑



At any specific flow rate pressure ↑ as weight ↓



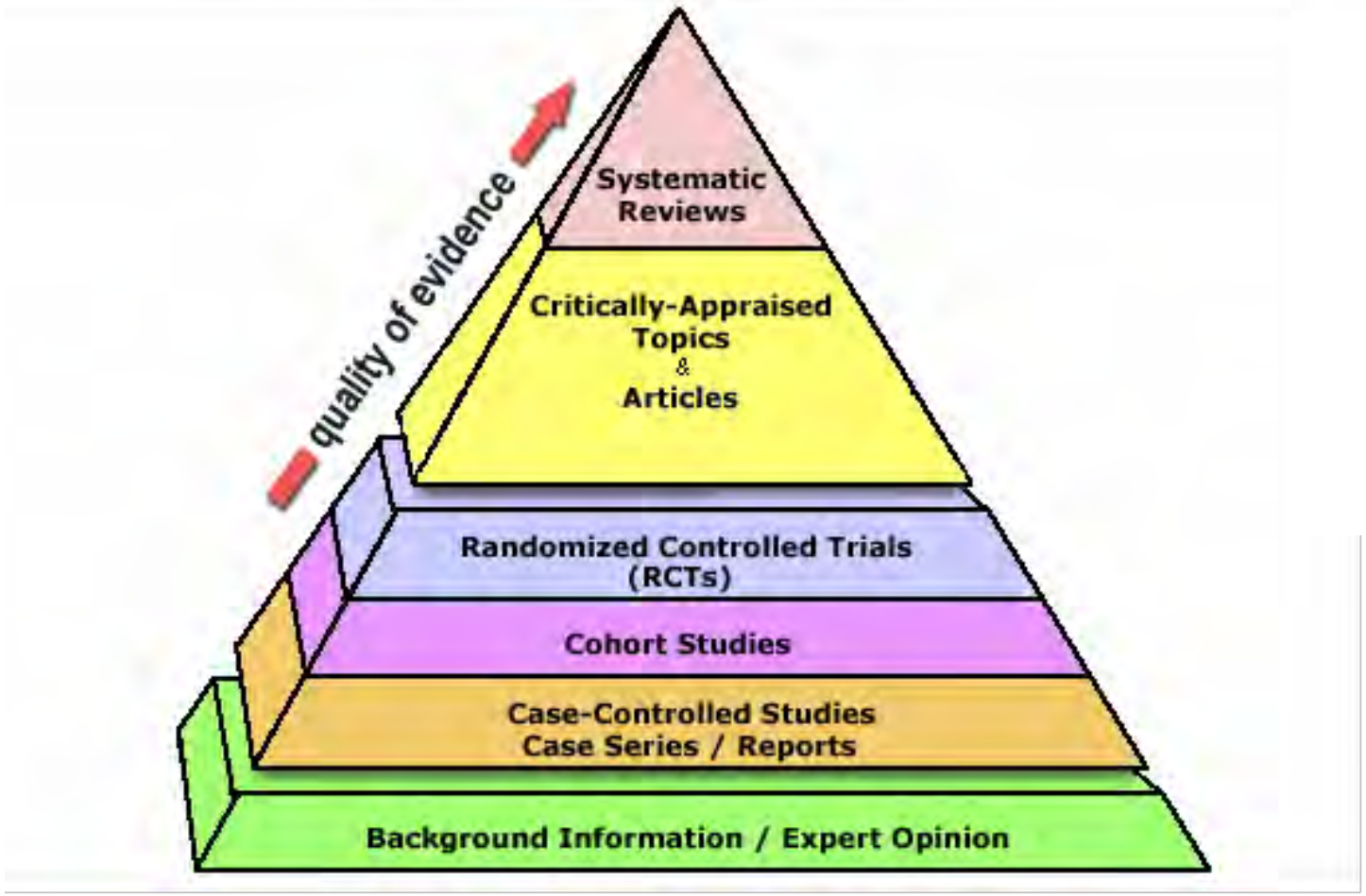
Liew Z et al ADCFNE 2019

Interim Summary # 1

- **<u>Increased Flow Promotes Gas Exchange</u>**
  - Neonates have relatively large Vds_{anat}
  - ↑ flow rate → ↑ Vds_{ana} gas washout → ↓ pCO_2 & ↑ pO_2 in NP
  - Result → more efficient gas exchange

- **<u>nHFT Delivers Some (+) Pressure</u>**
  - Studies suggest limited pressure delivery depending on:
  - Flow rate, weight, & relative leak
  - Pressure correlates to changes in EELV & SpO2/FiO2

nHFT:
What Does the Evidence Show?



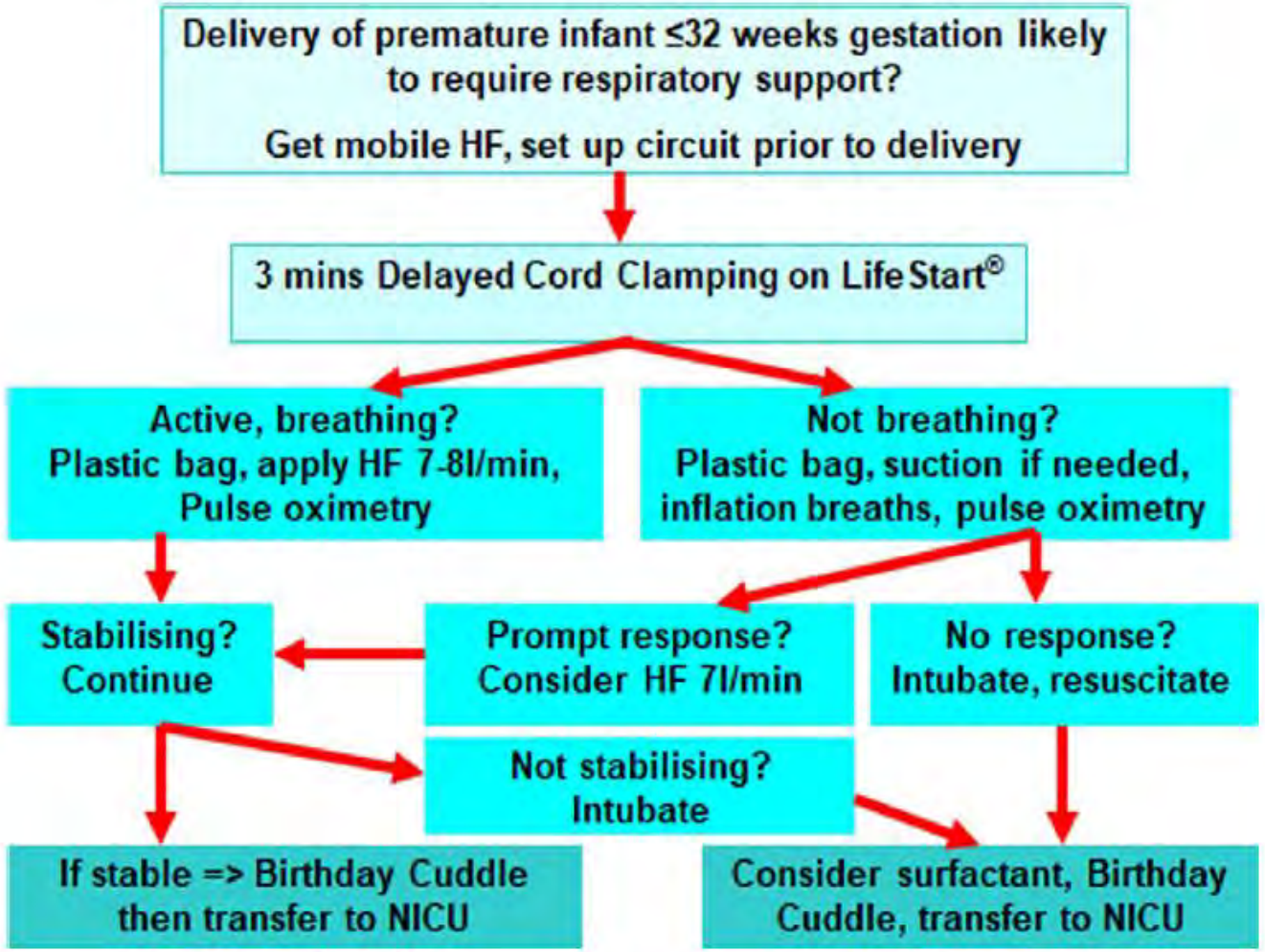
DR stabilization of preterms using nasal HFT: 5 - year retrospective analysis

Siva & Reynolds Acta Paediatr 2021

- 5-year review 2015-2020
- Primary DR approach with nasal high flow therapy
- 491 infants born at < 32 weeks
- Prior pilot study reported (Reynods P, ADCFNE 2016)

DR stabilization of preterms using nasal HFT

Siva & Reynolds Acta Paediatr 2021



- No exclusion criteria
- Immediately start, no SXN
  - Flow at 7-8 lpm
- Surfactant 1^{o} by LISA
- FiO2 threshold 40% → 30%
- Early caffeine Rx

60% of preterms < 32 wks stabilized in DR w/ nHFT

Siva & Reynolds Acta Paediatr 2021

	Group A (n=292) nHFT only in DR	Group C (n=93) ETT in DR	Group B (n=85) Mask-CPAP in DR	Group D (n=21) NC/RA in DR
Gestation (wks)	28.14 (26.43-29.96)			31.14 (31.0-31.57)
Birth Wt (g)	942 (732-1245)			1610 (1340-1770)
Admit FiO2	25 (21-30)			21 (21-21)
Max Fio2	32 (24-50)			21 (21-27)
Surf w/in 72 hrs	130 (45%)			2 (10%)
PTX w/in 72 hrs	14 (5%)			0
Severe IVH	14 (5%)			0
nHFT/NC at 72 hrs	228 (78%)			21 (100%)

nHFT group was moderately preterm

Consistently had low FIO2 needs

Had low rates of acute morbidity

Majority remained on nHFT support

60% of preterms < 32 wks stabilized in DR w/ nHFT

Siva & Reynolds Acta Paediatr 2021

	Group A (n=292) nHFT only in DR	Group C (n=93) ETT in DR	Group B (n=85) Mask-CPAP in DR	Group D (n=21) NC/RA in DR
Gestation (wks)	28.14 (26.43-29.96)	25.29 (24.0-26.43)		
Birth Wt (g)	942 (732-1245)	680 (570-840)		
Admit FiO2	25 (21-30)	30 (21-44)		
Max Fio2	32 (24-50)	46 (30-100)		
Surf w/in 72 hrs	130 (45%)	93 (100%)		
PTX w/in 72 hrs	14 (5%)	13 (14%)		
Severe IVH	14 (5%)	15 (16%)		
nHFT/NC at 72 hrs	228 (78%)	8/10 (80%)		

ETT group significantly more premature

Consistently higher FIO2 needs

Higher rates of acute morbidity

Most remained on IMV support

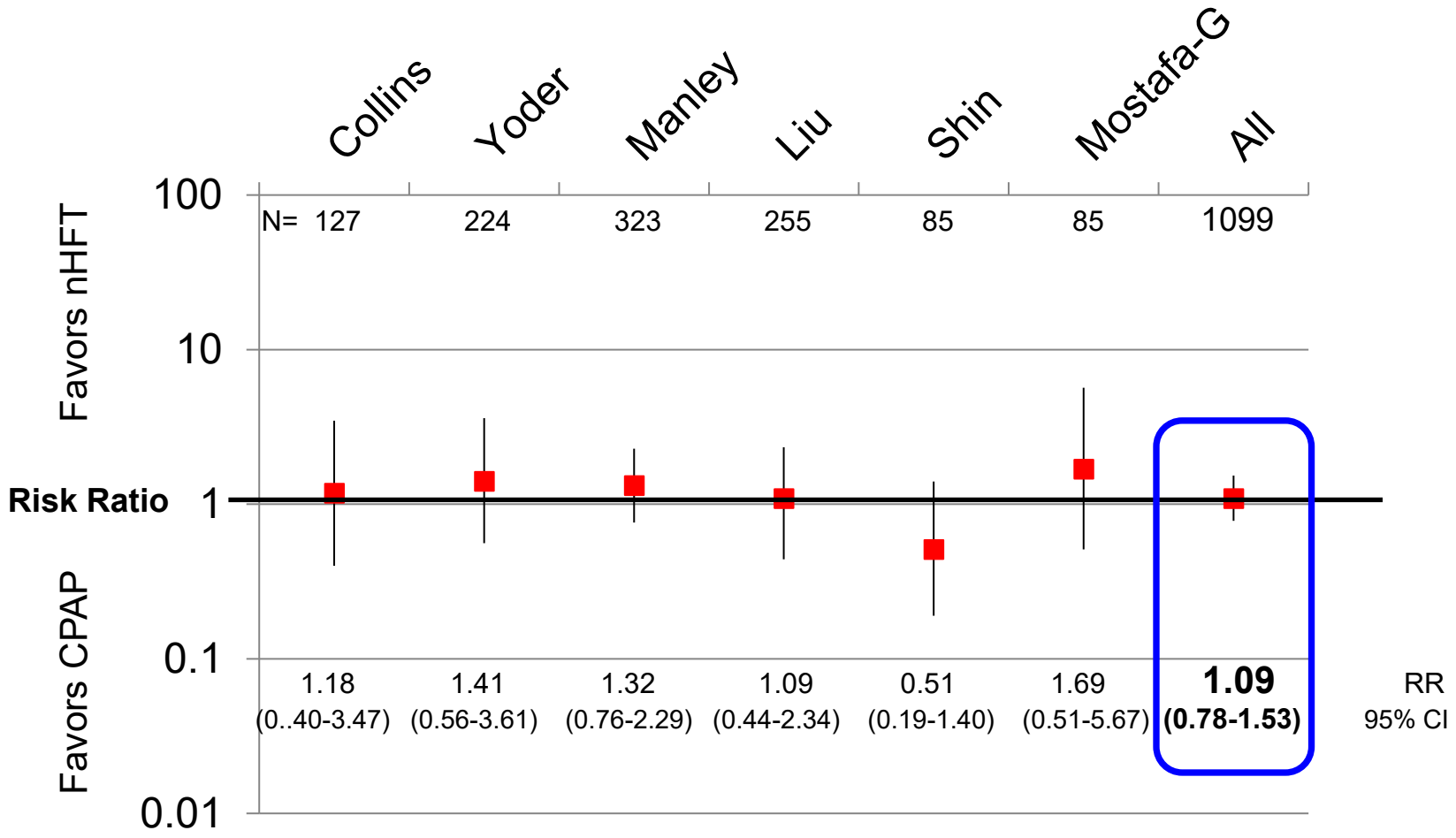
What about preterms < 27 wks stabilized w/ nHFT?

Siva & Reynolds Acta Paediatr 2021

- 65% (62/96) were sustained on nHFT through 72 hrs
- ~1/3 vs 100% treated w/ surfactant
- Less air leak, pulmonary hemorrhage, & severe IVH
- ETT at 7 days: 15% vs 38%
- Death/BPD at 36 wks: 55% vs 74%

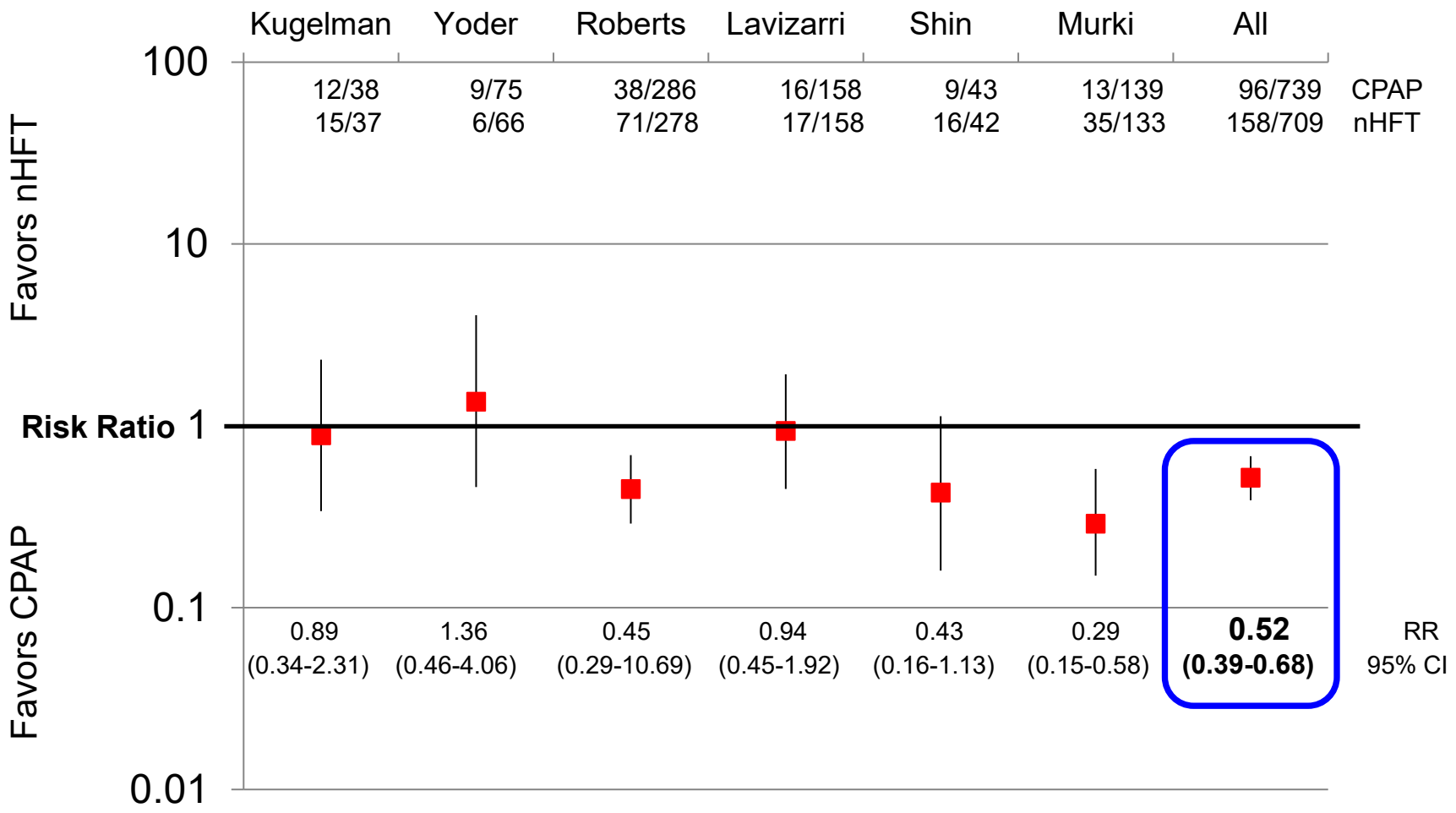
“Meta-Analysis”: Similar Risk for Post-extubation ETT

More than 1200 neonates have been included in RCTs



“Meta-Analysis”: Increased Failure as 1º Therapy

Over 700 neonates have been included in RCTs



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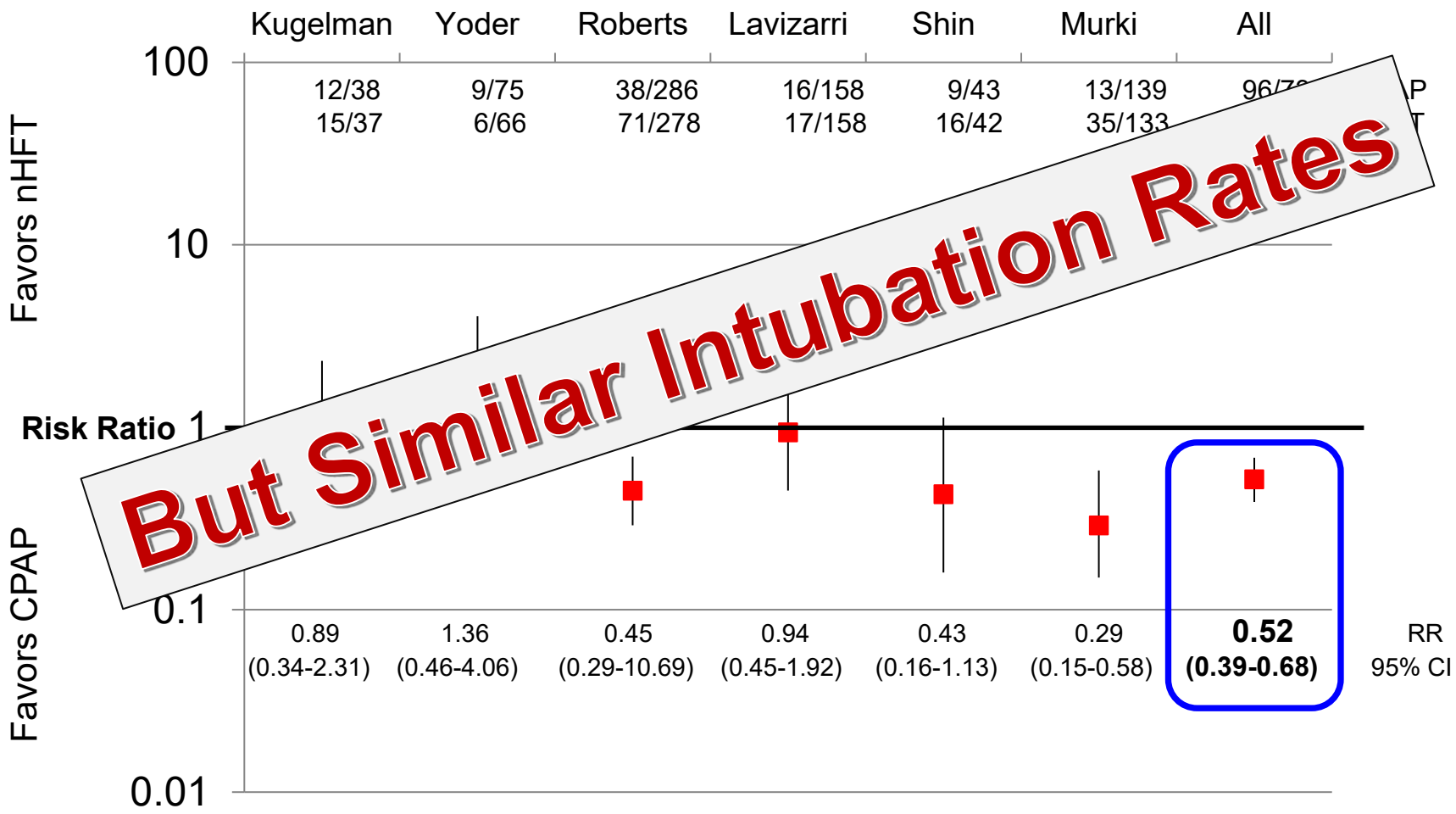
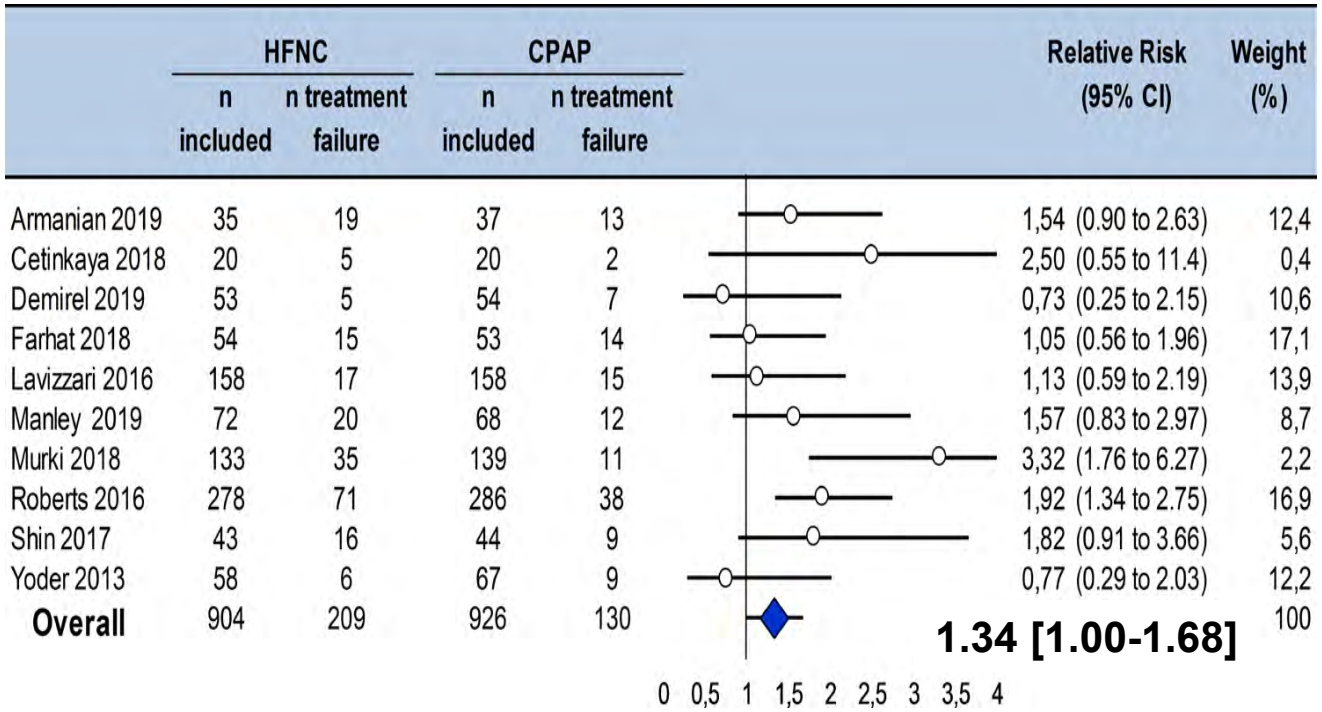


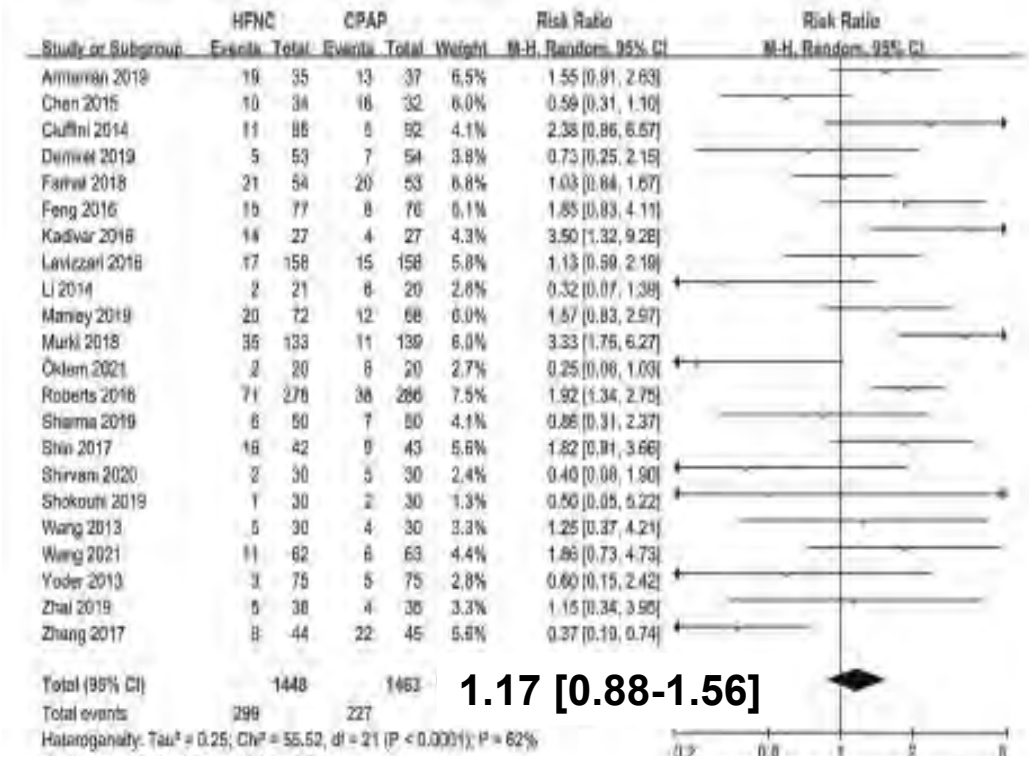
Meta-analysis: HFNC v nCPAP as Primary Therapy for Preterm Respiratory Failure



Bruet S, ADCFNE 2021; 10 trials, n=1830

ETT Risk 0.90 [0.66-1.15]

"…taking all into account (higher risk of treatment failure but same risk of intubation and lower risk of nasal trauma), HFNC may be proposed as primary respiratory support…..



Luo K, Front Peds 2022; 27 trials, n=3351

ETT Risk 1.00 [0.841.19]

"…compared with CPAP, the use of HFNC for preterm infants might be more effective in reducing the use of mechanical ventilation and oxygen therapy…..

Interim Summary # 2
nHFT vs nCPAP

<u>Meta-analyses have reached same conclusions:</u>

Similar post-extubation failure rates ….

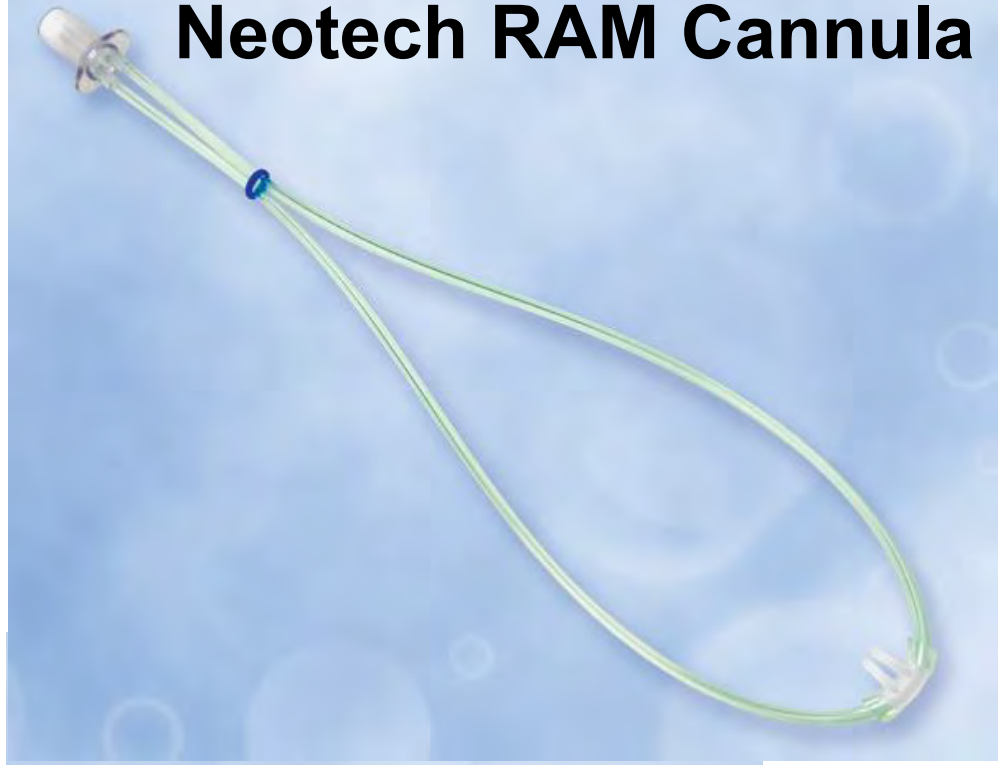
CPAP probably superior to nHFT for Rx 1^{o} RDS

No difference in intubation rates

No difference in BPD but not rigorously tested
Limited data from RCTs for GA < 28 wks

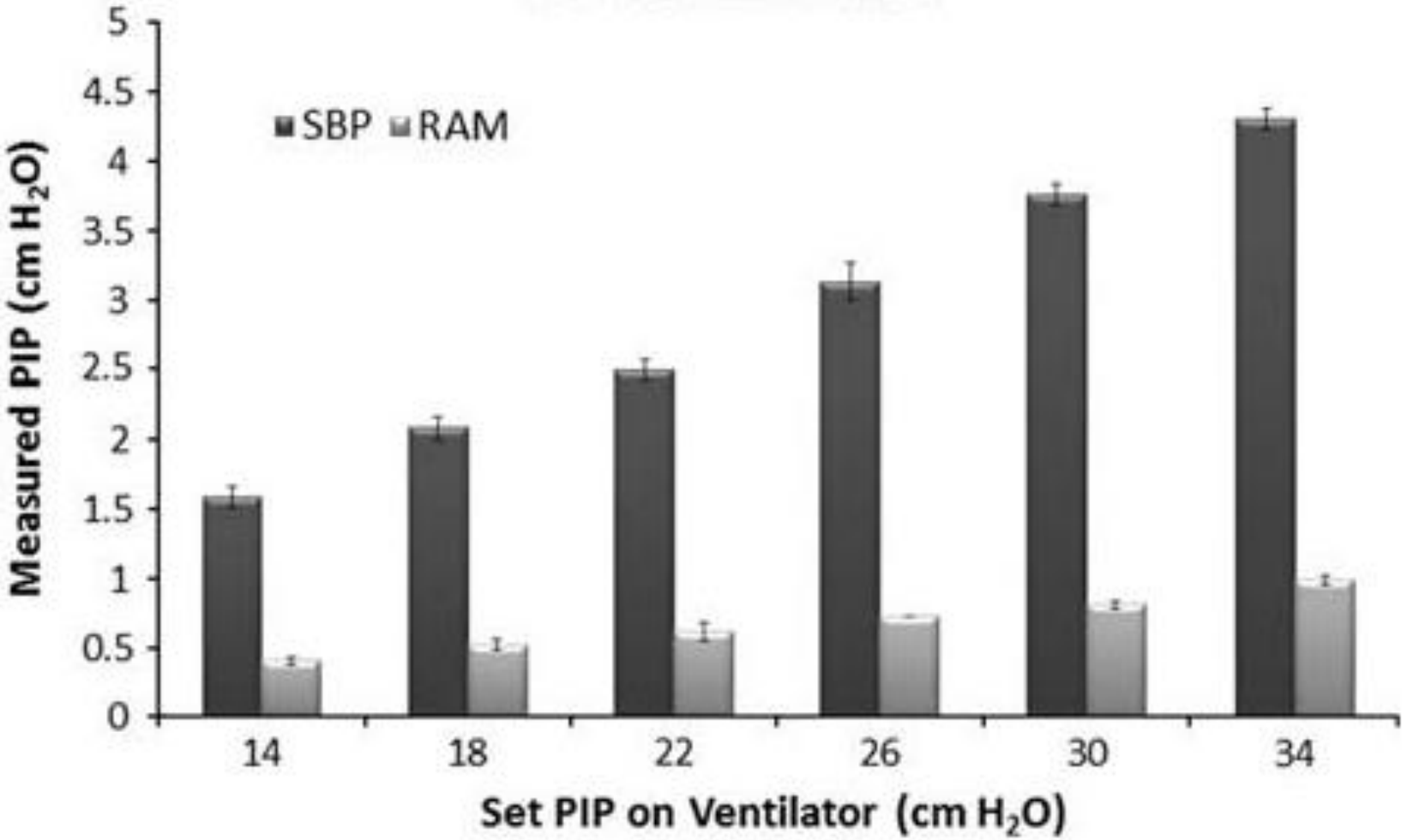
Bruets S et al, ADCFNE 2021
De Jesus Brito S et al, BMC Pediatr 2021
Luo K et al, Front Pediatr 2022
Martins C et al, Turk Arch Pediatr 2022

Neotech RAM Cannula



No more pig nose!?

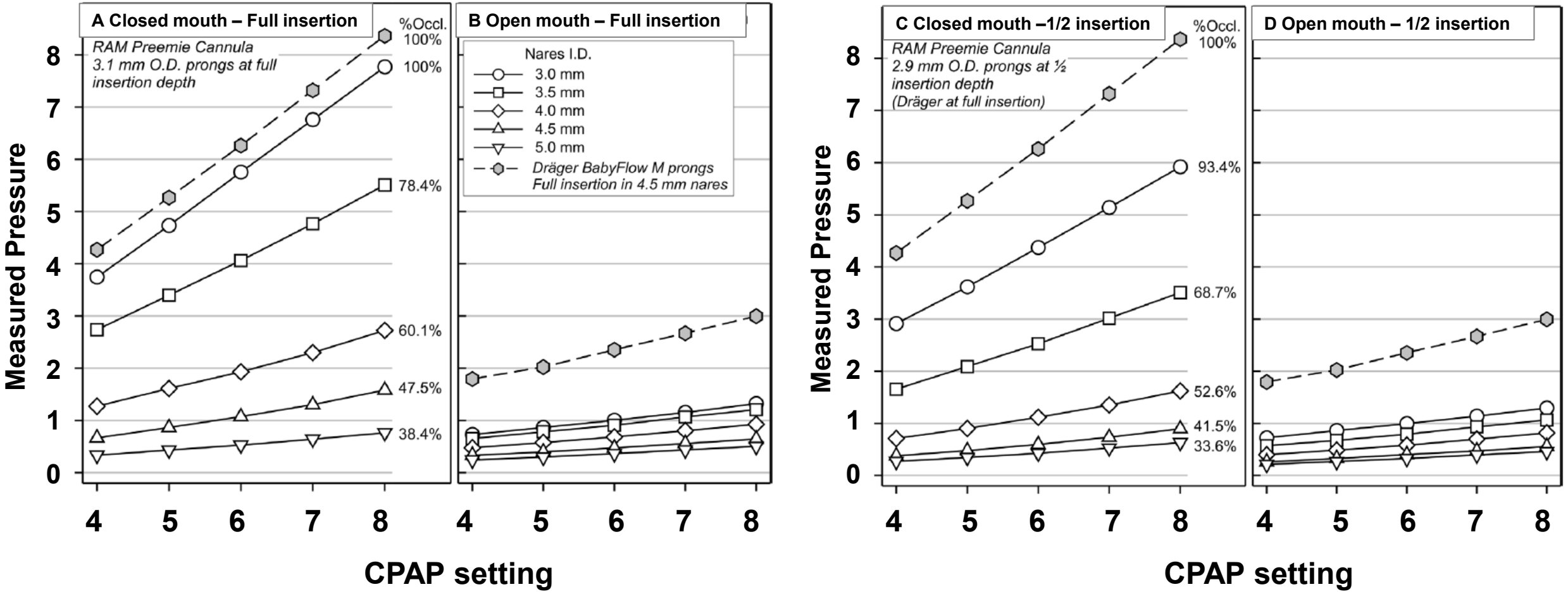
“Gentle”, but effective “CPAP”?



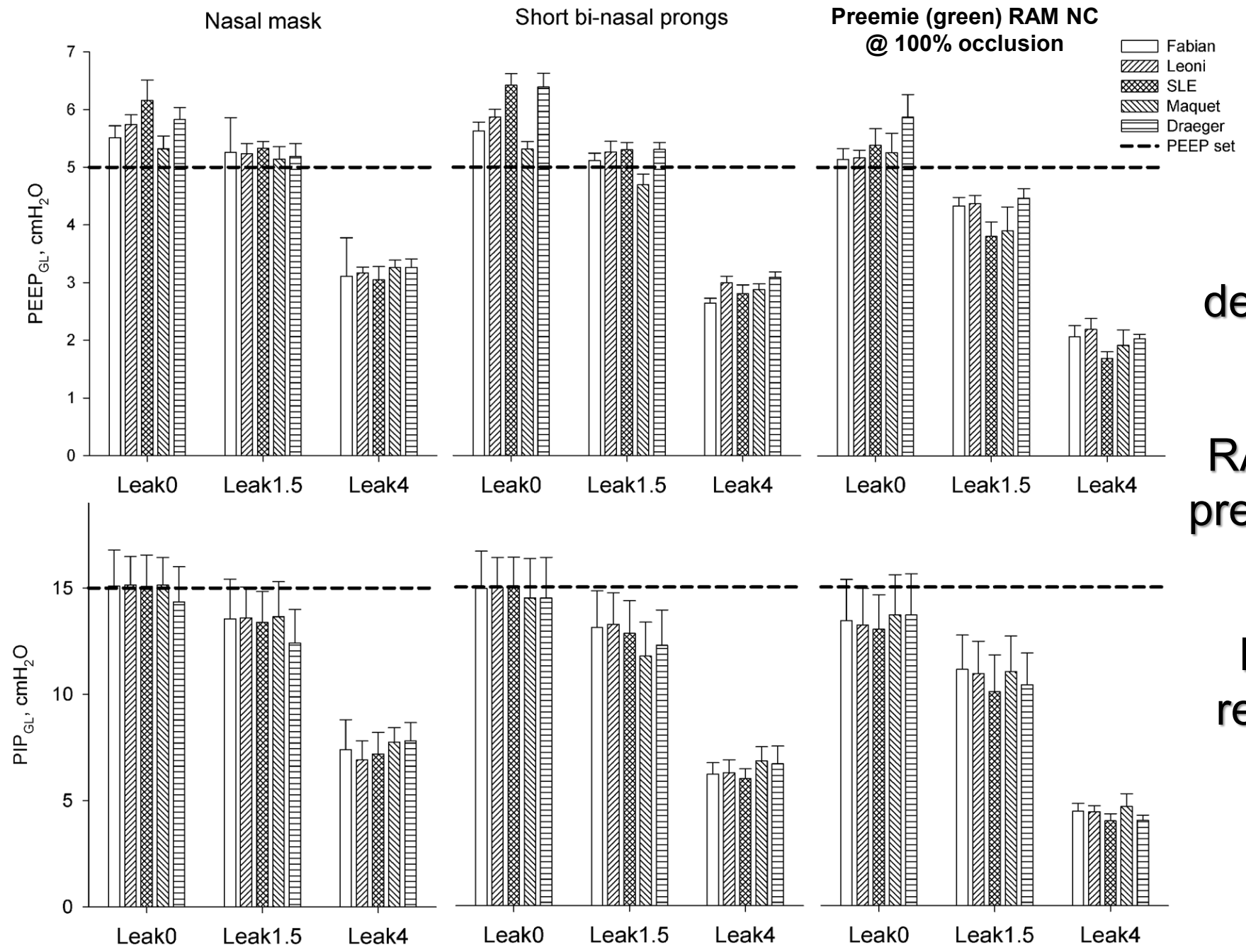
RAM NC may deliver significantly less pressure than "set" pressure

Mukerji A, J Perinatol 2015

Type & size of nasal prong, % occlusion, mouth position, & prong insertion depth all impact relative pressure delivery



Gerdes JS et al Peds Pulm 2015



All neonatal ventilators deliver equivalent PIP/PEEP

RAM NC delivers less of set pressure than sBNPs or mask

Increasing leak markedly reduces delivered pressure across all interfaces

Rigotti C et al, Peds Pulm 2021

Dynamic Approach to RAM NC: Impact of "Higher" Pressure Settings

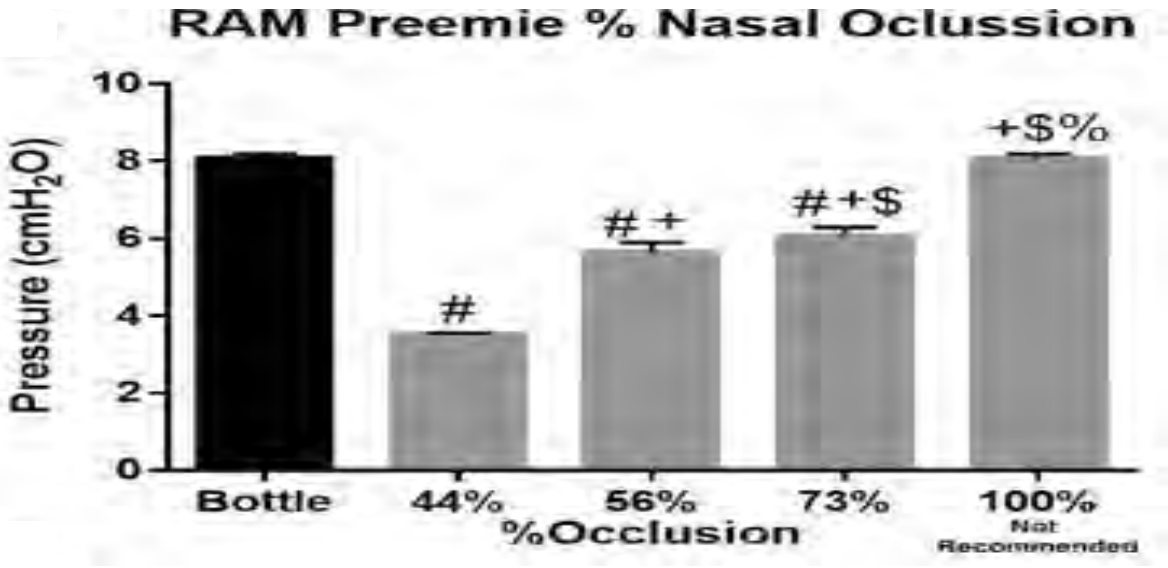
Classen CC et al, Am J Perinatol 2021

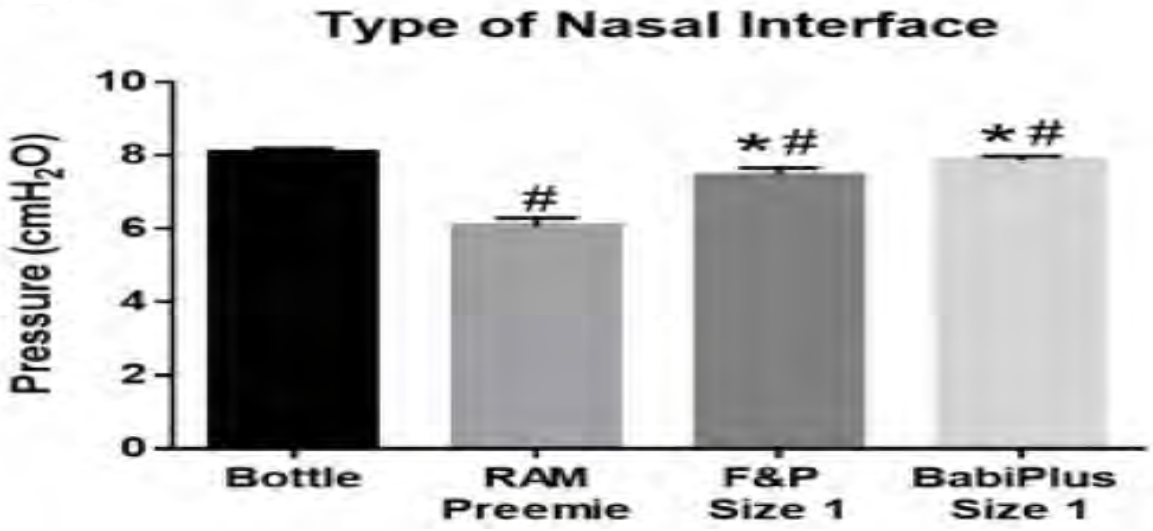
- RAM NC adopted/used for ease of patient care
- High resistance interface – limited transmission of set pressure
- Attenuates "oscillatory" effect of "bubble CPAP"
- 6-year retrospective study of 735 preterms < 1250g
- *In vitro* analysis of pressure transmission

RAM NC pressure related to interface & occlusion

Classen CC et al, Am J Perinatol 2021

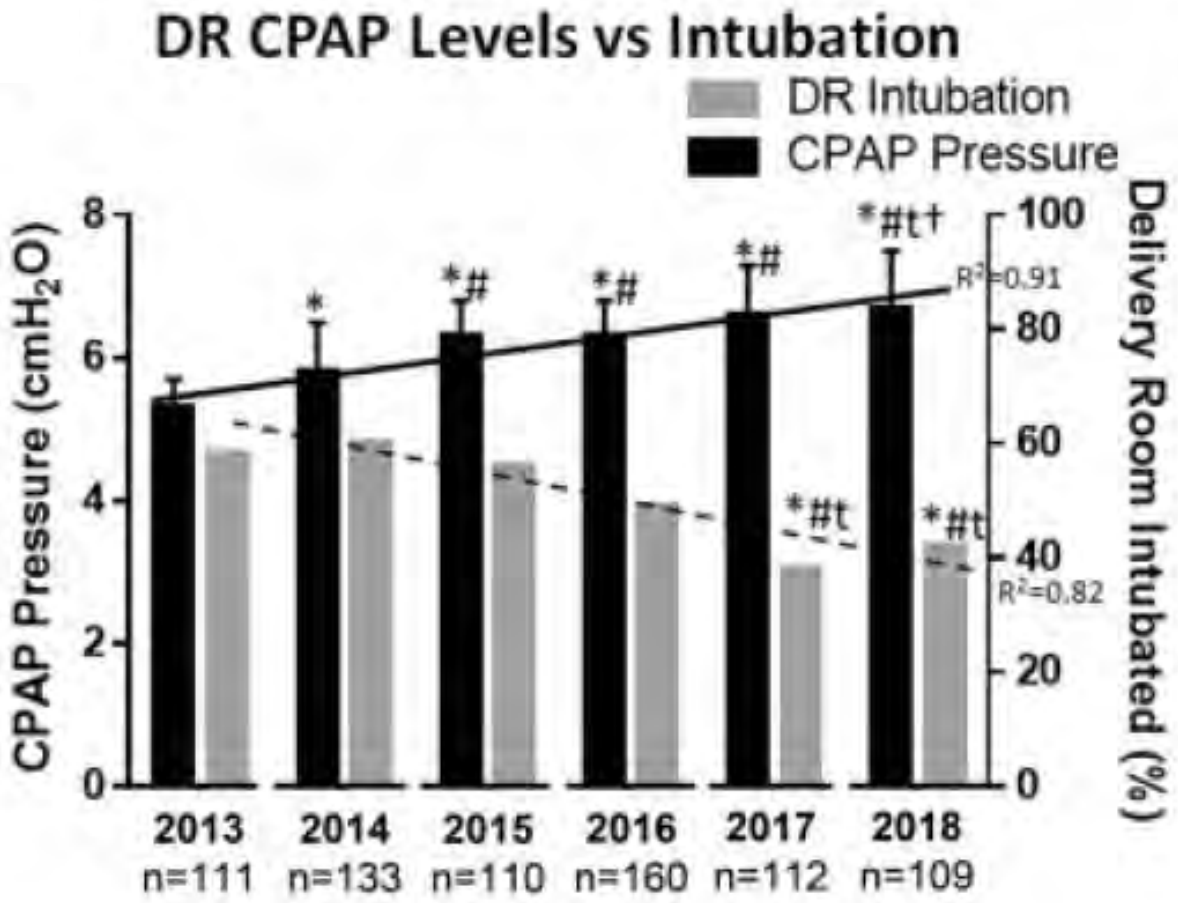
Cannula	Color	Prong diameter	Simulated nostril diameter	% Occlusion
RAM Micro-preemie	White	2.5 mm	3.0 mm	69%
RAM Preemie	Green	3.0 mm	3.5 mm	73%
RAM Newborn	Blue	3.8 mm	4.5 mm	71%
RAM Infant	Orange	4.5 mm	5.0 mm	81%
BabiPlus	Size 1	3.0 mm	3.5 mm	73%
F&P	Size 1	3.0 mm	3.5 mm	73%

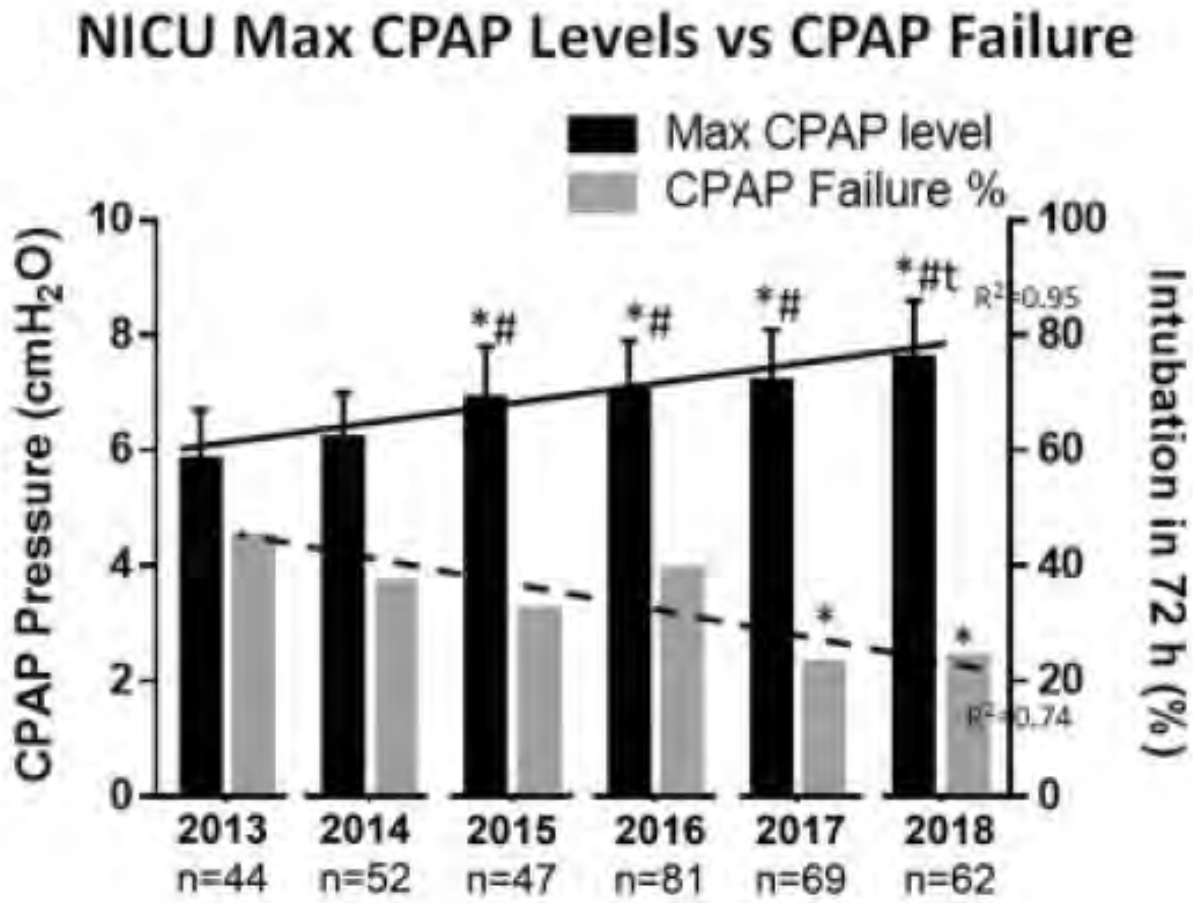




Over time, escalating approach to RAM NC pressures was associated w/ less DR intubation

Classen CC et al, Am J Perinatol 2021





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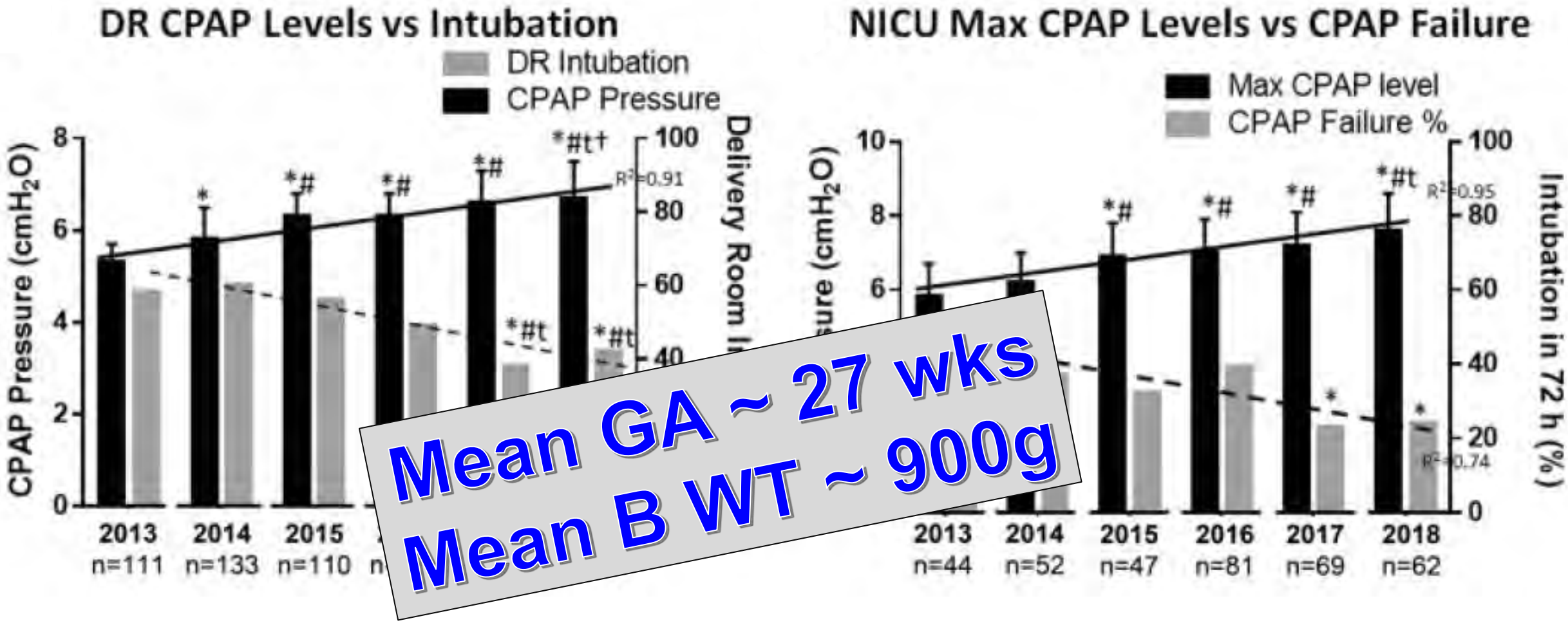
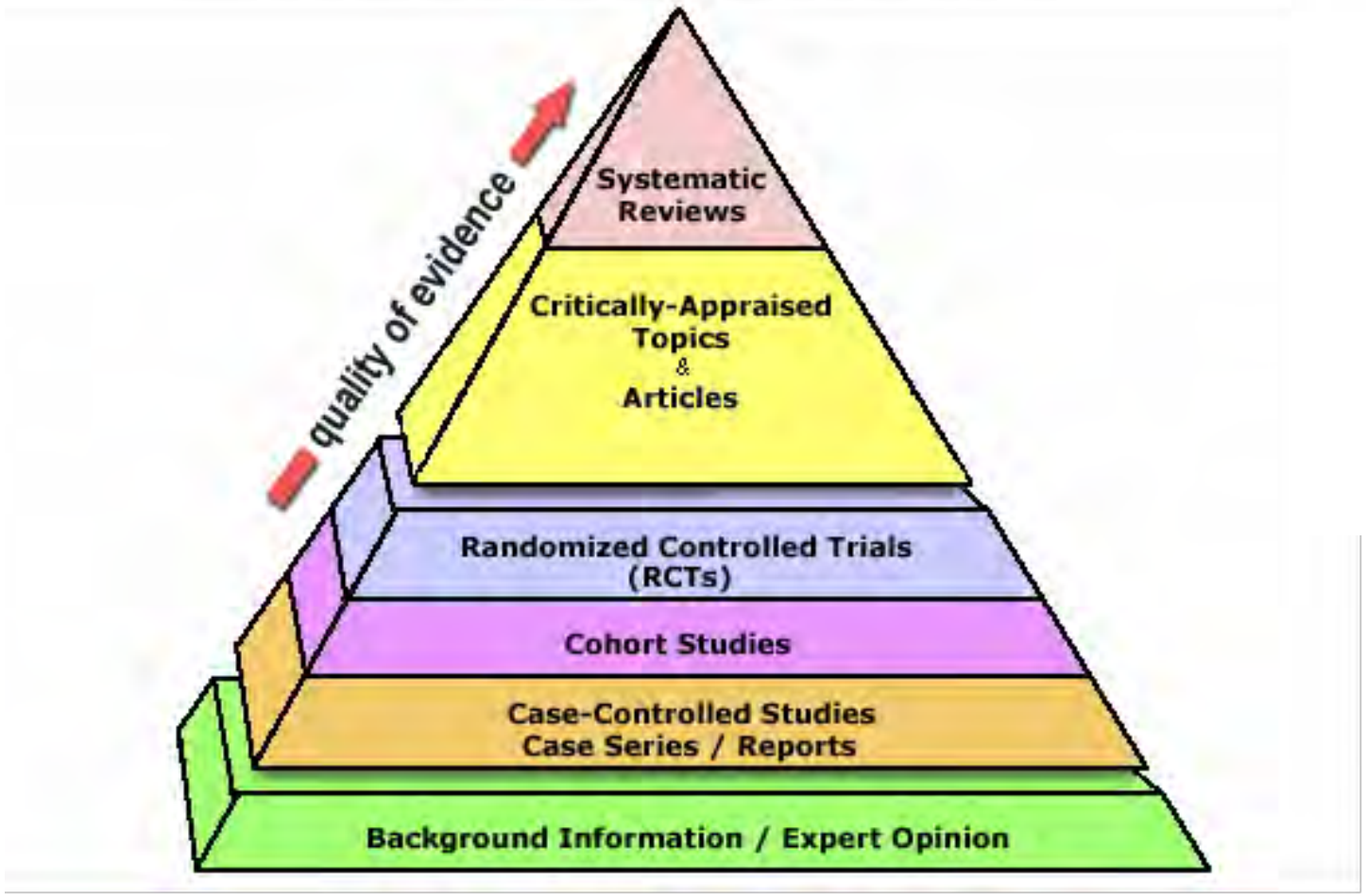


RAM NC:
What Does the Evidence Show?



RCTs & RAM NC in Neonates

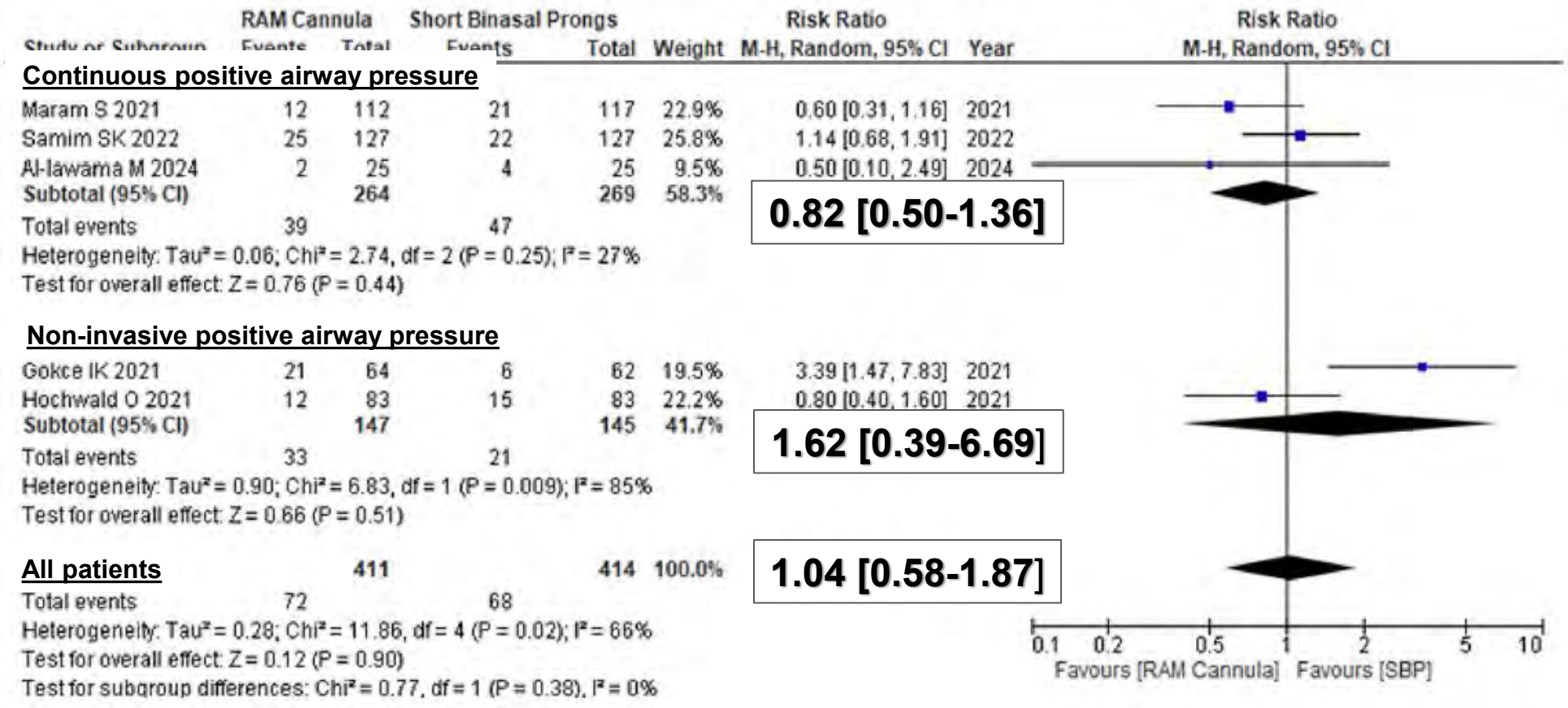
- There are several published RCT's w/ RAM NC
- Gokce IK et al, J Mat Fetal Neo Med 2019
- Hochwald O et al, JAMA Peds 2021
- Maram S et al, Sci Rep 2021
- Samim SK et al, Eur J Pediatr 2022
- Al-lawama M et al, J Clin Med Res 2024

Meta-analysis RAM NC vs sBN prongs

- Kumar J et al, Indian J Pediatr 2024
- 5 RCT's, n= 825
- No US/Canadian trials
- Study populations mostly ≥ 28 weeks
- Variable pressures & modes (NIPPV or CPAP)

Similar success for RAM NC & sBP CPAP as 1º treatment for respiratory failure

Failure of Primary Respiratory Support



Kumar J, Ind J F

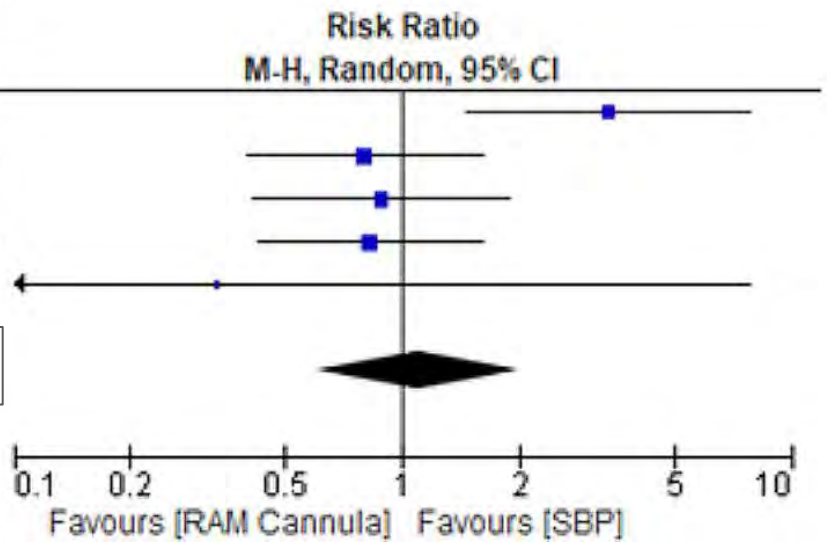
No difference between RAM NC & sBP CPAP in MV support in 1st 72 hours of life

Invasive ventilation in 72 hours

Study or Subgroup	RAM Cannula Events	RAM Cannula Total	Short Binasal Prongs Events	Short Binasal Prongs Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gokce IK 2021	21	64	6	62	21.9%	3.39 [1.47, 7.83]	2021
Hochwald O 2021	12	83	15	83	25.2%	0.80 [0.40, 1.60]	2021
Maram S 2021	11	112	13	117	23.6%	0.88 [0.41, 1.89]	2021
Samim SK 2022	14	127	17	127	26.0%	0.82 [0.42, 1.60]	2022
Al-Iawama M 2024	0	25	1	25	3.3%	0.33 [0.01, 7.81]	2024
Total (95% CI)		**411**		**414**	**100.0%**	**1.10 [0.60-2.00]**	
Total events	58		52				

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 9.38$, $df = 4$ ($P = 0.05$); $I^2 = 57\%$

Test for overall effect: $Z = 0.31$ ($P = 0.76$)



Kumar J, Ind J Peds 2024

Interim Summary # 3
RAM Nasal Cannula

- **NOT approved as CPAP device/interface**
- **MUST be aware of variable pressure loss across tubing due to size & leak**
- **RCTs limited by numbers, design, & outcome but appears "non-inferior" to std BNP nCPAP**
- **NO identified safety issues**

Is gentlest better?

NO!

At least when it comes to initial NIV

Is it “adequate”?

...probably….most of time…

CPAP:

Is the 1st

still the best?

• CPAP:

- Most commonly applied
  - Longest history
  - Clearly effective
  - Widely available
  - Multiple approaches

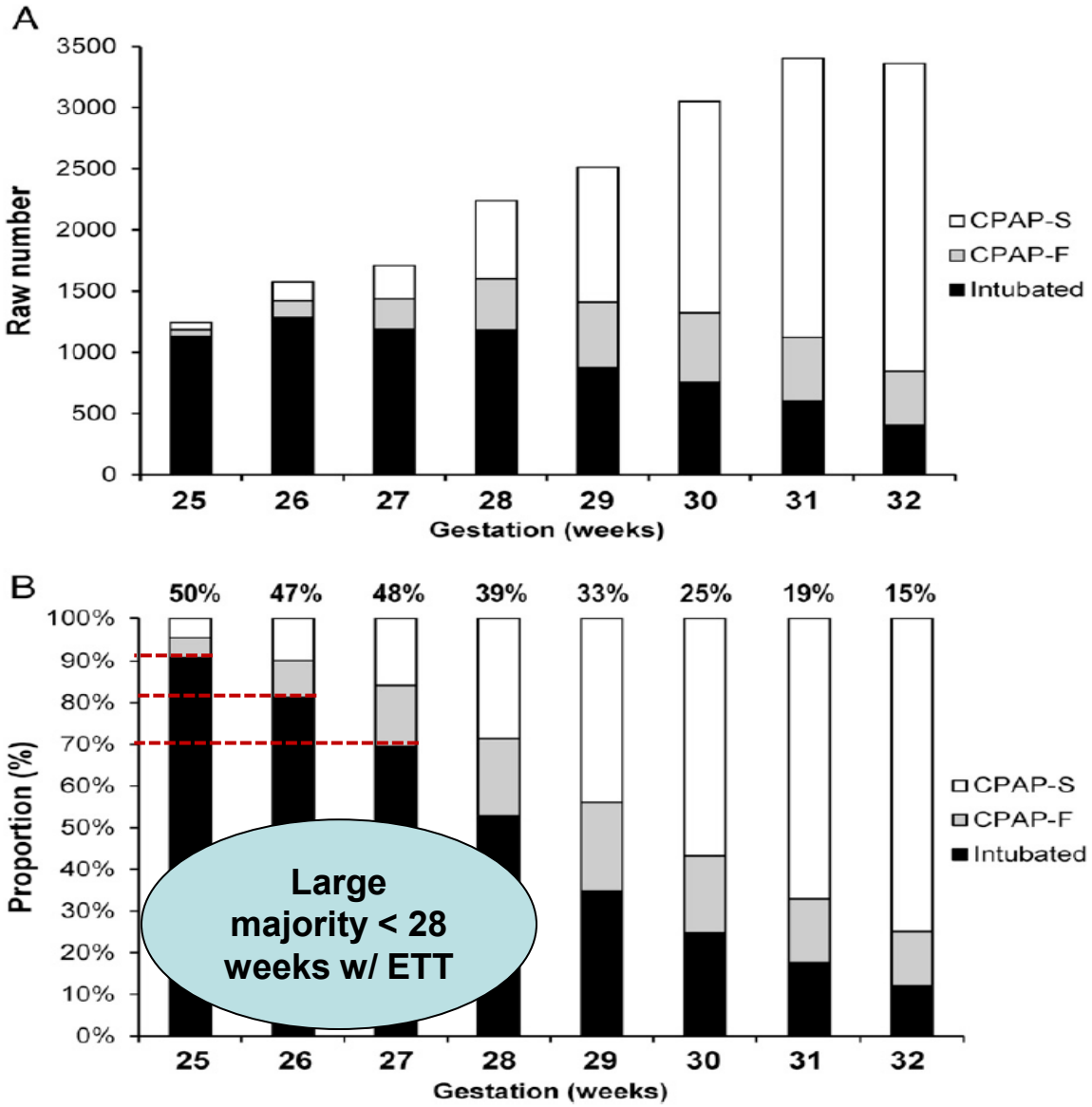
Failure Rates & Outcomes for nCPAP

Dargaville PA et al, Pediatrics 2016

- Retrospective review AU-NZ Neo Network
- 19,103 infants born at 25-32 weeks in 2007-2013
- Analyzed for initial support mode & success vs failure
- Evaluated subsequent outcomes by CPAP success/failure

CPAP Failure is Common in ELGANs

Dargaville PA et al, Pediatrics 2016



	25-28 wks (n=6771)	29-32 wks (n=12,322)
Initial ETT	4782 (**71%**)	2637 (21%)
Initial CPAP Failed	1989 (29%) 863 (**43%**)	9695 (79%) 2061 (21%)
CPAP success	1126 (**17%**)	7634 (62%)

Study period prior to implementation of less invasive surfactant approaches

Failure w/ CPAP Associated w/ Worse Outcomes

Dargaville PA et al, Pediatrics 2016

Outcome	25-28 weeks		25-28 weeks	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR
BPD	2.3 (1.7-3.0)	1.9 (1.4-2.6)	3.8 (2.9-4.9)	3.3 (2.5-4.4)
Death	2.8 (1.5-5.4)	2.8 (1.4-5.7)	7.0 (3.0-16.4)	6.0 (2.5-14.8)
Death or BPD	2.5 (1.9-3.2)	2.3 (1.7-3.1)	4.1 (3.2-5.2)	3.6 (2.8-4.7)
Death/major morbidity	2.3 (1.8-3.0)	2.2 (1.7-2.9)	3.1 (2.5-4.0)	3.0 (2.4-3.8)

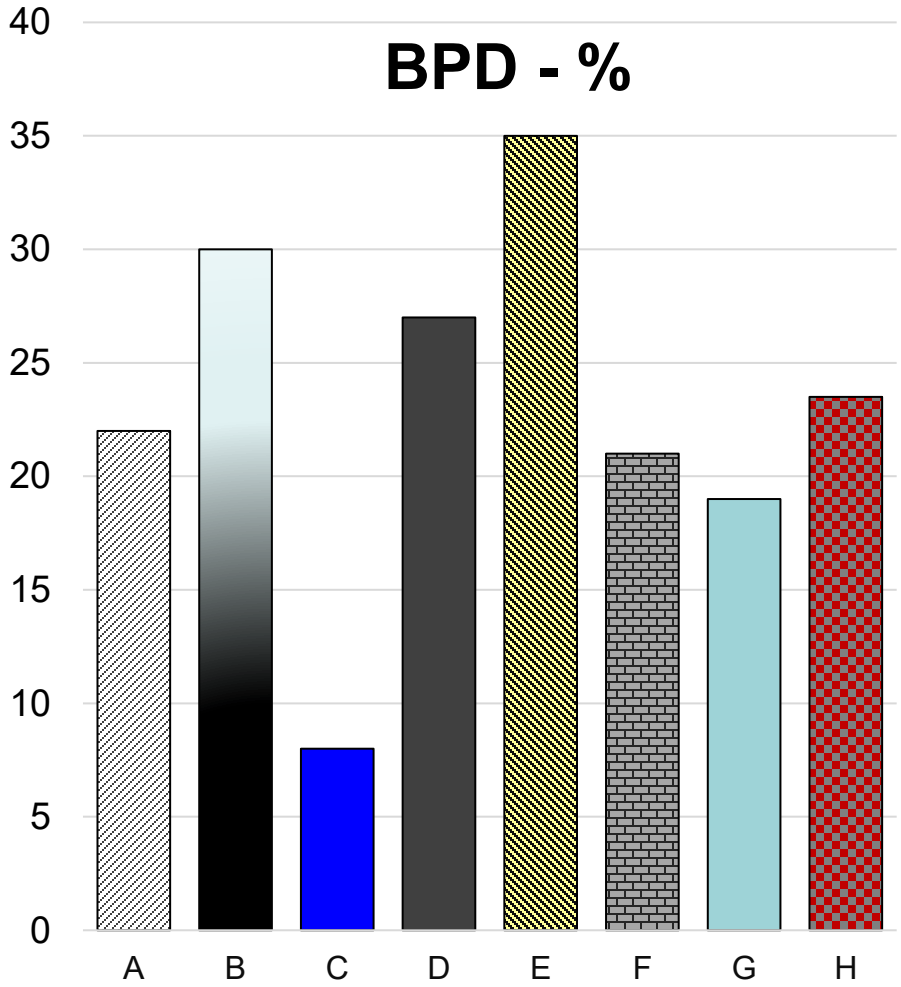
Adjusted odds ratio from multiple logistic regression modeling, with: GA, BWT <10%, sex, delivery mode, plurality, ANS exposure, & 5-minute <7

However, outcomes w/ primary intubation were always worse than w/ initial trial CPAP

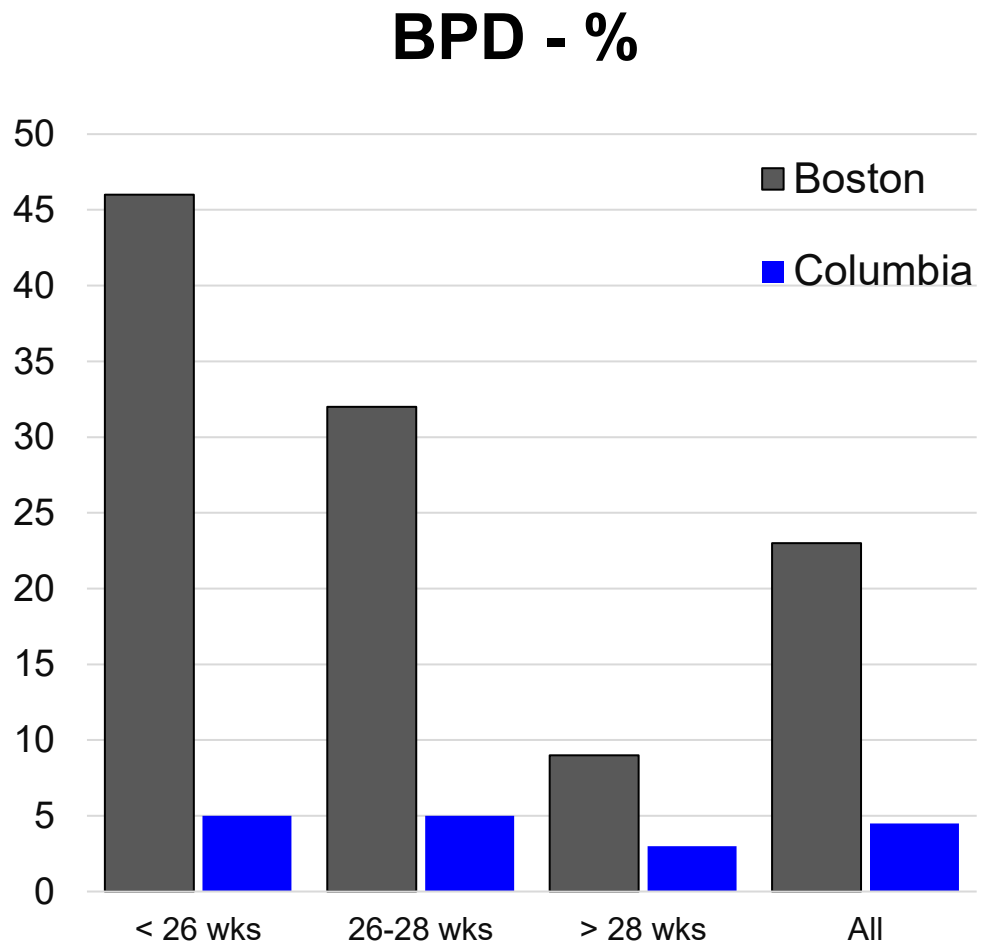
Aggressive nCPAP Programs

- Individual centers report significant ↓ in vent days & BPD w/ aggressive nCPAP use
  - Van Marter LJ, Pediatrics 2000
  - Aly H, Pediatrics 2004
  - Levesque B, Pediatrics 2011
  - Mehler K, Acta Paediatr 2012

Center Effect of CPAP & BPD



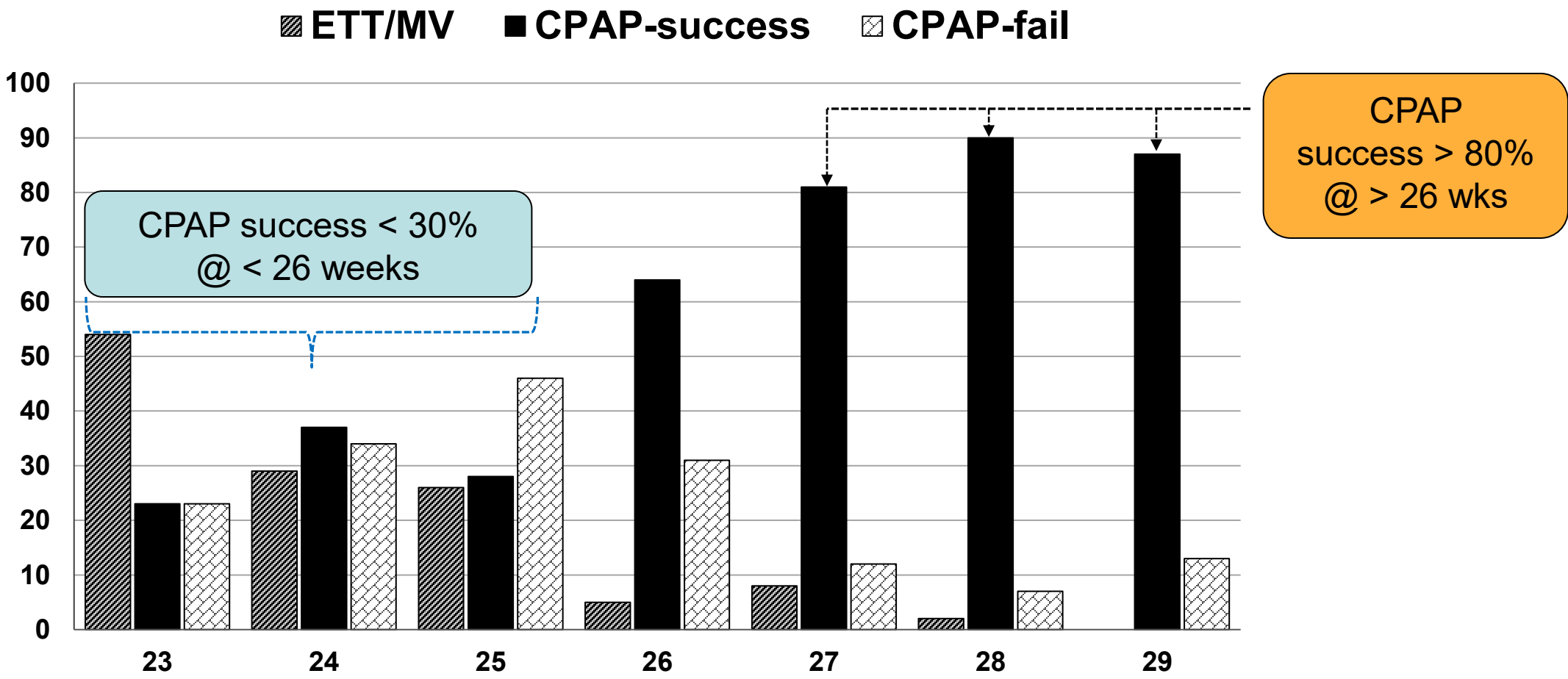
Avery ME et al, Pediatrics 1987



Van Marter L et al, Pediatrics 2000

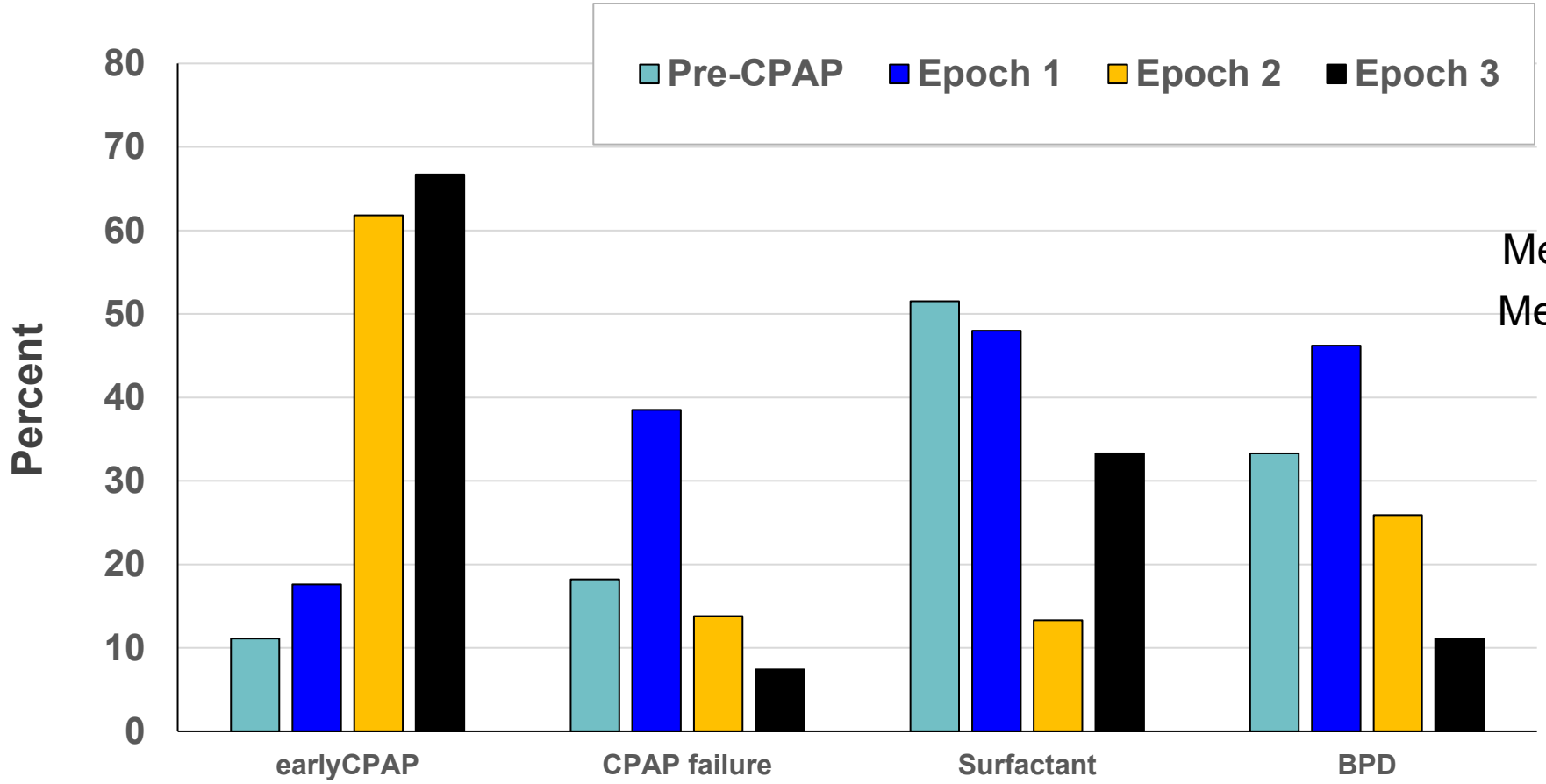
Effect of Gestation on nCPAP Failure

The Columbia Experience



Ammari A et al; J Peds 2005; 147:341-7

Success with nCPAP in ELBWIs
There's a *"Learning"* Curve



Mean GA ~ 26 wks

Mean B WT ~ 800g

Aly H et al, Pediatrics 2004

Interim Summary # 4
nasal CPAP

- Best studied approach – the “Gold Standard”
- Success improves w/ experience
- Interface & Driver are key to success
- RCTs support lower BPD rates as 1º Rx
- Failure is common below 26-27 weeks

You want to do *what* through my nose?

Nasal IMV

Approaches to NIMV/NIPPV

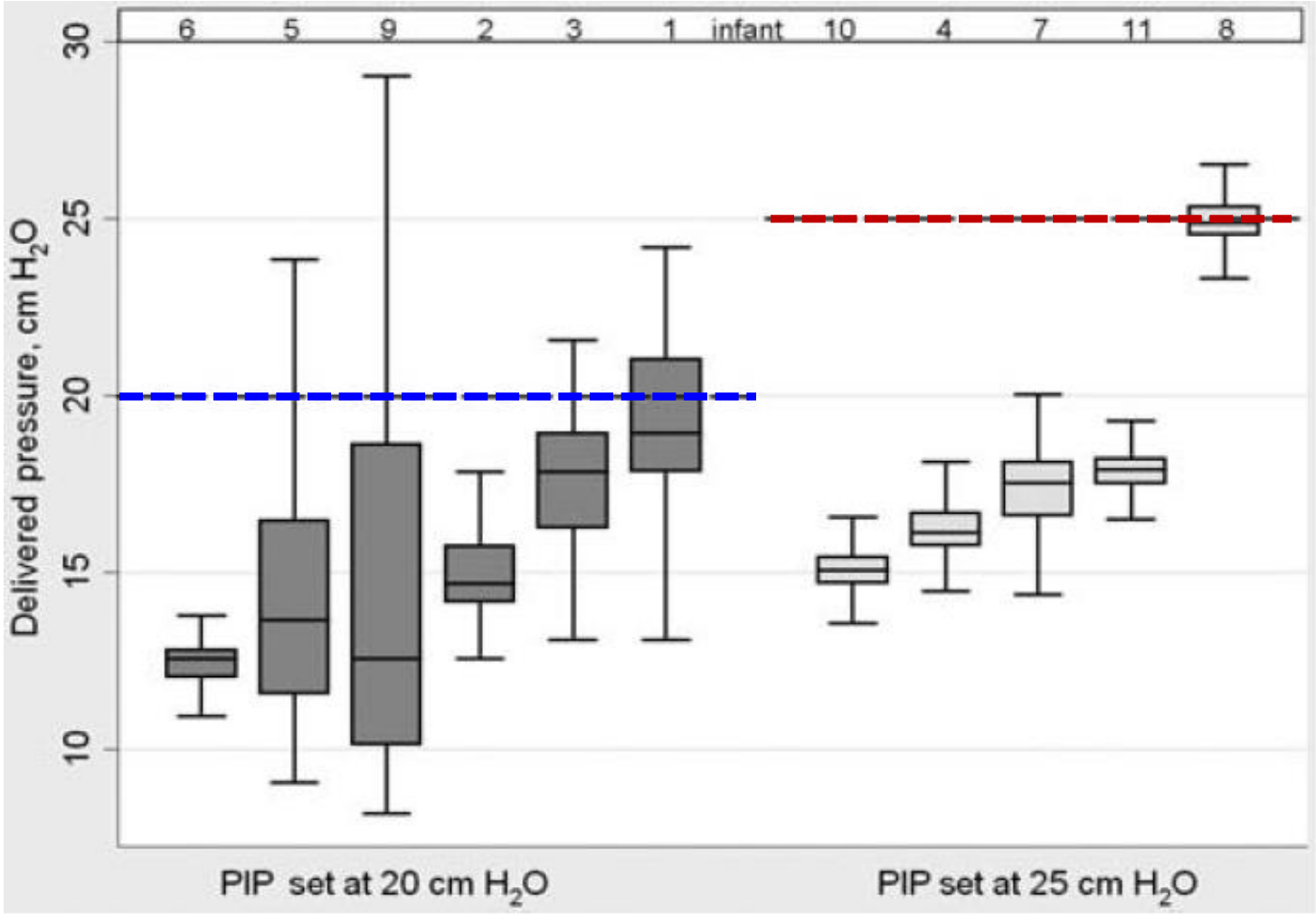
"Bi-PAP"

Synchronized

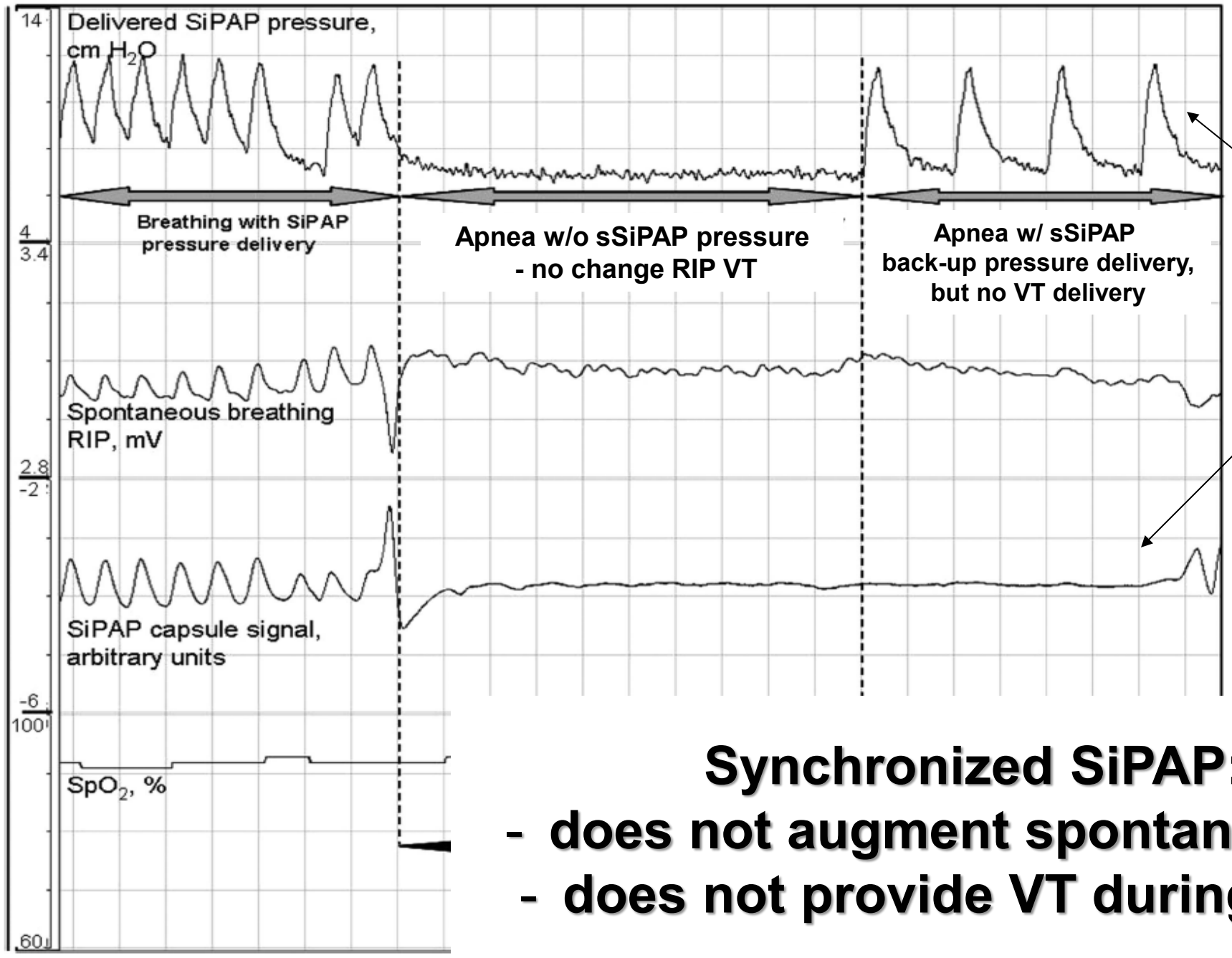
Non-synchronized

"High-frequency"

Delivered PIP during ns-NIPPV is variable & much lower than set pressure



Owen LS et al, ADCFNE 2010



PIP but

no VT

Synchronized SiPAP:

- does not augment spontaneous VT

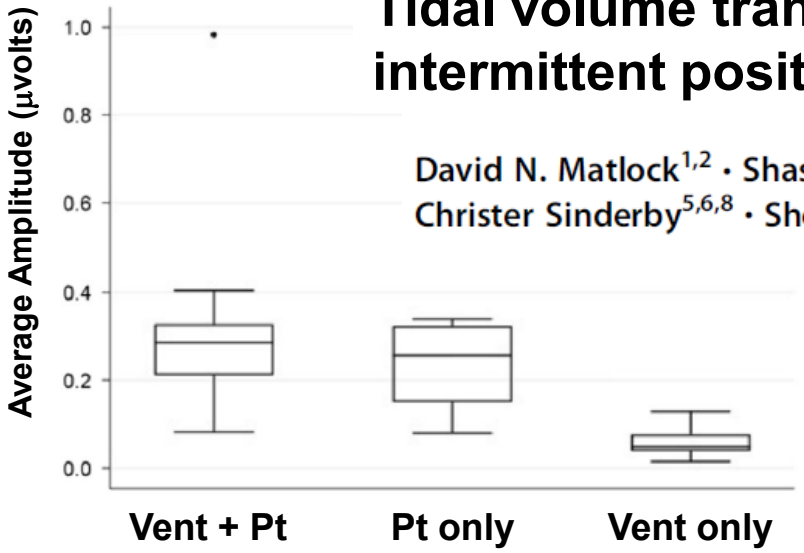
- does not provide VT during apnea

Owen LS et al, ADCFNE 2015

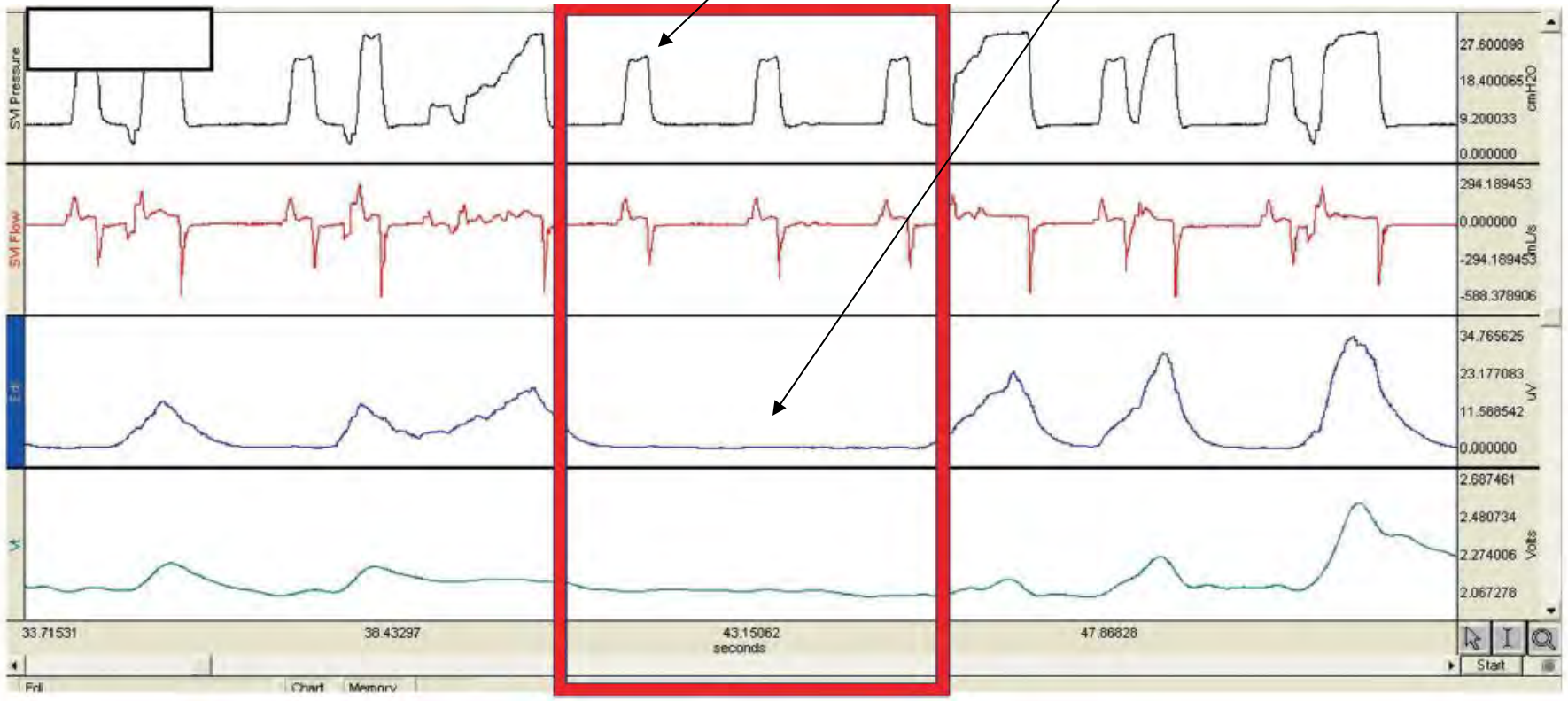
Tidal volume transmission during *non-synchronized* nasal intermittent positive pressure ventilation via RAM cannula

J Perinatol 2019

David N. Matlock[1,2] · Shasha Bai[3] · Michael D. Weisner[4] · Norman Comtois[5] · Jennifer Beck[5,6,7,8] · Christer Sinderby[5,6,8] · Sherry E. Courtney[2]



Despite "delivered" PIP - w/o spontaneous breath VT not delivered



Effects of Synchronization During Nasal Ventilation in Clinically Stable Preterm Infants

Chang H-Y, et al Pediatr Res 2011

Infant Star	nCPAP	NIMV-20	sNIMV-20	NIMV-40	sNIMV-40
VT	10.6	11.6	10.2	10.4	10.1
MinVent	508	681	535	546	581
RR	54	54	51	50	52
TcPCO2	55	55	55	56	56
SpO2	93	93	93	93	92
FiO2	0.25	0.25	0.26	0.25	0.25

No difference in median values between nCPAP, NIMV & sNIMV…

…but sNIMV reduced WOB & prevented active exhalation

Higher V_T generated during S-NIPPV

Moretti C et al, Early Hum Dev 1999; 56:167-177

Mode	RR (bpm)	Pe (cm H2O)	VT (ml/kg)	Ve (ml/kg/min)
nCPAP	44 (3)	6.2 (0.6)	5.5 (0.5)	256 (25)
nSIPPV	38 (3)*	4.2 (0.6)*	7.9 (0.6)*	320 (33)*

* = P < 0.05

Improved tidal volumes & minute ventilation

Short-term assessment only

Majority of infants ≥ 28 wks

Can NIMV minimize risk for post-extubation failure?

Cochrane Library

2017

Cochrane Database of Systematic Reviews

Nasal intermittent positive pressure ventilation (NIPPV) Versus nasal continuous positive airway pressure (NCPAP) for Preterm neonates after extubation (Review)

Lemyre B, Davis PG, De Paoli AG, Kirpalani H

Post-extubation failure → 10 studies, 1431 neonates

Risk ratio 0.70 (0.60-0.80) favoring NIMV

“Synchronized”, n=272; RR 0.33 (0.19-.57)

Can NIMV Reduce the Risk for BPD?

Cochrane Library

Cochrane Database of Systematic Reviews

2017

Nasal intermittent positive pressure ventilation (NIPPV) Versus nasal continuous positive airway pressure (NCPAP) for Preterm neonates after extubation (Review)

Lemyre B, Davis PG, De Paoli AG, Kirpalani H

Diagnosis of "BPD" → 6 studies, 1140 neonates

Risk ratio 0.94 (0.80-1.10) – no difference

"Synchronized", small #'s……but RR 0.64 (0.44-0.95)

Nasal SIMV & Extubation

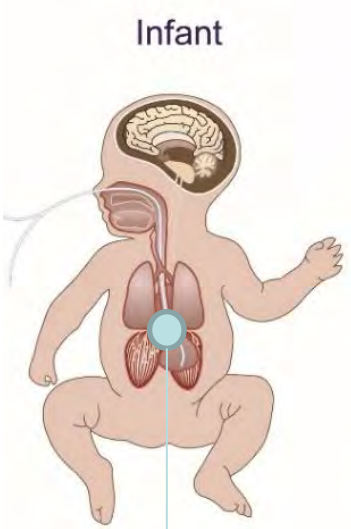
Extubation to sNIMV seems more effective

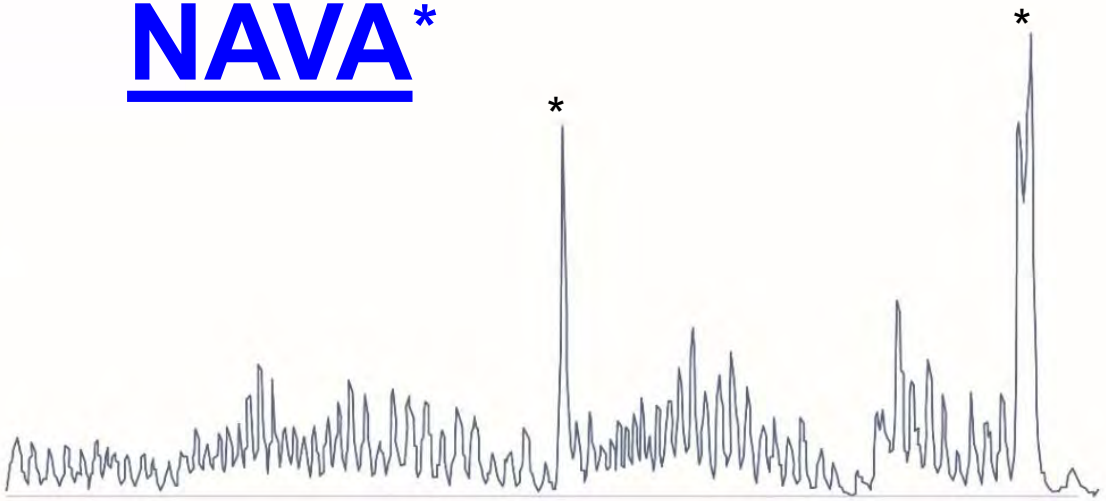
at maintaining extubation, minimizing apnea,

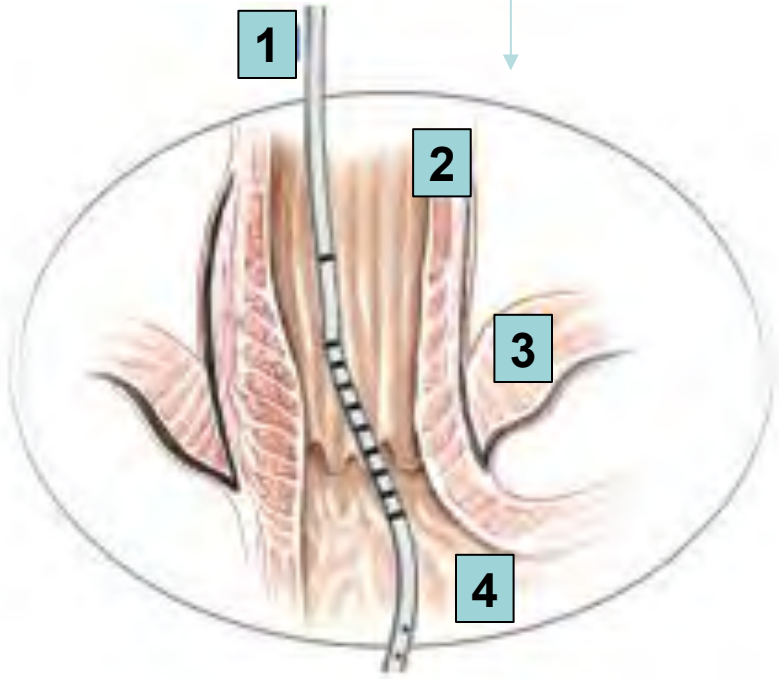
& lowering pCO_2 than nCPAP alone…

…but unclear benefit on BPD, later lung function

NAVA*







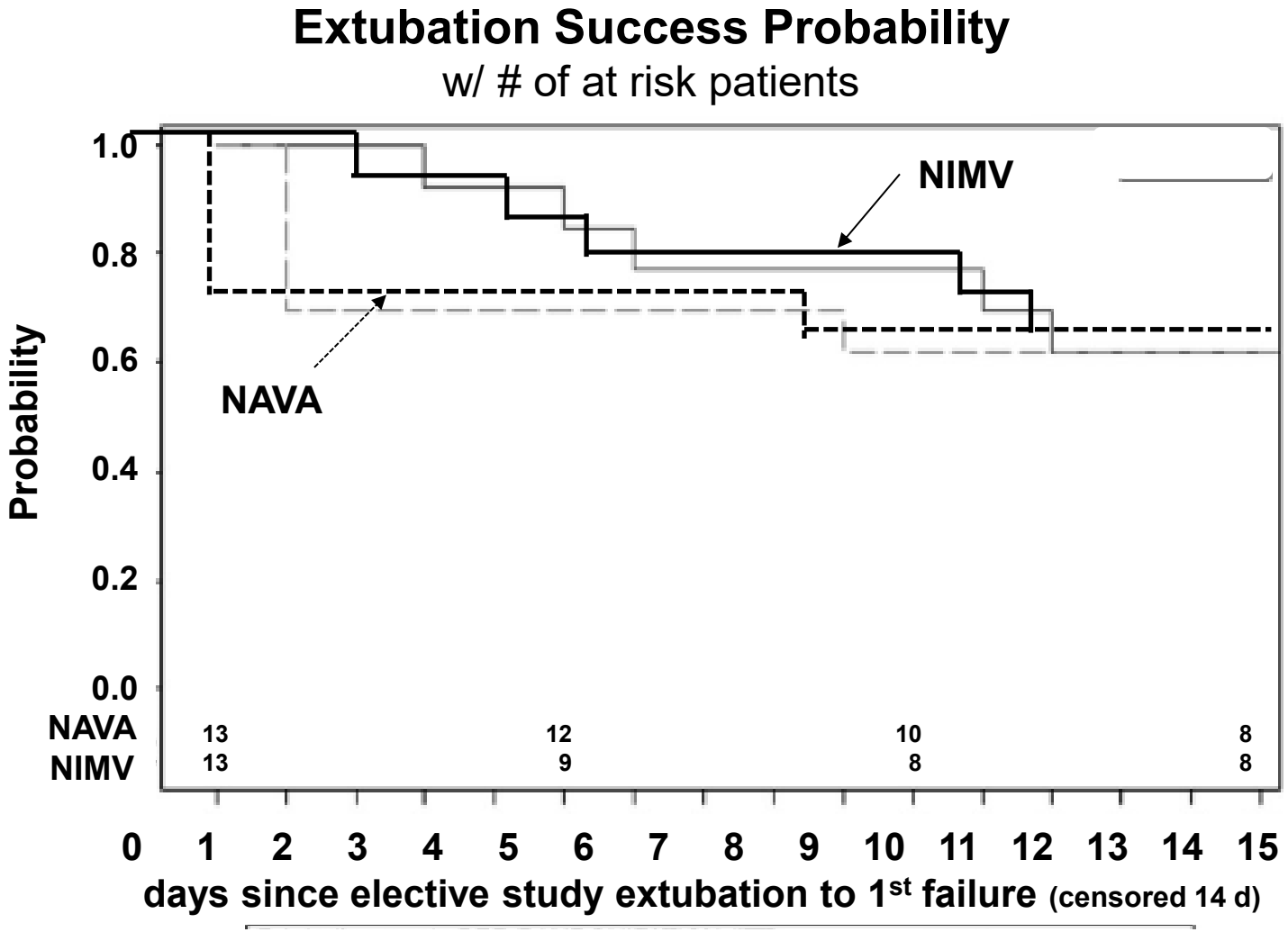
1. Edi catheter – electrod
   black
   1st line
   No phragm
2. Esc
3. Diap gm
4. Stomach

Is Synchronization the Key??

* Neurally Adjusted Ventilatory Assist

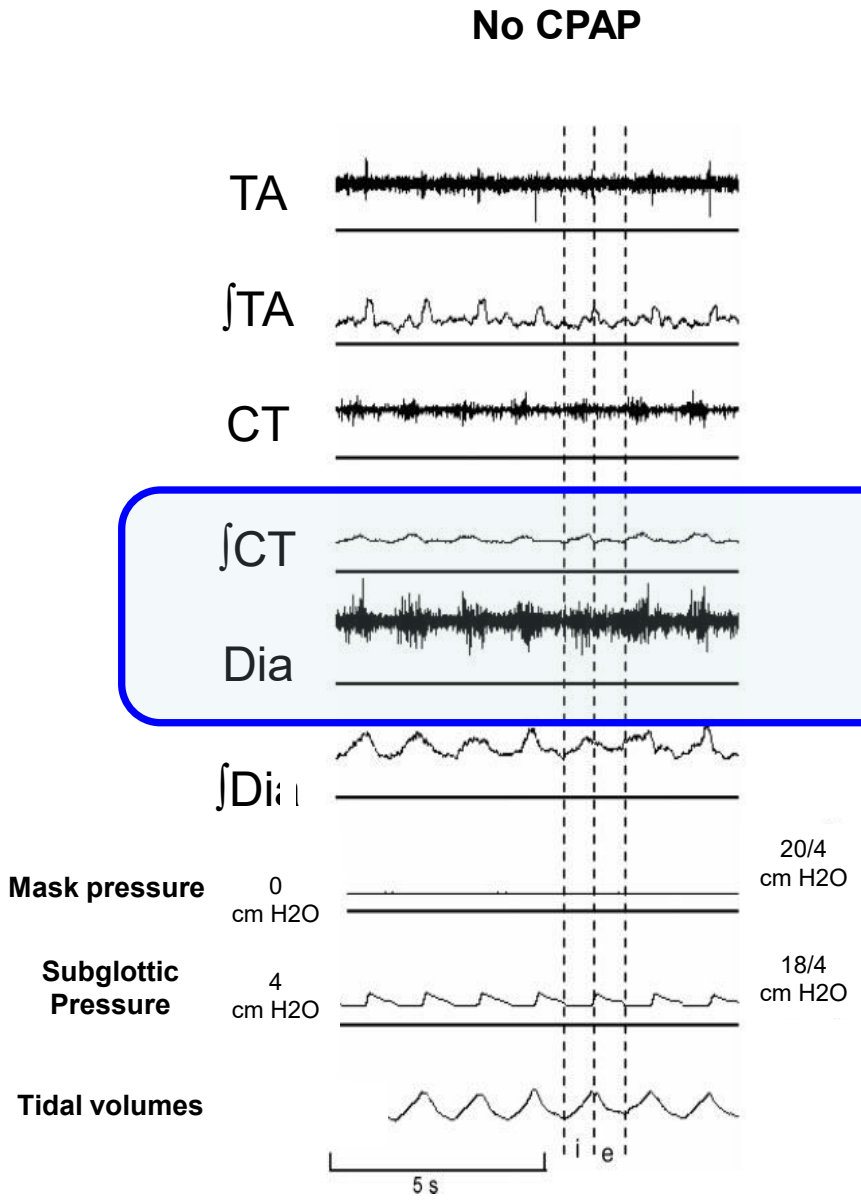
NIV-NAVA may increase probability of NIV success in VLBWI

	NAVA N=13	NIMV N=13
EGA	27 [25-28]	27 [26-30]
DOL 1st extubated	3 [3-5]	3 [2-5]
Success at 120 hrs	12 (92%)	9 (69%)
PN Steroid	4 (31%)	2 (15%)



Makkar K et al, J Perinatology 2020

Why Might NIMV *NOT* Be Better??



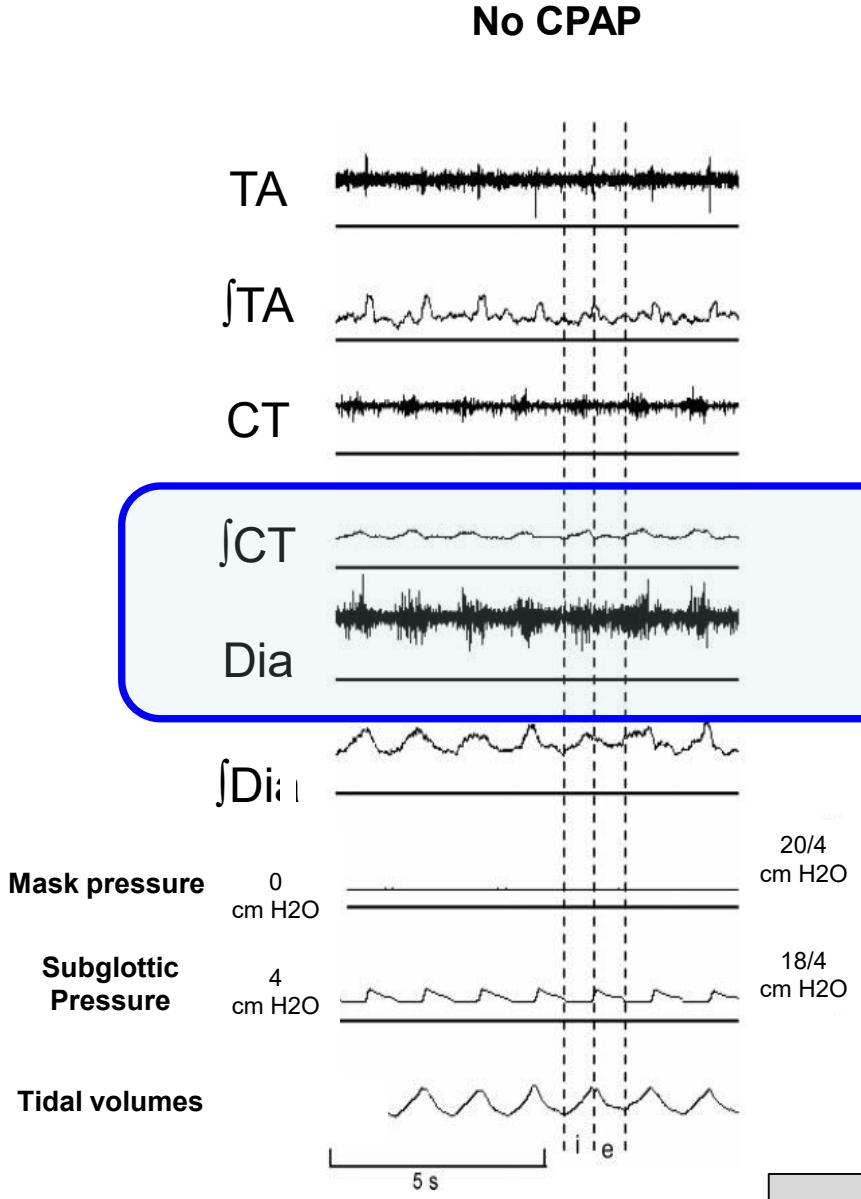
Normal breathing:

Minimal activity of glottic constrictor muscles (TA)

Active ***relaxation*** of glottic muscles (CT) to "open"/dilate the upper airway

Allows easier gas flow
Enhances tidal volume
Minimizes work of breathing
Less inspiratory pressure

Moreau-Bussie`re, JAP 2007



Normal breathing:

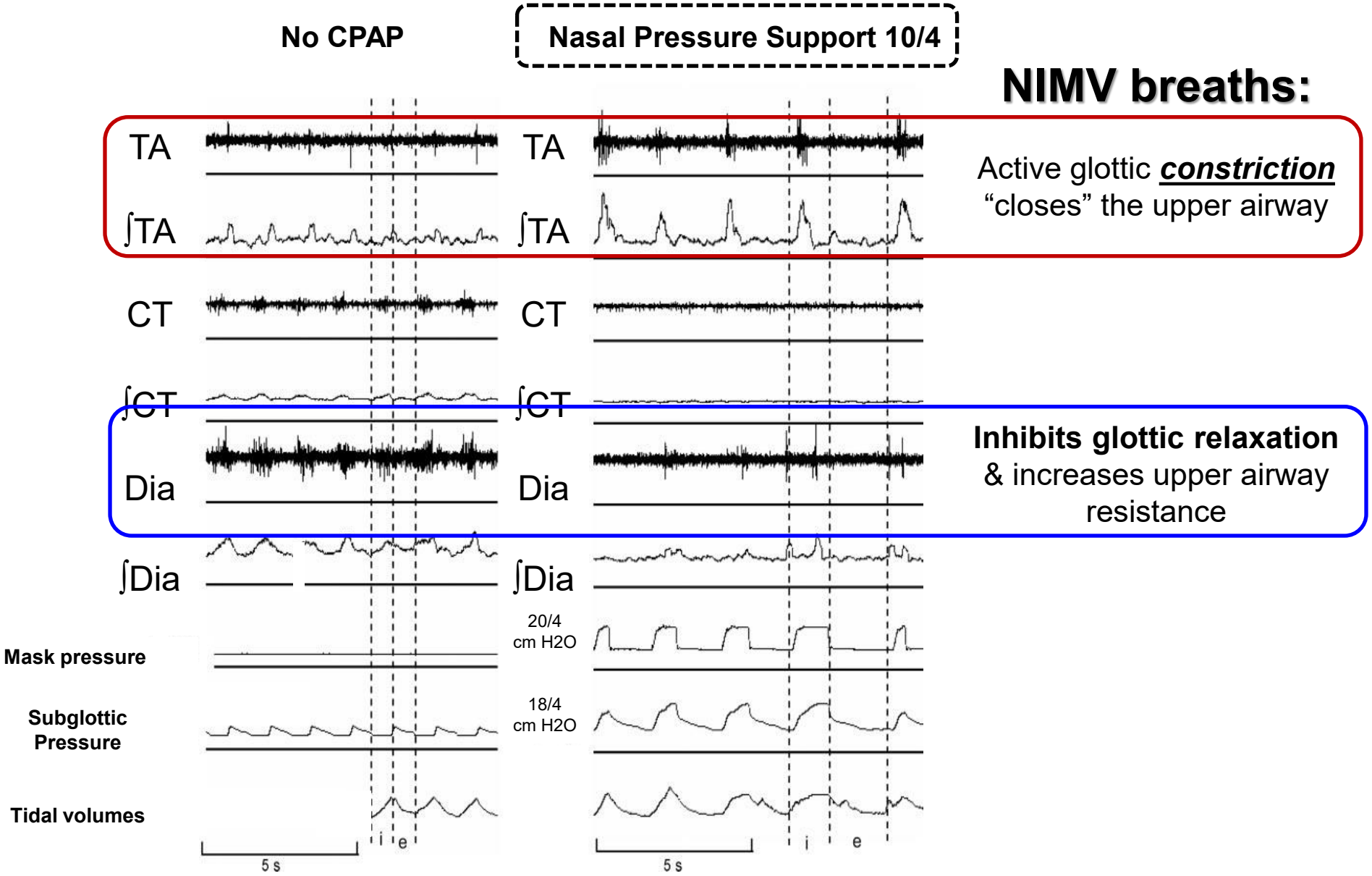
Minimal activity of glottic constrictor muscles (TA)

Active ***relaxation*** of glottic muscles (CT) to "open"/dilate the upper airway

Allows easier gas flow
Enhances tidal volume
Minimizes work of breathing
Less inspiratory pressure

CPAP alone does not alter this

Moreau-Bussie`re, JAP 2007



NIMV breaths:

Active glottic ***constriction*** "closes" the upper airway

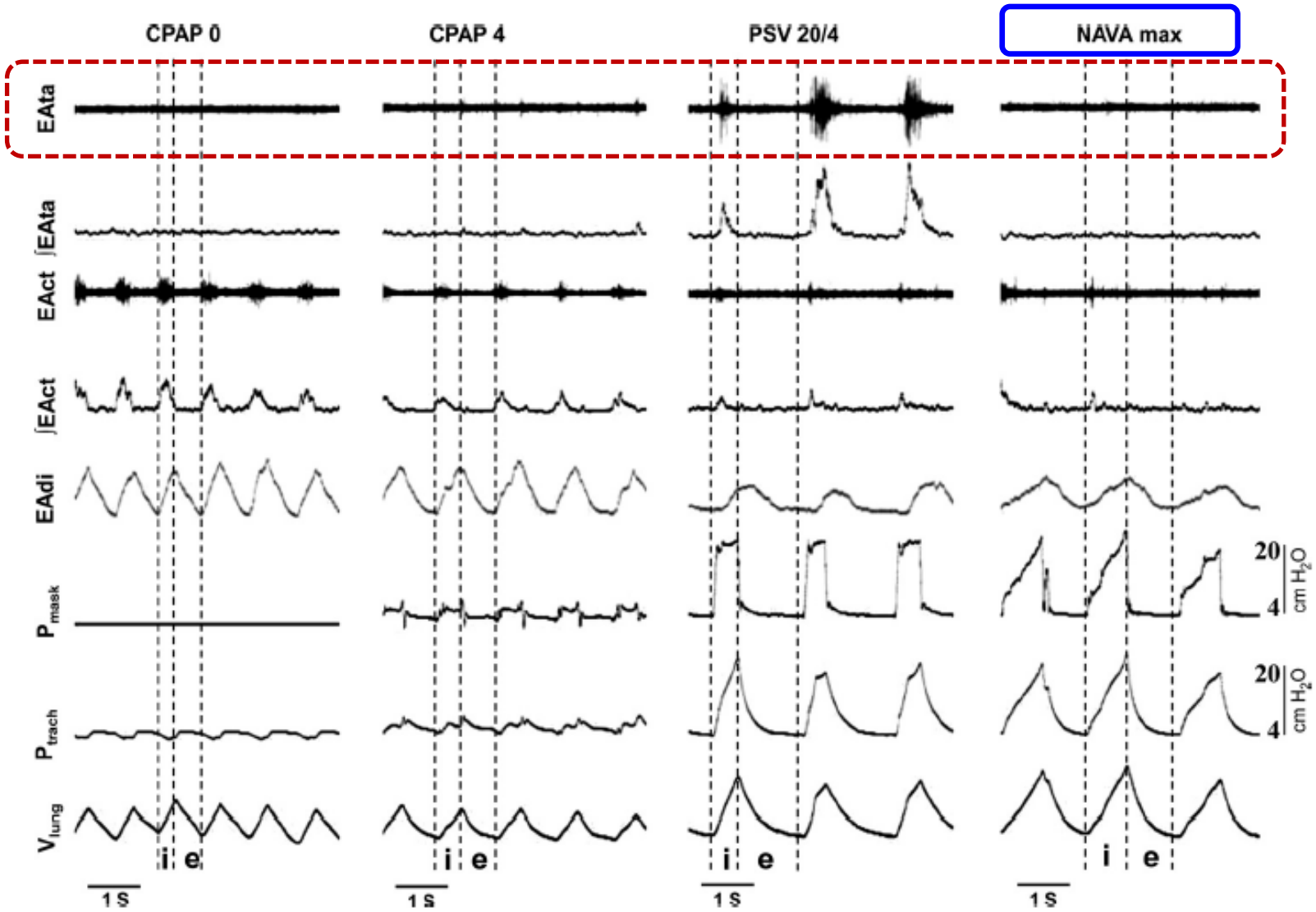
Inhibits glottic relaxation & increases upper airway resistance

NIMV disturbs normal physiology

Moreau-Bussie`re, JAP 2007

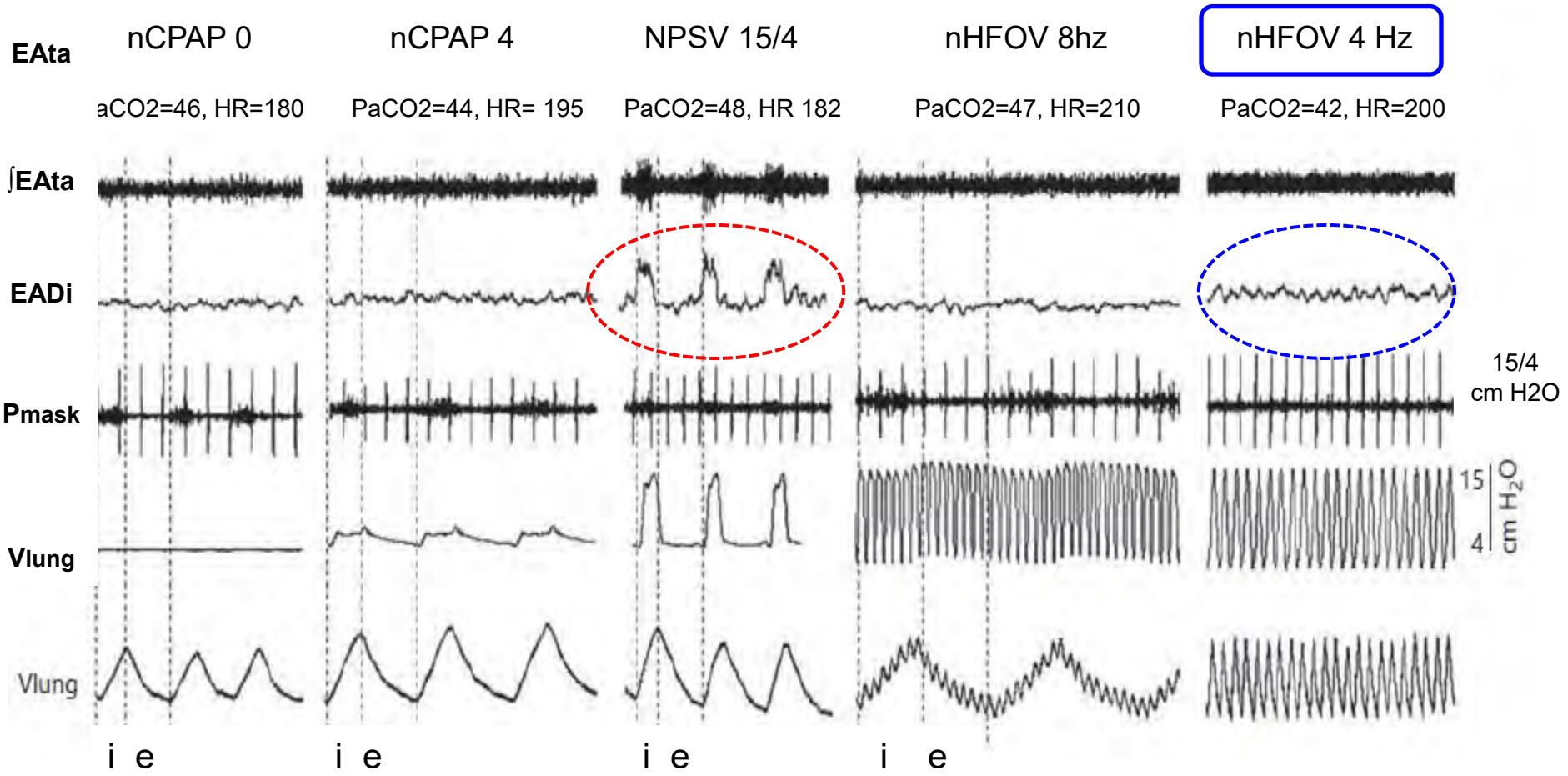
but…..NIV-NAVA supports normal glottis muscle activation in newborn lambs

Hadj-Ahmed MA, JAP 2012



Interestingly……so does Nasal HFOV

Support normal/active ***relaxation*** of glottis muscles w/ minimal activity of glottis constrictor muscles

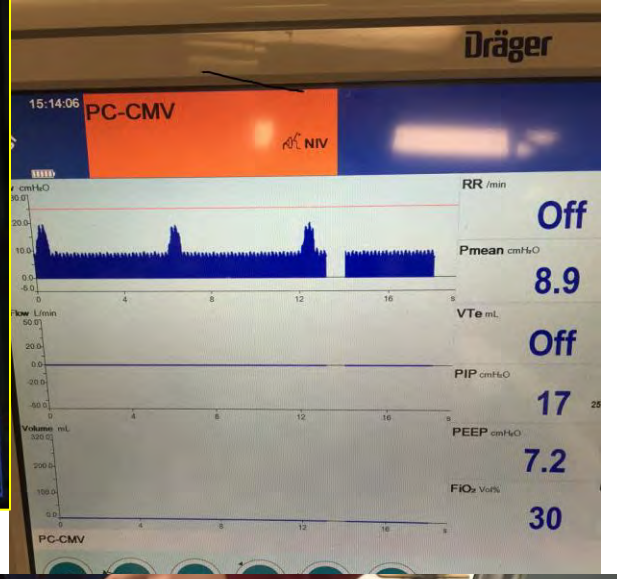


Hadj-Ahmed, Neonatology 2015

Interim Summary # 5
nasal IMV

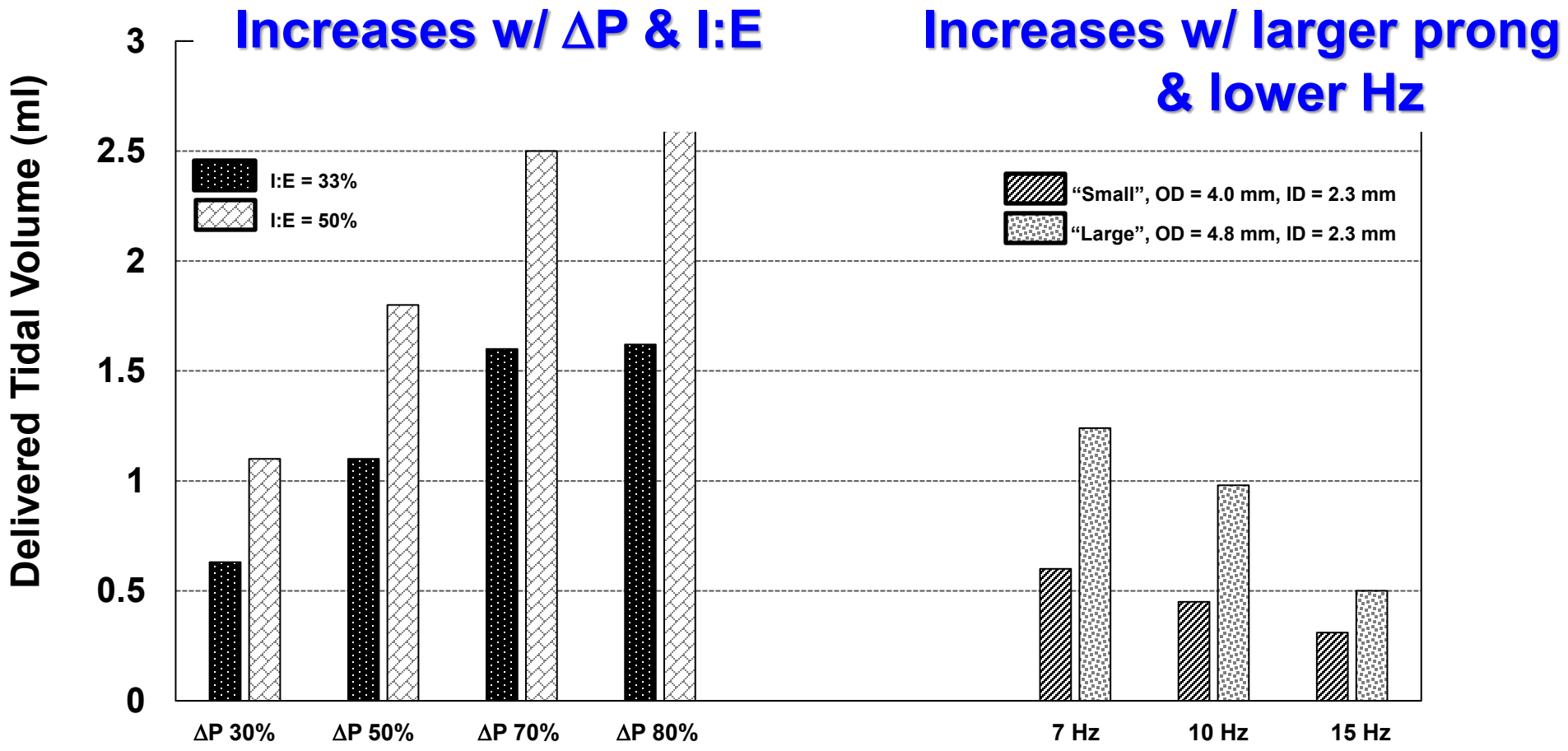
- Studies support less extubation failure v CPAP
- RCTs do not support lower BPD rates
- Synchronization may be key to reducing BPD
- No significant tidal volume delivery when apneic
- Large MCT RCT's w/ NAVA are needed

What about nasal HFV?



Extubated lamb on NIV-HFJV
Comfortable respirations noted
HF vibrations visible & audible over upper airway and chest

VT during nasal-HFO



f = 10 Hz
P_{aw} = 10 cm H2O

I:E = 33%
ΔP = 45 cm H2O

* *HFOV 3100A*

De Luca et al, Int Care Med 2010

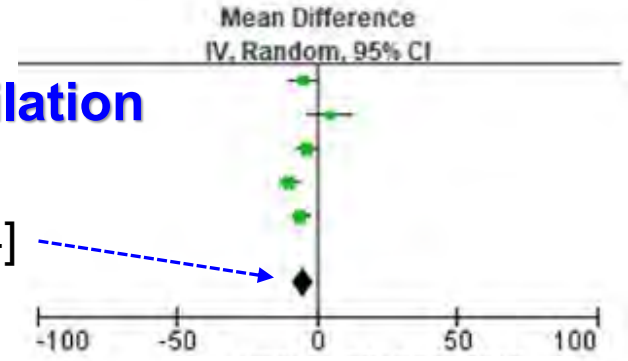
Meta-analysis for nHFV

Jing Li et al, Respir Res 2019

Improved ventilation

ΔpCO2

-4.9 [-8.4, -1.4]



nHFOV vs nCPAP/bCPAP

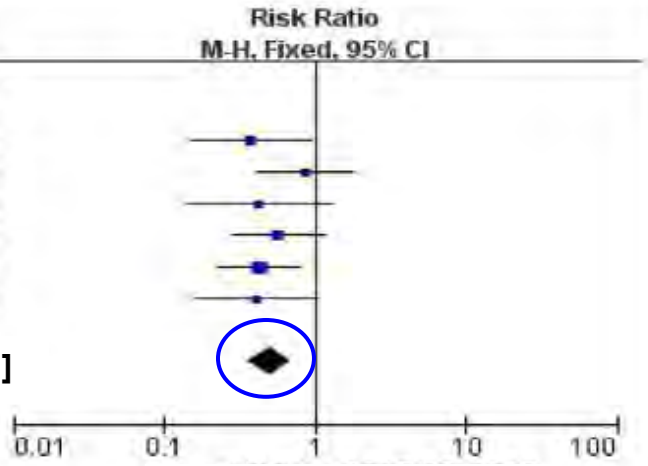
Reduced rate of intubation

Study or Subgroup	nHFOV Events	Total	nCPAP/BP-CPAP Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bottino 2018	0	15	0	15		Not estimable
Klotz 2017	0	13	0	13		Not estimable
Lou 2017	5	34	12	31	16.4%	0.38 [0.15, 0.96]
Lou 2018	9	33	10	32	13.3%	0.87 [0.41, 1.86]
Malakian 2018	4	63	9	61	12.0%	0.43 [0.14, 1.32]
Mukerji 2016	6	16	15	23	16.1%	0.57 [0.29, 1.16]
Zhu 2017	9	37	22	39	28.1%	0.43 [0.23, 0.81]
Zhux 2017	4	17	12	21	14.1%	0.41 [0.16, 1.05]
Total (95% CI)	**37**	**228**	**80**	**235**		**0.50 [0.36, 0.70]**

Total events

Heterogeneity: Chi² = 3.01, df = 5 (P = 0.70); I² = 0%

Test for overall effect: Z = 4.14 (P < 0.0001)



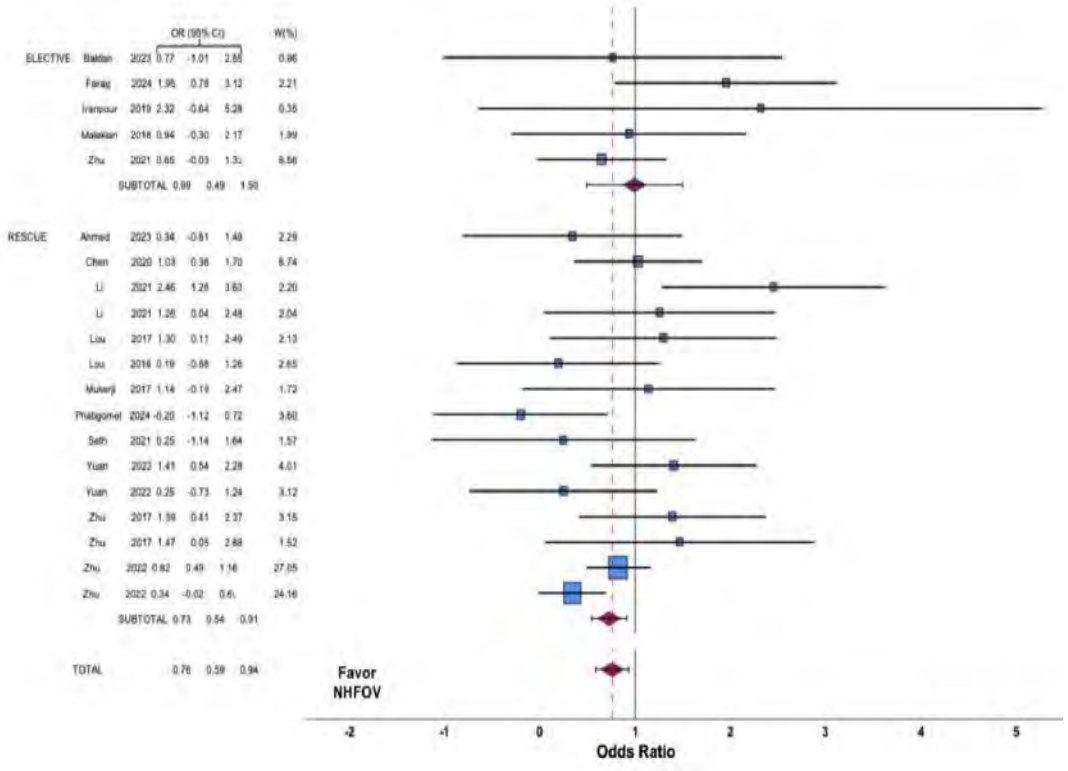
nHFOV vs nCPAP/bCPAP

Meta-analysis for rate of intubation for nHFOV vs nCPAP/bCPAP

Meta-analysis for nHFV

De Luca D et al, Semin Perinatol 2025

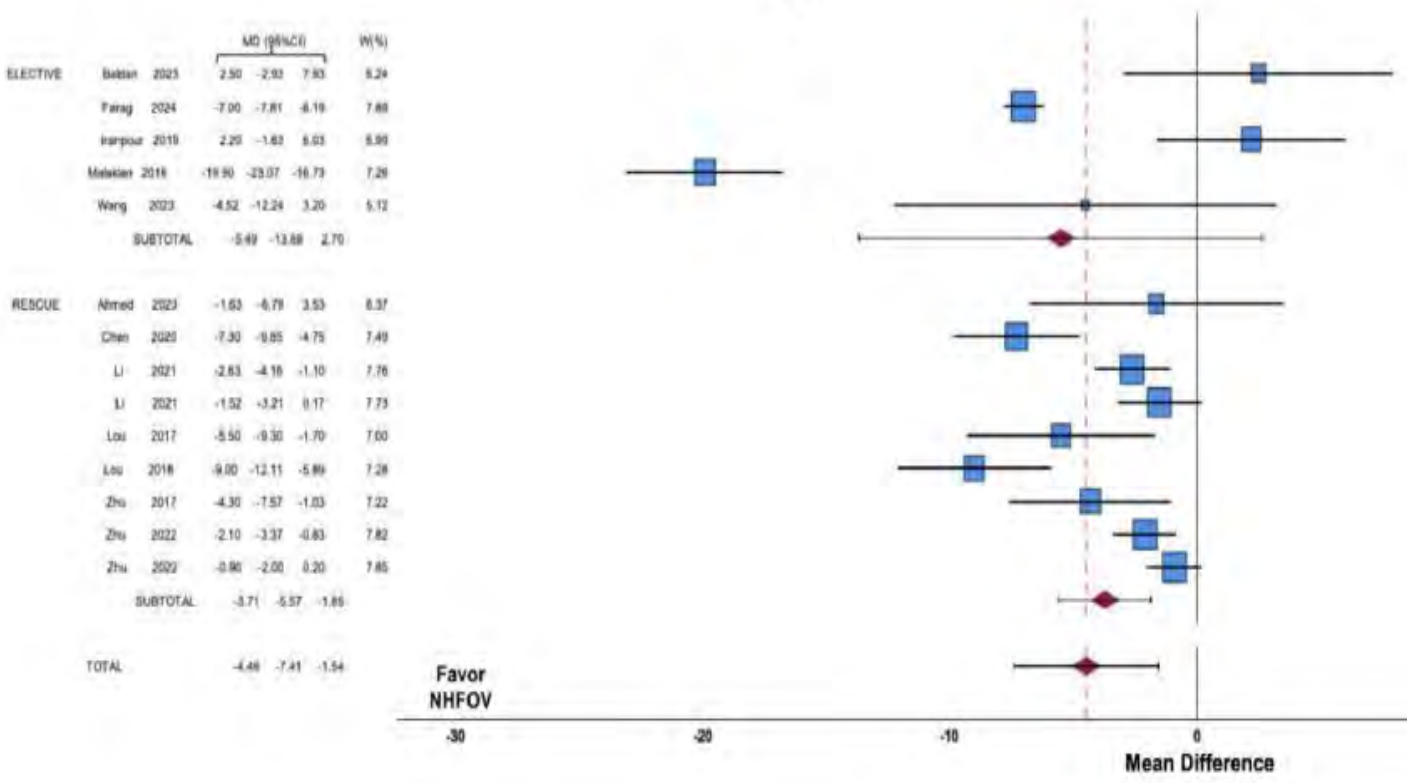
Extubation Failure



20 trials, n=3219

Favors nHFV; 0.76 [0.59-0.94]

Δ pCO2



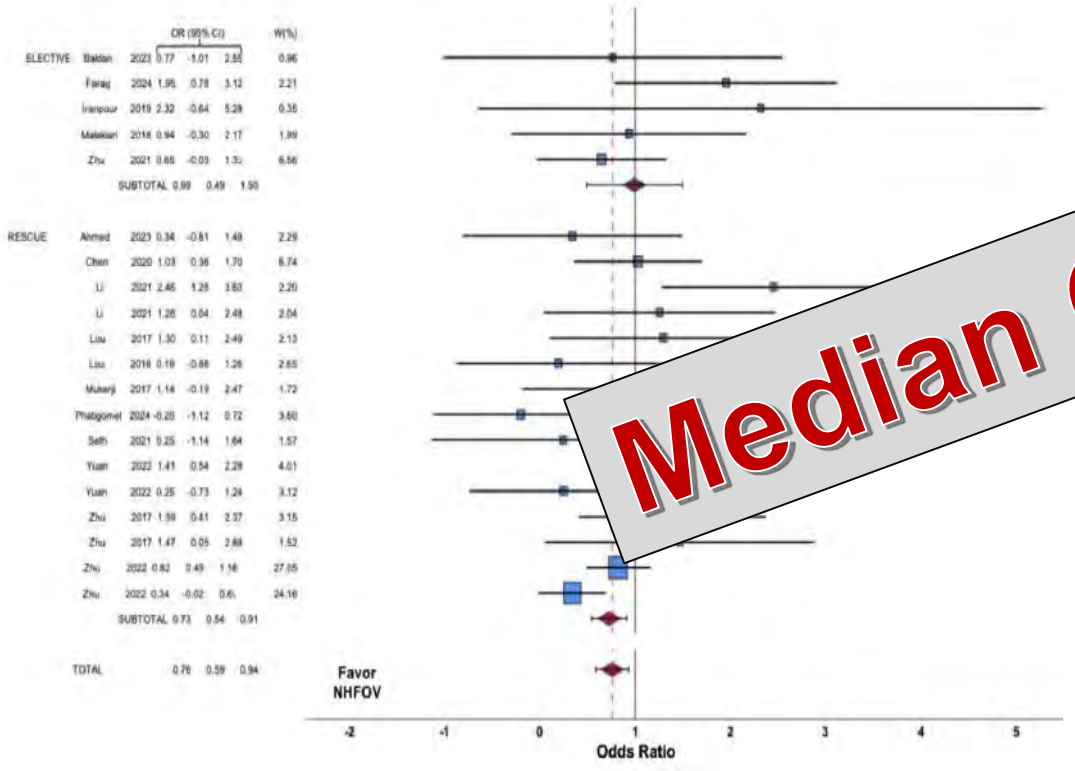
14 trials, n=2343

Favors nHFV; -4.5 [-7.4, -1.5]

Meta-analysis for nHFV

De Luca D et al, Semin Perinatol 2025

Extubation Failure

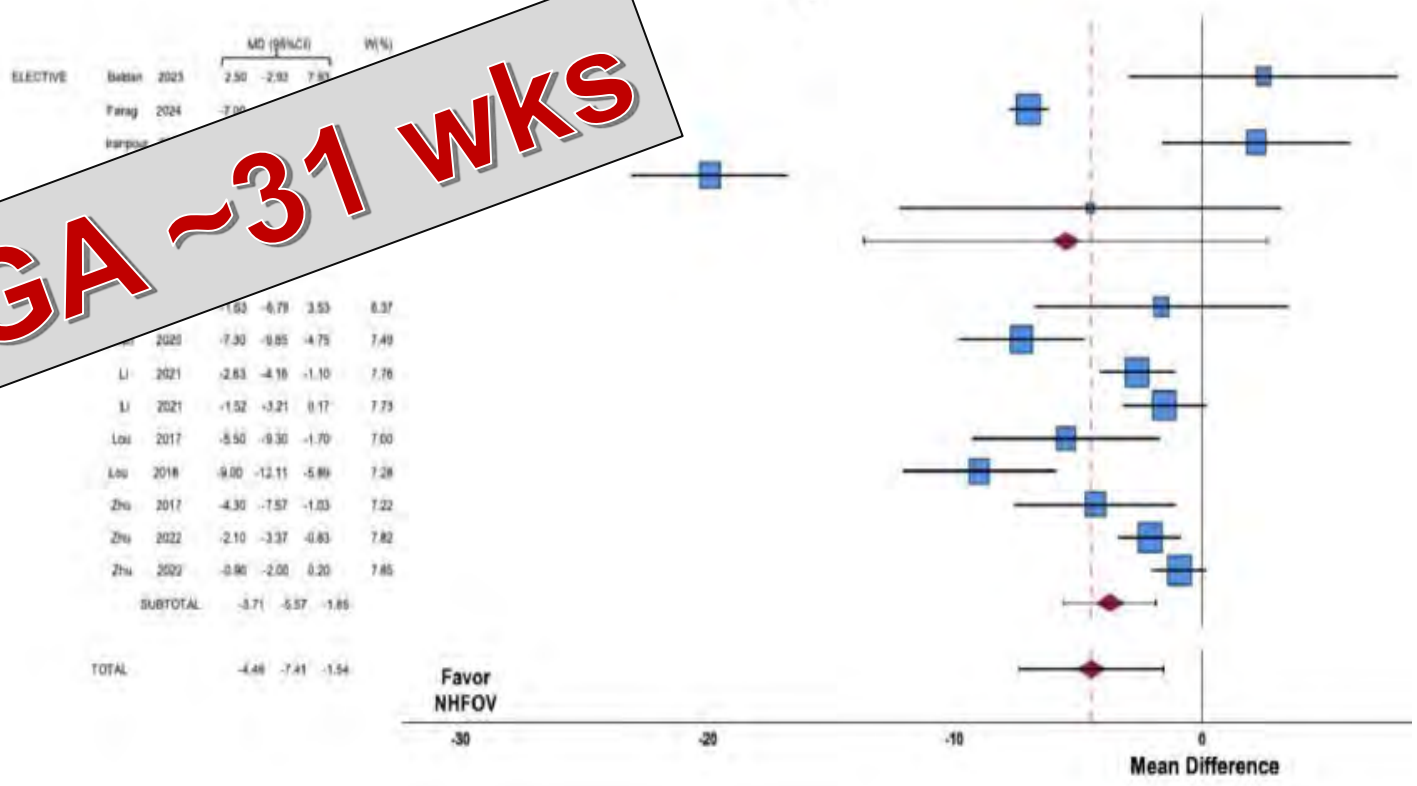


20 trials, n=3219

Favors nHFV; 0.76 [0.59-0.94]

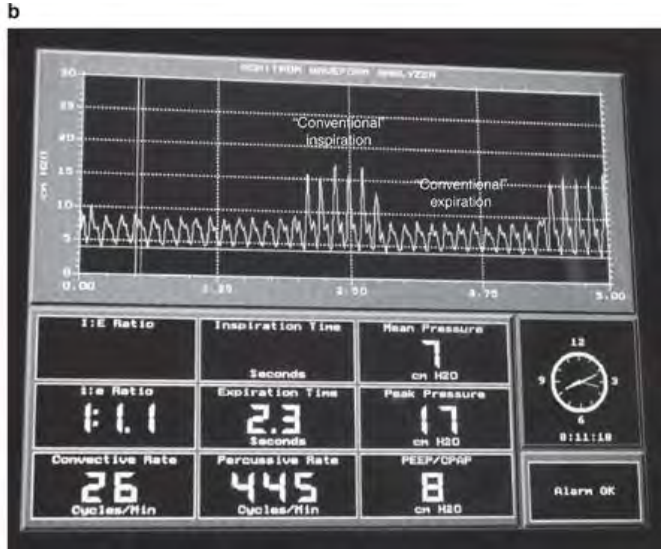
Median GA ~31 wks

Δ pCO2



14 trials, n=2343

Favors nHFV; -4.5 [-7.4, -1.5]



Nasal HFV in the Neonate

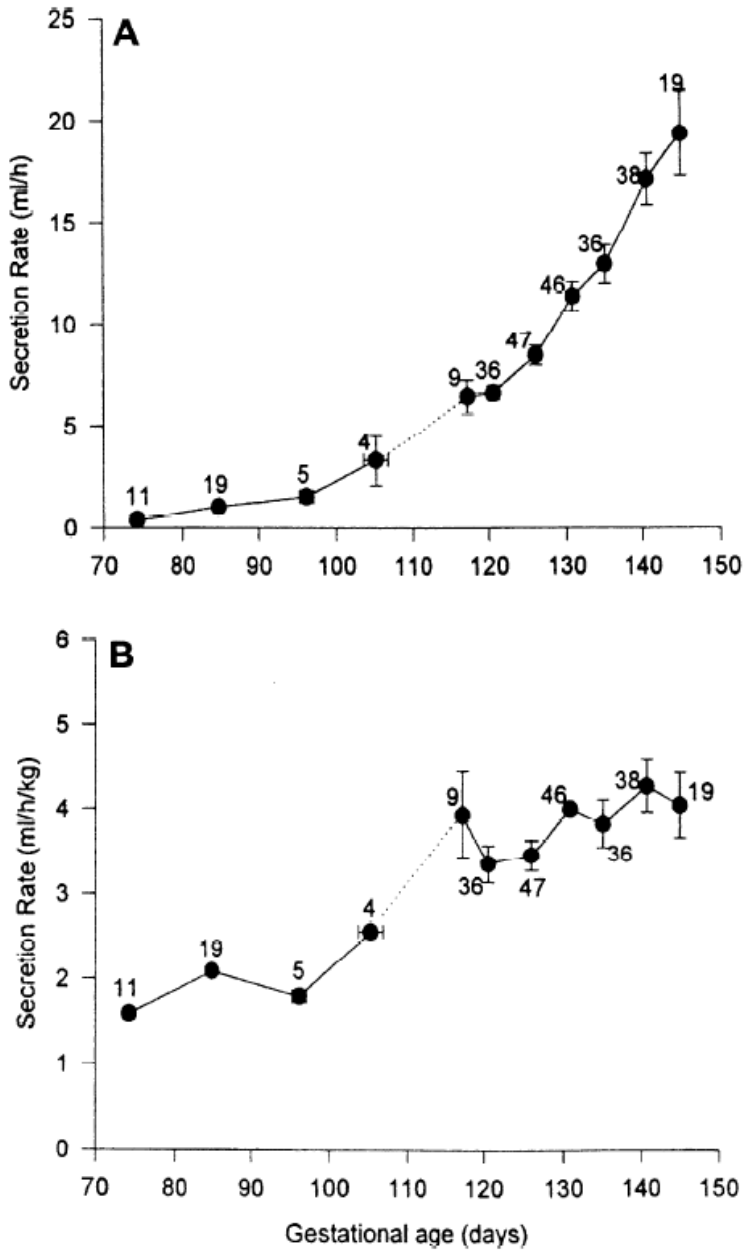
- It can be done
- What device, interface & how?
- Who should be considered?
- High-quality RCT's are needed

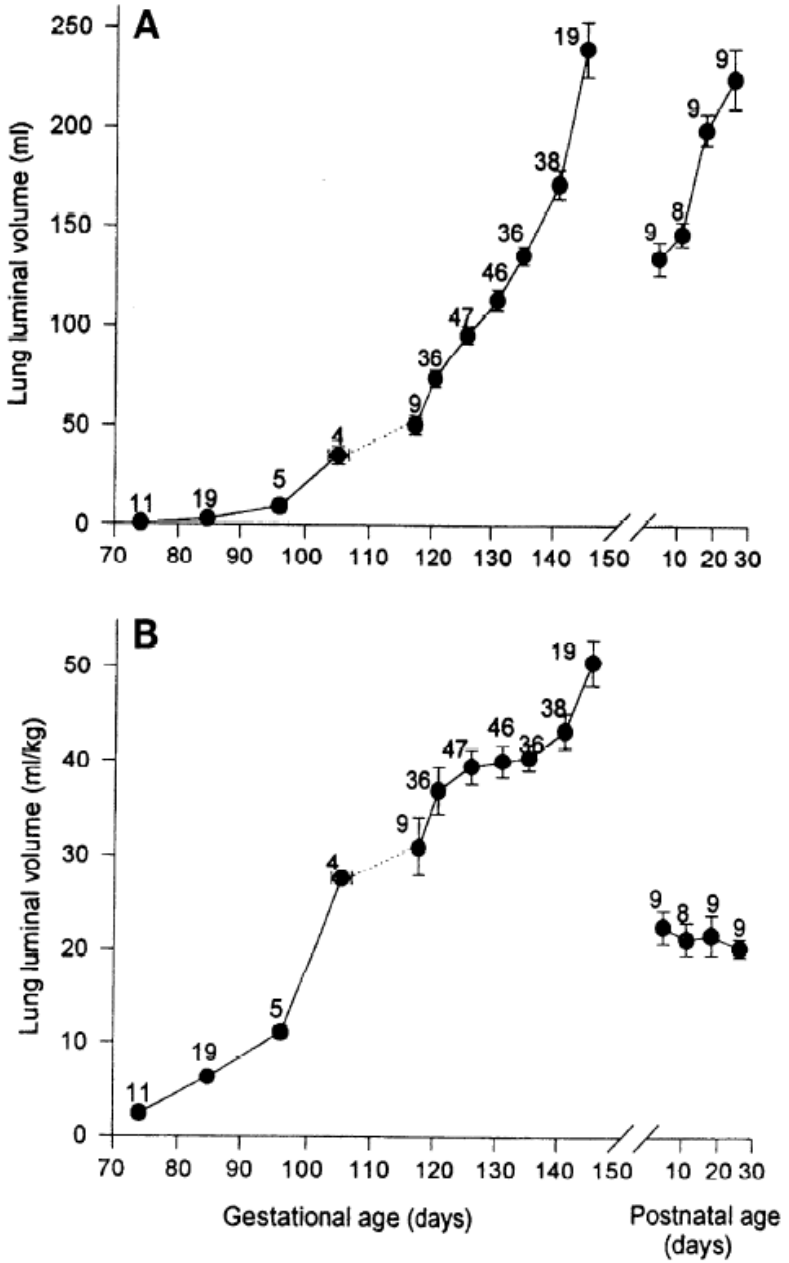
Interim Summary # 6
nasal HFV

- Meta-analyses suggest as optimal NIV approach
- RCTs limited by inadequate ELGAN's
- Synchronization not needed
- Optimal interface, driver & approach not established
- Large MCT RCT's w/ ELGAN's needed

How long should we provide NIV support ?

How long should we use NIV?





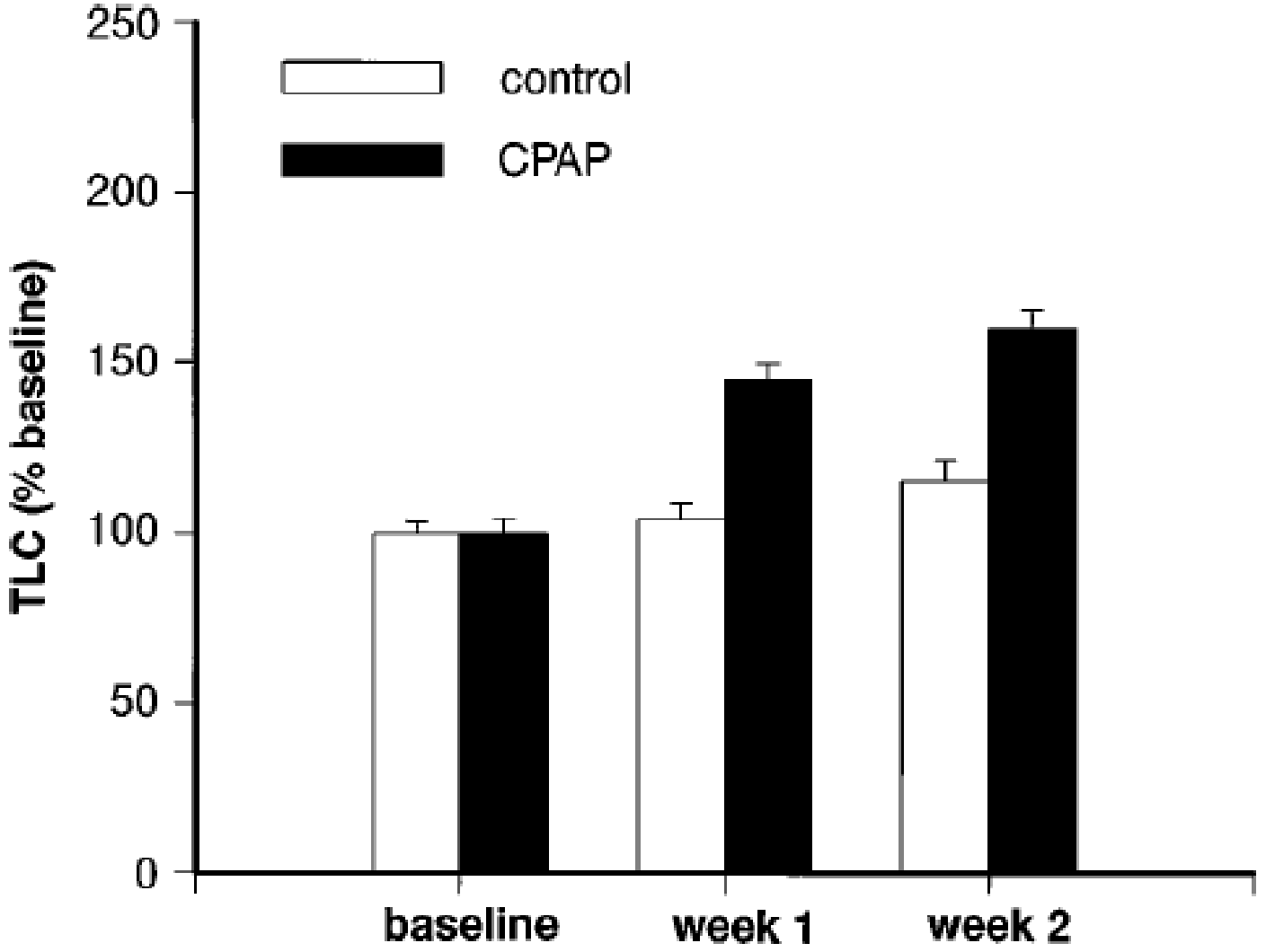
Continuous fetal lung liquid production

Intraluminal pressure of fetal lung varies from 2-3 cmH2O

Harding R, JAP, 1996

How long should we use NIV?

Ferret's exposed to 6 cm H2O CDP showed increased lung volumes



Zhang S, JAP, 1996

The Effect of Extended Continuous Positive Airway Pressure on Changes in Lung Volumes in Stable Premature Infants: A Randomized Controlled Trial

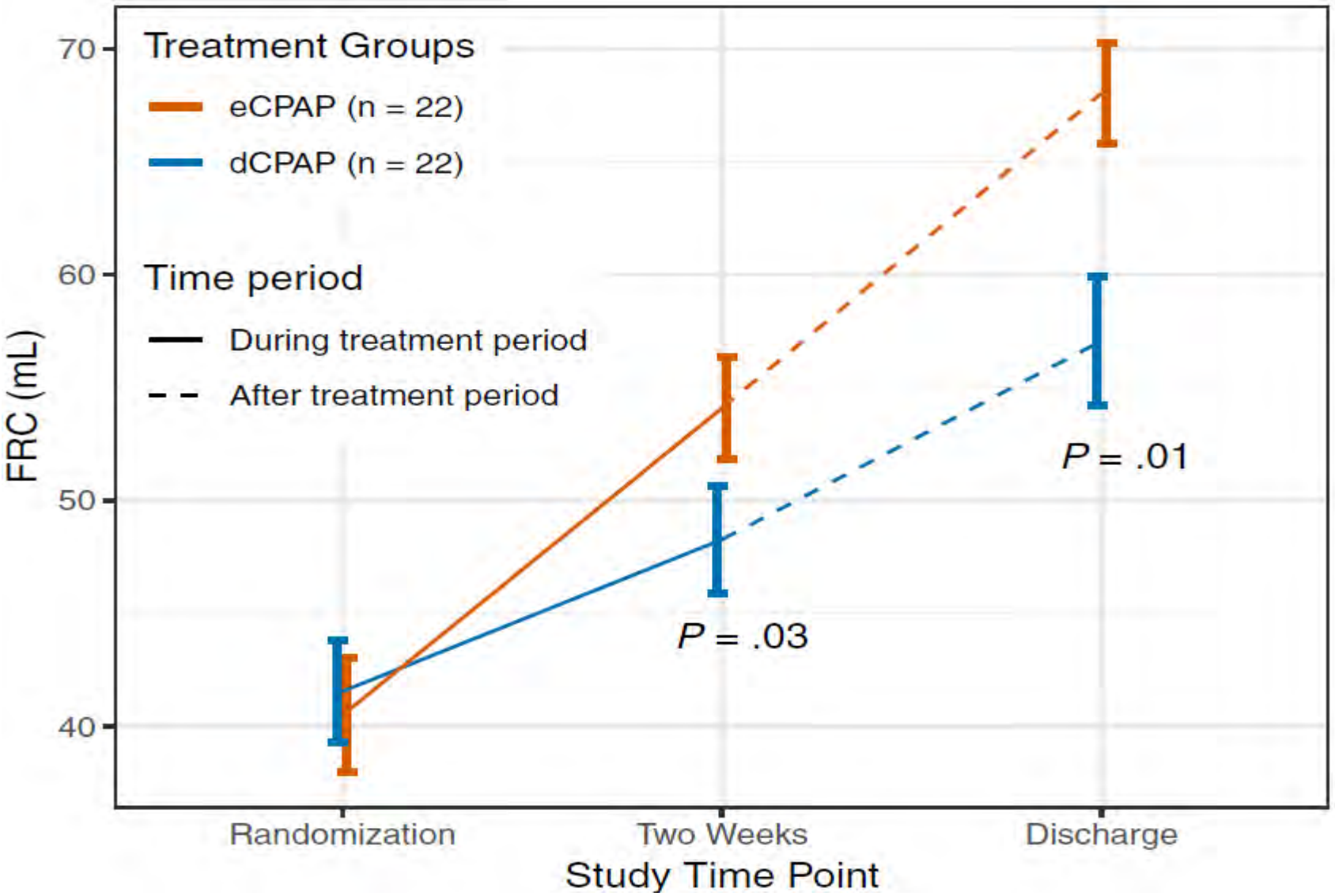
J Peds 2019

Ryan Lam, MD[1], Diane Schilling, RRT[1], Brian Scottoline, MD, PhD[1], Astrid Platteau, MD[1], Meike Niederhausen, PhD[2], Kelli C. Lund, MD[1], Robert L. Schelonka, MD[1], Kelvin D. MacDonald, MD, RRT[3], and Cindy T. McEvoy, MD, MCR[1]

- Bubble CPAP via Hudson
- "Stability" =
  - 4-5 cm H2O
  - 21% FiO2
  - RR < 70
  - Minimal A/B/D's
  - Tolerating 15 minutes off

	extCPAP n=22	**offCPAP** n=22
GA	29.5 (1.9)	28.7 (2.2)
BWT	1405 (417)	1222 (389)
ANS	91%	77%
Male	41%	64%
Surf	18%	46%
Vent days	0 (0,1)	0 (0,1)
CPAP days	12 (6-29)	17 (10-32)
PMA	32.2 (0.7)	32.0 (0.8)

RCT: Effect of extended CPAP on Lung Volumes in Stable Preemies



Lam et al, J Peds 2019

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- No differences in:
  - Lung compliance
  - Airway resistance
  - Age to full PO feeds
    - (36 weeks)
  - Rates for home O2 use

- Extended CPAP increased FRV after 2 weeks & at D/C
  - FRV ~ 28 ml/kg vs ~ 25 ml/kg
- Need larger trials w/ long-term f/u to determine benefit vs risk
- Need cost analysis

J Peds 2019

RCT on Extended CPAP in Preterm Infants: Lung Growth & Function at 6 Months

McEvoy CT et al, Am J Resp CCM 2025

- Enrolled 100 infants 25-32 weeks stable on CPAP
  - Minimum 24 hours of CPAP…. & 12 hours “stable”
  - “Stable” = CPAP 5, 21%, RR < 70, minimal A/Bs
  - Bubble CPAP via Hudson prongs w/ chin strap
- Intervention: extended CPAP x 14 days vs to LFNC
- Primary outcome: Alveolar volume at 6 months
  - Secondary includes DL_{CO} & FEF

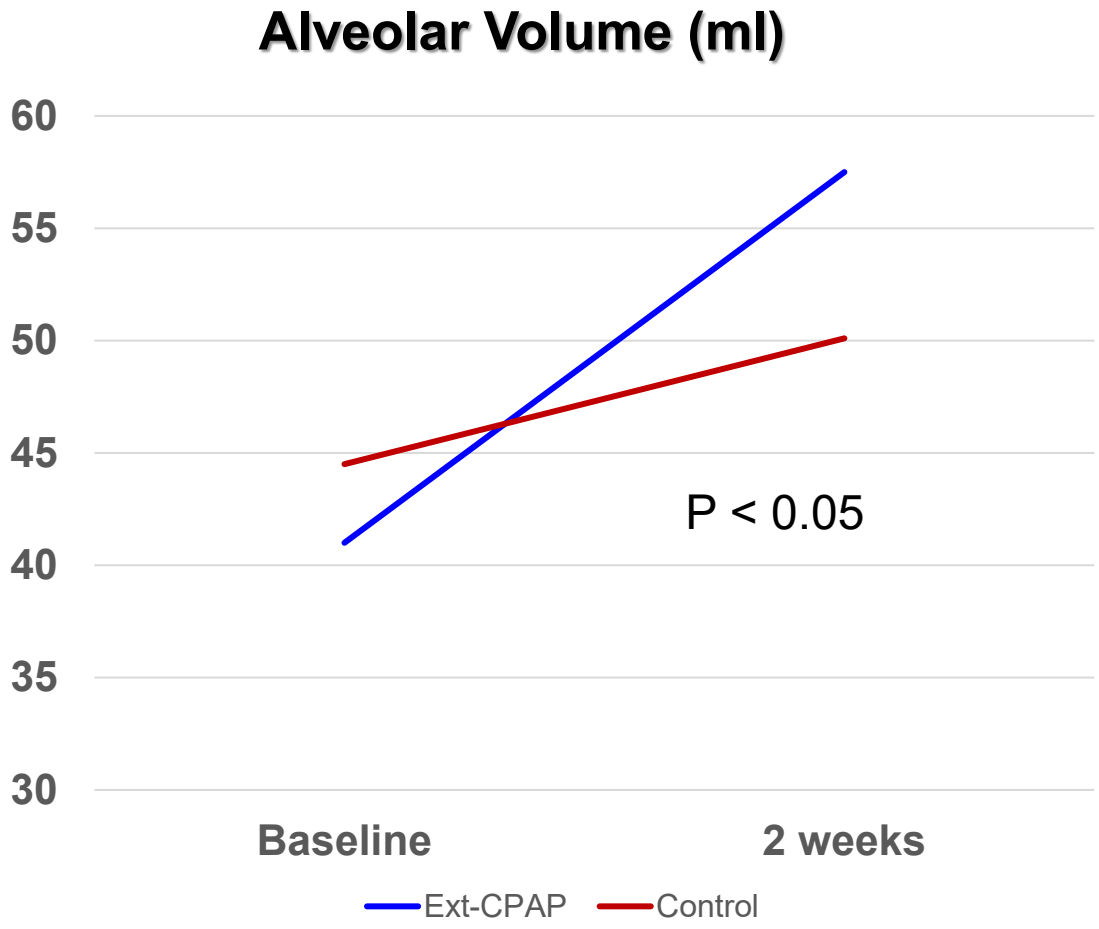
RCT on Extended CPAP in Preterm Infants: Lung Growth & Function at 6 Months

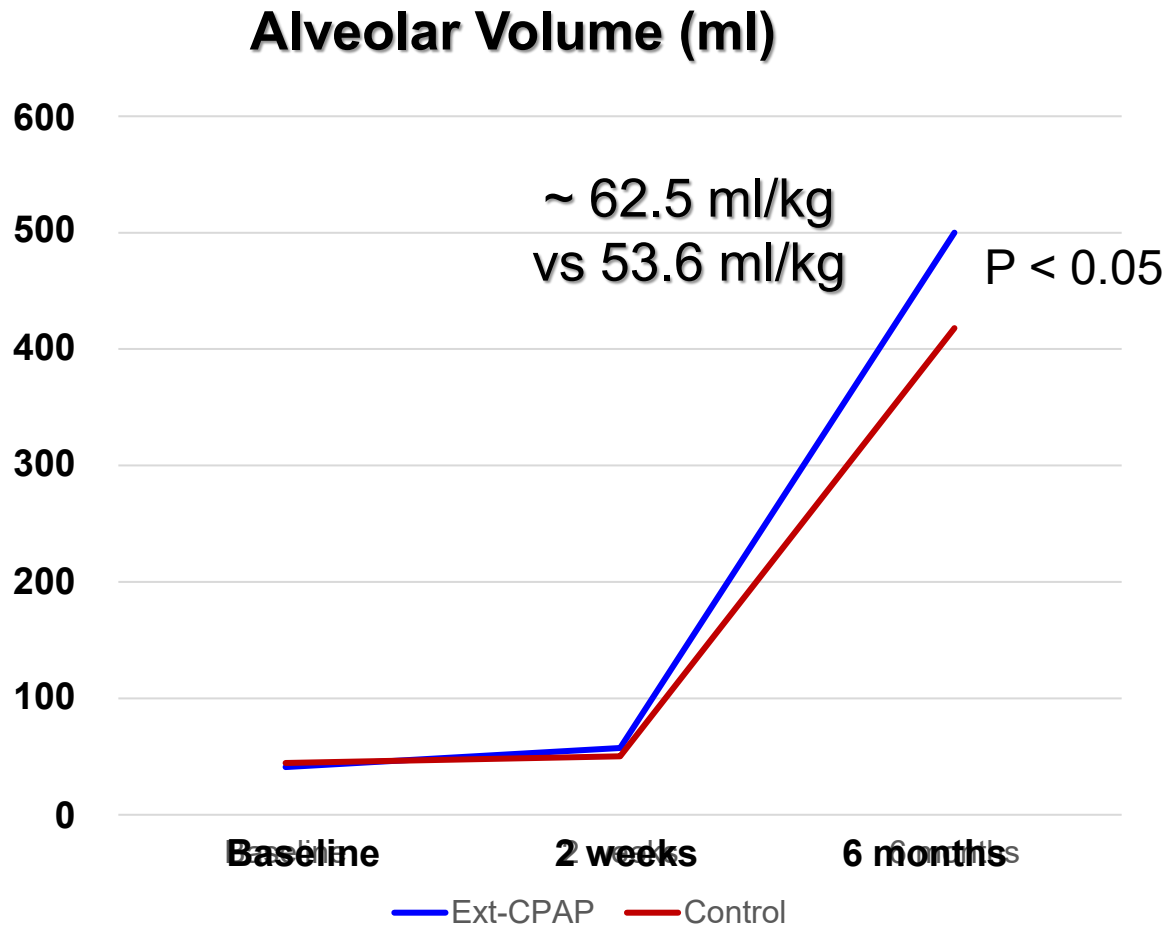
McEvoy CT et al, Am J Resp CCM 2025

	Extended CPAP (n=54)	Usual CPAP (n=46)
Gestation (wks) < 29 wks	30.2 (1.8) 12 (26%)	30.2 (2.0) 12 (28%)
Birth weight (g)	1420 (328)	1434 (359)
Any surfactant	14 (26%)	17 (37%)
Any MV > 1 hr	19 (41%)	17 (37%)
Age/PMA randomization	Not defined	Not defined

RCT on Extended CPAP in Preterm Infants: Lung Growth & Function at 6 Months

McEvoy CT et al, Am J Resp CCM 2025





Interim Summary # 7
How Long Should We Support w/ NIV?

- Large RCT needed to assess benefit of prolonged NIV
- Is the Interface critical (i.e., BNP vs RAM NC vs nHFT) ?
- What pressure &/or flow is needed/optimal?
- To what PMA → 32 vs 34 weeks….or other?
- MCT underway by McEvoy at Oregon
- Proposed MCT under review by NRN

What About Role of Adjunct Rx's?

CaLI Trial: Caffeine plus LISA or nCPAP

- 24^0 - 29^6 weeks: in DR or NICU w/in 2 hours age
- Outcome ETT or “resp failure”

	LISA (n=92)	nCPAP (n=88)
Gestation < 27 wks	28 ± 2 29%	28 ± 2 34%
B Weight	1042 ± 272	1019 ± 275
ETT/Fail	21 (23%)	47 (53%) *
BPD – any Grade 2 or 3	24 (26%) 10 (11%)	52 (39%) * 8 (9%)

Katheria A, NEJM Evid 2024

OPTIMIST Trial: MIST vs “sham”

- 25-28 weeks; randomized once FiO2 ≥ 0.30 & < 6 hrs age
- Outcome: survival w/o BPD at 36 wks

	MIST (n=241)	SHAM (n=244)
Gestation	27.3 (26.3-28.1)	27.3 (26.4-28.0)
B Weight	929 ± 221	928 ± 216
ETT in 1st 72 hrs	37%	72% *
Surv w/o BPD	56.4%	50.4%
Any BPD	37%	45% *

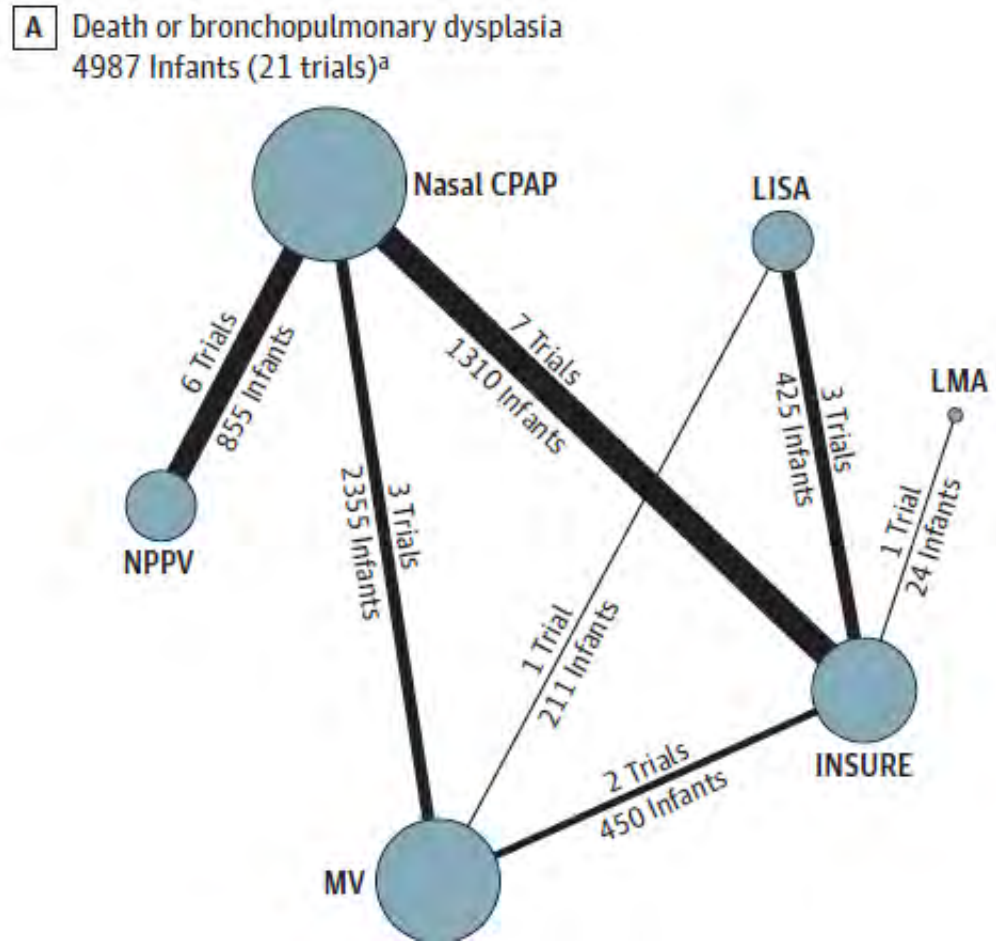
Dargaville P, JAMA 2022

JAMA | Original Investigation

Association of Noninvasive Ventilation Strategies With Mortality And Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis

JAMA 2016

Tetsya Isayama, Hiroko Iwami, Sarah McDonald, Joseph Beyene



Conclusions limited by study numbers & quality

LISA coupled w/ NIV support has lowest risk for death &/or BPD as outcome

What Should You Use & When Should You Use it??

Most effective

Most familiar

Least invasive

Least costly

nCPAP

- Best studied & most experience
- **Should probably still be default mode**
  - Consider for all babies ≥ 24 weeks
  - Consider w/ MIST/LISA at < 30 weeks
  - Post-extubation for preterms < 28 weeks
  - Optimal interface → binasal prongs or mask

NIMV

- **NIMV** may ⬇ extubation failure….BUT
- Large RCT showed no difference in BPD
- Consider if nCPAP not effective
- **Equivalent alternative to nCPAP as first choice** for NIV support in ELBWI
- Synchronized may be better….but need RCTs

nHFT

- Consider in lieu of nCPAP if:
  - Extubation from low PAW & FiO2
  - Stabilized on nCPAP for > 24/48 hrs and FiO2 < 30% and pressure ≤ 6 cm H2O
  - Start high (7-8 lpm) and wean like CPAP

nHFV

- Small trials indicate feasibility
- Best driver w/ VT-HFV ability
- Optimal settings not clear/established
- Large trials needed w/ focus on < 27 wks

Bundled Care

- Best outcome centers use care “bundles”
- Time, effort & team – need “champions”
- Significant evidence base supports individual components of such bundles
- Larger effect size than “1-intervention” RCT’s

NIV Support – Unanswered ?'s

- Should we change modes? If so, when?
- Should we preferentially minimize exposure to FiO2, pressure or flow?
- Any advantage to extending lung expansion into saccular/early alveolar stage?

(What mode, what pressure, how long?)

Conclusions

Any form of PPV contributes to lung injury & may have systemic effects

Non-invasive ventilation (NIV) is an important adjunctive therapy

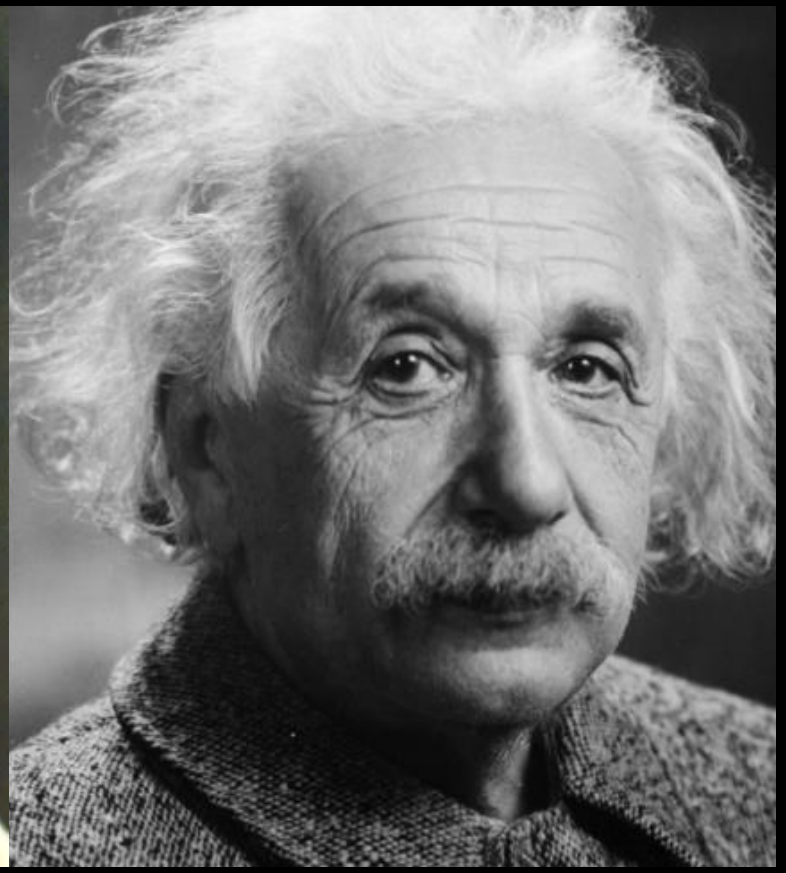
Relatively few contraindications to NIV

Conclusions

Limited evidence suggests optimal approach for ELGAN's couples NIV w/ early caffeine and LISA/MIST

Conclusions

Each unit should develop own bundled approach to optimize NIV support in ELGAN/ELBW infants



Learn from yesterday, live for today, hope for tomorrow

The important thing is to never stop questioning

nCPAP use ↑ in 2005 versus 1991-1992 & 1997

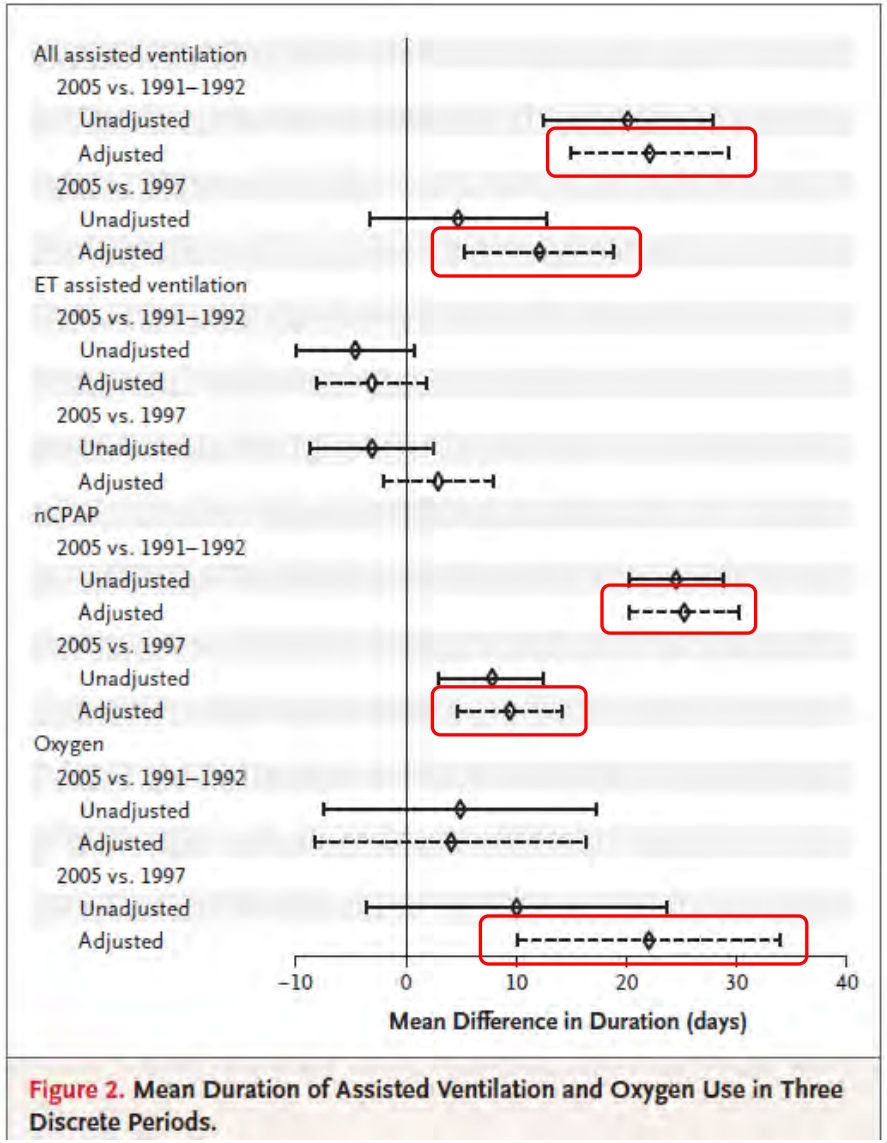


Figure 2. Mean Duration of Assisted Ventilation and Oxygen Use in Three Discrete Periods.

Despite ↑ CPAP use lung function was not improved

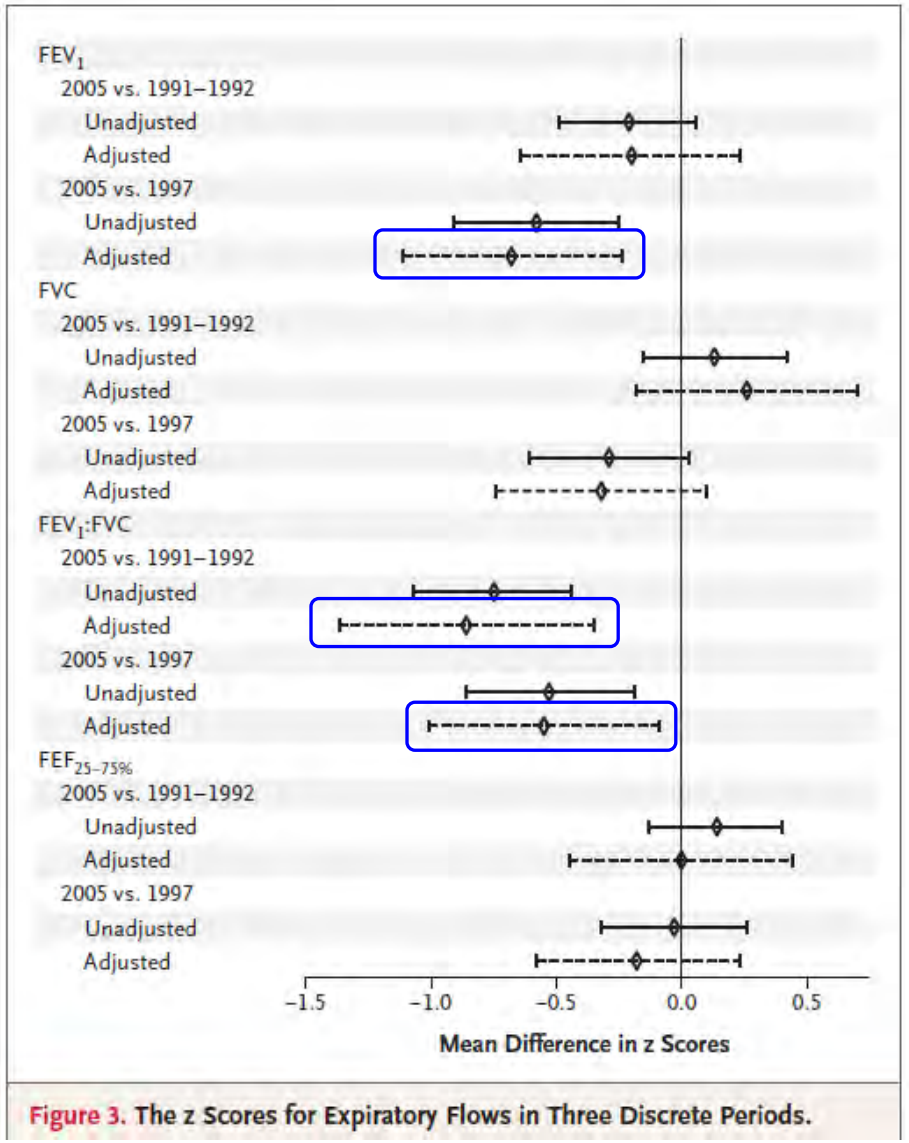


Figure 3. The z Scores for Expiratory Flows in Three Discrete Periods.

Doyle LW et al NEJM 2017