1º SIMPÓSIO INTERNACIONAL
DE NEONATOLOGIA DO DISTRITO FEDERAL
1º SIMPÓSIO INTERNACIONAL DE NEONATOLOGIA DO HMIB
"DR. PAULO ROBERTO MARGOTTO"
25 A 27 DE OUTUBRO DE 2018

CPAP ou ventilação não invasiva: é necessário intubar?

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DR. PAULO ROBERTO MARGOTTO
Neonatologia em Ação
Sobre
Galeria de Fotos
1o Simpósio Internacional de Neonatologia do Distrito Federal
NEONATOLOGIA EM AÇÃO


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Assistência
ao recém-nascido
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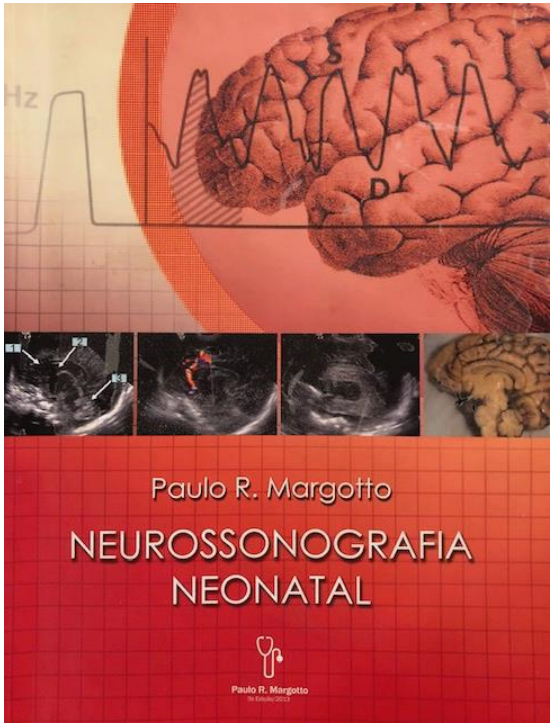
Paulo Roberto Margotto
Pinfiro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Declaração

Nenhuma relação financeira a declarar e nenhum conflito de interesse a resolver


06


B I
K E

- 1971 – Gregory et al → primeiro relato de uso de CPAP com sucesso em RNs com SDR

The New England
Journal of Medicine

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Volume 284 JUNE 17, 1971 Number 24

TREATMENT OF THE IDIOPATHIC RESPIRATORY-DISTRESS SYNDROME WITH CONTINUOUS POSITIVE AIRWAY PRESSURE*

GEORGE A. GREGORY, M.D., JOSEPH A. KITTERMAN, M.D., RODERIC H. PHIBBS, M.D., WILLIAM H. TOOLEY, M.D., AND WILLIAM K. HAMILTON, M.D.

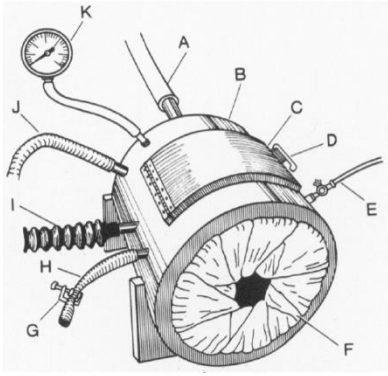


Figure 2. System for Applying Continuous Positive Airway Pressure without an Endotracheal Tube.

20 pacientes com SDR – 16 sobreviventes
2 tratados com CPAP sem IOT

- 1971 – P. Swyer (Toronto) → primeiro relato de ventilação não invasiva (máscara facial)

Course of the disease		Mortality
Rate of intubation:	Age of intubation (h):	Survival rate:
Std = 20/22	Std = 27.2 ± 3.3	Std = 8/22
Mask = 13/22	Mask = 45.4 ± 10.9	Mask = 12/22

9/12 sobreviventes no grupo de VNI nunca foram intubados

De 1971 a 1987 em torno de 170 publicações sobre uso de CPAP em RN com SDR

Apenas alguns ECR - com resultados conflitantes

McGill

Hyaline membrane disease: the era of CPAP, CNP and PEEP
Canadian Medical Journal 1972

Rhodes and Hall. (1973). Continuous positive airway pressure delivered by face mask in infants with the idiopathic respiratory distress syndrome. A controlled study. *Pediatrics*

Durbin, G. M., et al. (1976). Controlled trial of continuous inflating pressure for hyaline membrane disease. *Archives of Disease in Childhood*

N. R. C. ROBERTON - *Archives of Disease in Childhood*, 1976

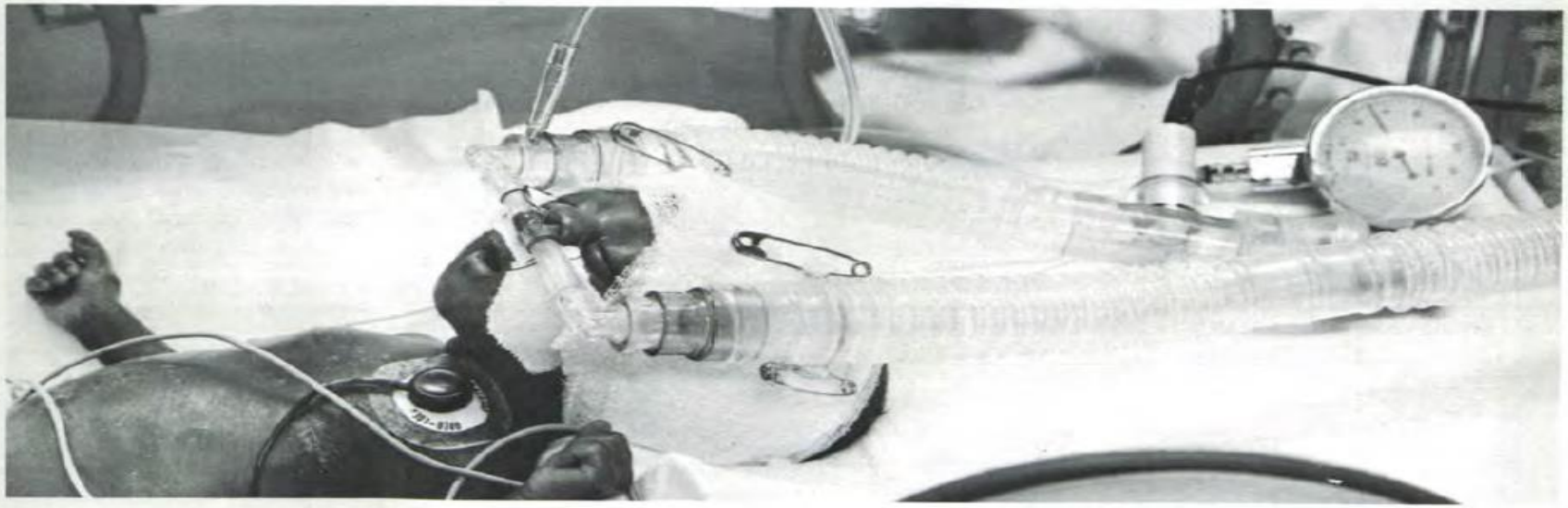
"In the past 5 years there has been a considerable increase in the survival rate of infants suffering from the idiopathic respiratory distress syndrome (RDS). Though considerable changes in treatment have occurred during this period, many workers attribute …
a large part of the fall in mortality to the technique of **continuous positive airways pressure**".

A new device for CPAP by nasal route

McGill

JEN-TIEN WUNG, MD; JOHN M. DRISCOLL, JR., MD; RALPH A. EPSTEIN, MD; ALLEN I. HYMAN, MD

Fig. 2—Nasal piece in place on a 860g premie.



Descreveu um tipo de CPAP em uso na sua unidade por 16m
Mais de 40 RNs com SDR tinham sido tratados com sucesso

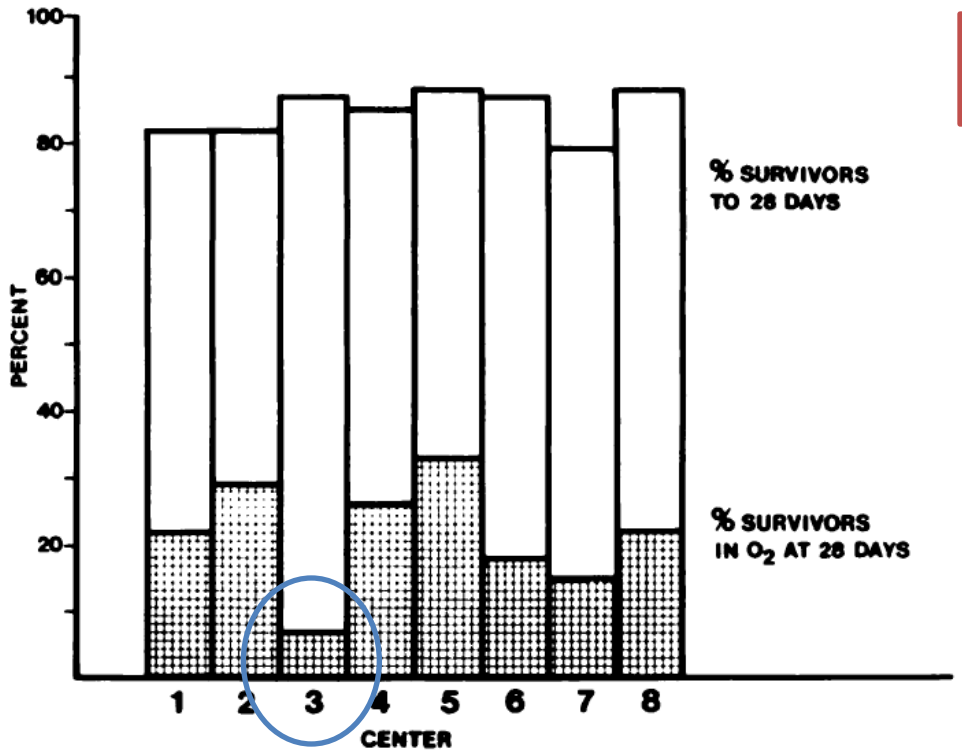
Critical Care Med, 1976

CPAP e Displasia Broncopulmonar

Is Chronic Lung Disease in Low Birth Weight Infants Preventable? A Survey of Eight Centers

Mary Ellen Avery, William H. Tooley, Jacob B. Keller, Suzanne S. Hurd, M. Heather Bryan, Robert B. Cotton, Michael F. Epstein, Pamela M. Fitzhardinge, Cheryl B. Hansen, Thomas N. Hansen, W. Alan Hodson, L. Stanley James, Joseph A. Kitterman, Heber C. Nielsen, Theresa A. Poirier, William E. Truog and Jen-Tien Wung

Pediatrics 1987;79;26



11 anos depois

A ‘nova’ era do suporte respiratório não-invasivo como primeira linha de tratamento (2000-2010) Carlo WA, 2012

- Novos ECRs
  - COIN trial (NEJM, 2008)
  - VON (Pediatr, 2011)
  - Support (NEJM, 2010)
  - Neocosur Network (J. Ped, 2012)

Em geral, observou-se uma diminuição de ~ 5% nas taxas de DBP/óbito com CPAP

A maior parte dos estudos mostrou uma redução na duração da VM

Os RNS mais pré-termos (24-25 sem) foram os que mais se beneficiaram – diminuição da mortalidade quando comparado com VM

Falha do CPAP

McGill

Continuous Positive Airway Pressure to Prevent Neonatal Lung Injury: How Did We Get Here, and How Do We Improve?

Clyde J. Wright, MD[1], Richard A. Polin, MD[2], and Haresh Kirpalani, BM, MSc[3]

J. Ped, June 2016

Table I. Incidence of CPAP failure in large RCTs evaluating CPAP vs routine intubation

Trial	Authors	Year	Subjects enrolled	GA	ACS (any)	CPAP failure 5-7 d
COIN	Morley et al[49]	2008	610	25 0/7-28 6/7	94%	46%
SUPPORT	Finer et al[50]	2010	1316	24 0/7-27 6/7	>95%	51.2%
	Dunn et al[48,*]	2011	648	26 0/7-29 6/7	>98%	45.1%

Definição de Falha do CPAP

McGill

Critérios da NICU - McGill

1. FiO_2 > 50% (por 2horas) para manter SpO_2 entre 91-95%
2. PCO_2 > 60 se pH <7.20 (acidose respiratória significativa)
3. Duas apnéias necessitando de VPP
4. Mais de 6 apnéias / 6h – que precisam de estímulo
5. Aumento significativo do trabalho respiratório

J. Ped, June 2016

- RNs que falham CPAP estão sob risco aumentado de desfechos desfavoráveis como DBP

Incidence and Outcome of CPAP Failure in Preterm Infants

Peter A. Dargaville, FRACP, MD,[a,b] Angela Gerber, MD,[b] Stefan Johansson, MD,[c] Antonio G. De Paoli, FRACP, MD,[b] C. Omar F. Kamlin, FRACP, DMedSci,[d,e,f] Francesca Orsini, BSc, MSc,[g] Peter G. Davis, FRACP, MD,[d,e,f] for the Australian and New Zealand Neonatal Network

Falha do CPAP:

25–28 sem = 43%

29–32 sem = 21%

19.103 RNs → 11 684 inicialmente tratados com CPAP

Falha do CPAP foi associada com:

- Maiores taxas de pneumotórax, óbito, displasia broncopulmonar e outras morbidades

↑ incidência de óbito/DBP:

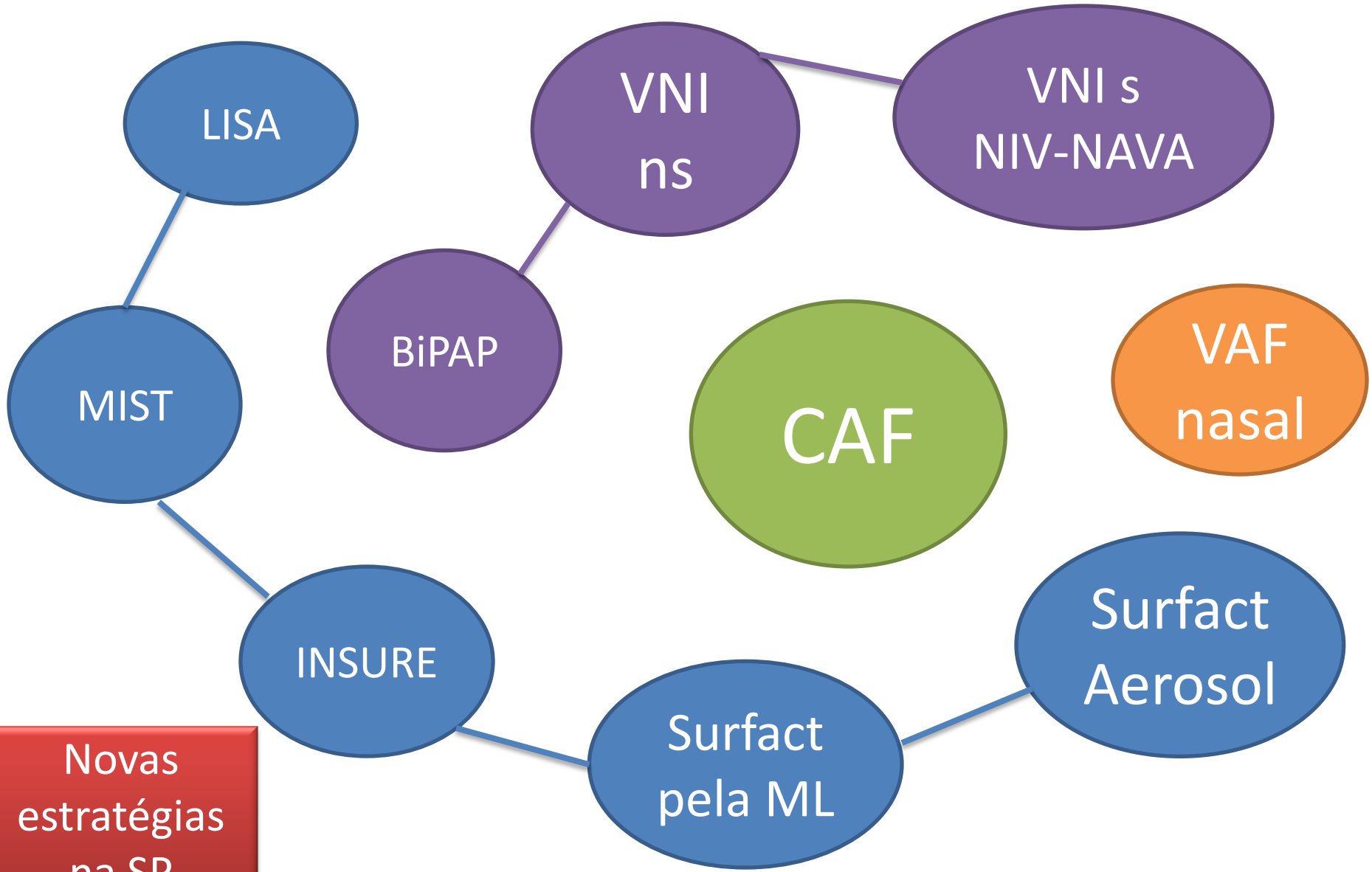
- 25–28 sem = 39% vs 20%, AOR 2.30 [1.71–3.10]
- 29–32 sem = 12% vs 3.1%, AOR 3.62 [2.76–4.74]

- ↑ tempo em suporte respiratório e hospitalização

Pediatrics 2016 Jul;138(1)

Portanto, estratégias capazes de reduzir falha do suporte não invasivo podem melhorar os desfechos desses RNs

Suporte respiratório “não-invasivo”



Tipos de suporte não invasivo

BiPAP

VNI

NIV-NAVA

VAFn

BiPAP

Oferece 2 pressões: alta (insp) and baixa (exp)

– tempo (0.5–1.0 s),

– frequência (10–30/min)

– diferença entre alta e baixa = ≤ 4 cmH_2O

A comparison of bilevel and ventilator-delivered non-invasive respiratory support *Arch Dis Child Fetal Neonatal Ed* 2015

David Millar,[1] Brigitte Lemyre,[2] Haresh Kirpalani,[3,4] Aaron Chiu,[5] Bradley A Yoder,[6] Robin S Roberts[4]

Patients Infants <1000 g and <30 weeks gestational age at birth.

Table 2 Primary and composite outcomes

Outcome	Mainly bilevel NIPPV N=241	Mainly CMV NIPPV N=215	Adjusted effect* (95% CI)	p Value
Death or BPD†	89/241 (36.9%)	83/215 (38.6%)	0.88‡ (0.57 to 1.35)	0.56
Death <36 weeks	23/245 (9.4%)	5/217 (2.3%)	5.01‡ (1.74 to 14.4)	0.0028
BPD† in survivors	66/218 (30.3%)	78/210 (37.1%)	0.64‡ (0.41 to 1.02)	0.061
Re/intubation ≤168 h	77/242 (31.8%)	84/211 (39.8%)	0.69‡ (0.46 to 1.06)	0.088
PMA in weeks at last ventilator support§	Mean (SD) 37.1 (4.1) n=212	Mean (SD) 36.5 (4.9) n=220	Mean difference 0.78 (−0.06 to 1.62)	0.069
Number of reintubations§	Mean (SD) 1.27 (1.47) n=207	Mean (SD) 1.07 (1.24) N=211	Rate ratio 1.23 (1.02 to 1.49)	0.032

*Adjusted for birthweight stratum and intubation status, gender, antenatal steroids, caffeine, mother's ethnicity, mother's education, mother's age, single parent family, birth location.

Mortalidade 4 x maior com uso de VNI / BiPAP vs VNI /respirador

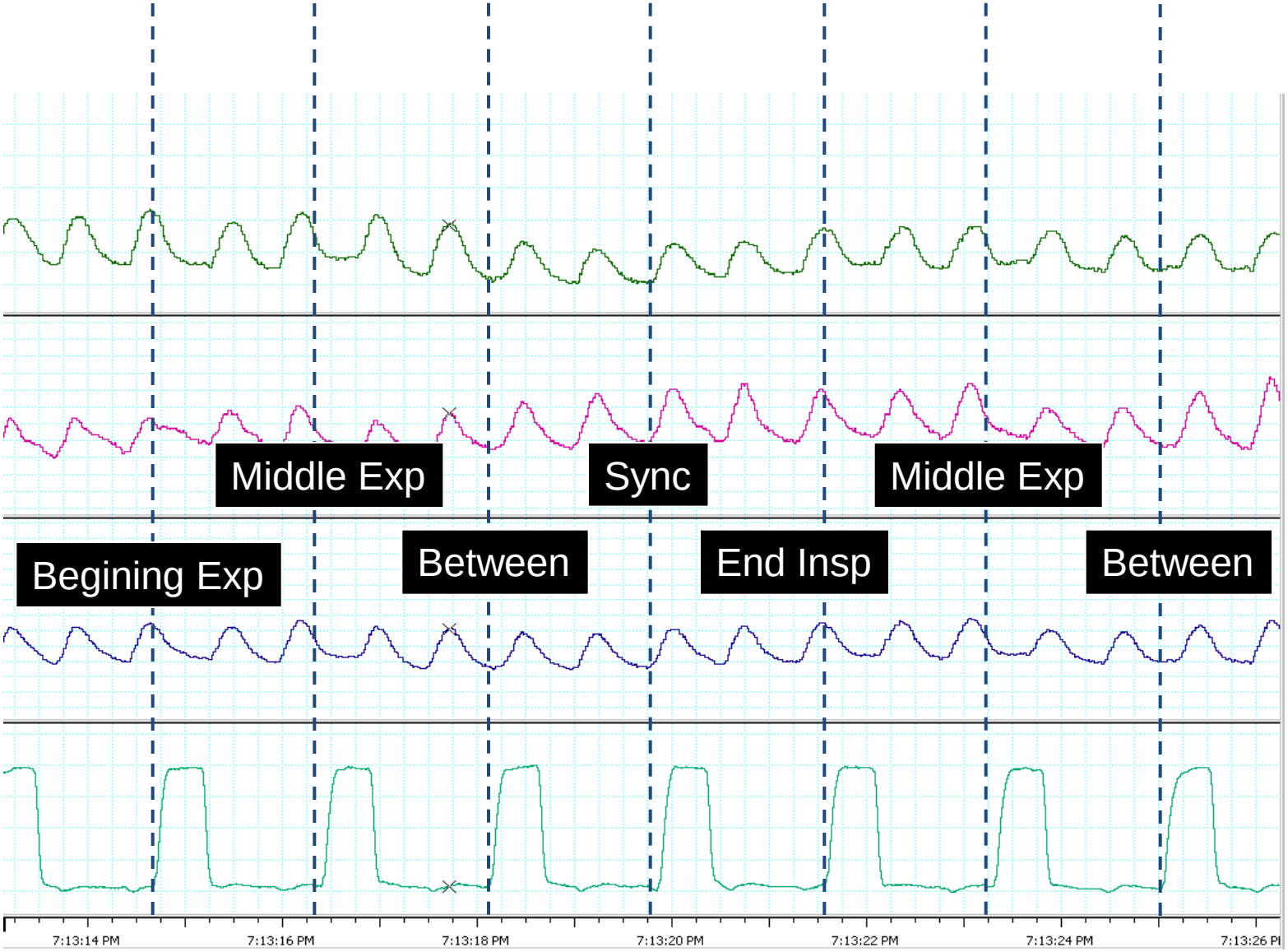
VNI

- Precoce – prevenir intubação
- Após extubação – prevenir re-intubação

Desafios com VNI

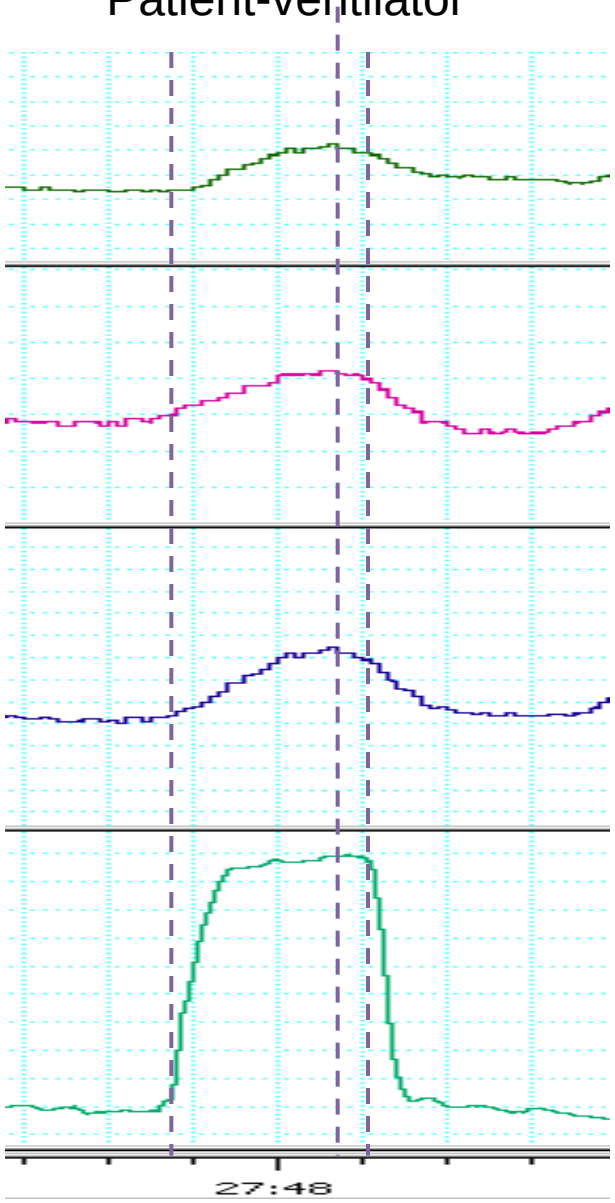
- Falta de sincronização
- Presença de escapes
- Patência das vias aéreas superiores

Exemplo (12 seconds)

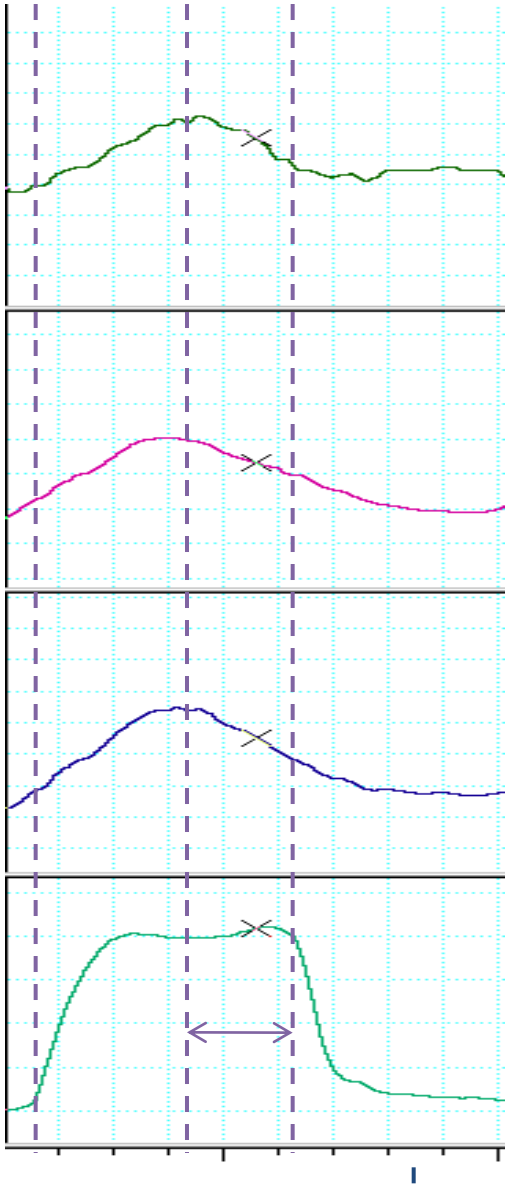


Jardin B and Sant'Anna, E-PAS 2012

Synchrony between Patient-ventilator



Synchrony but with long inspiratory time



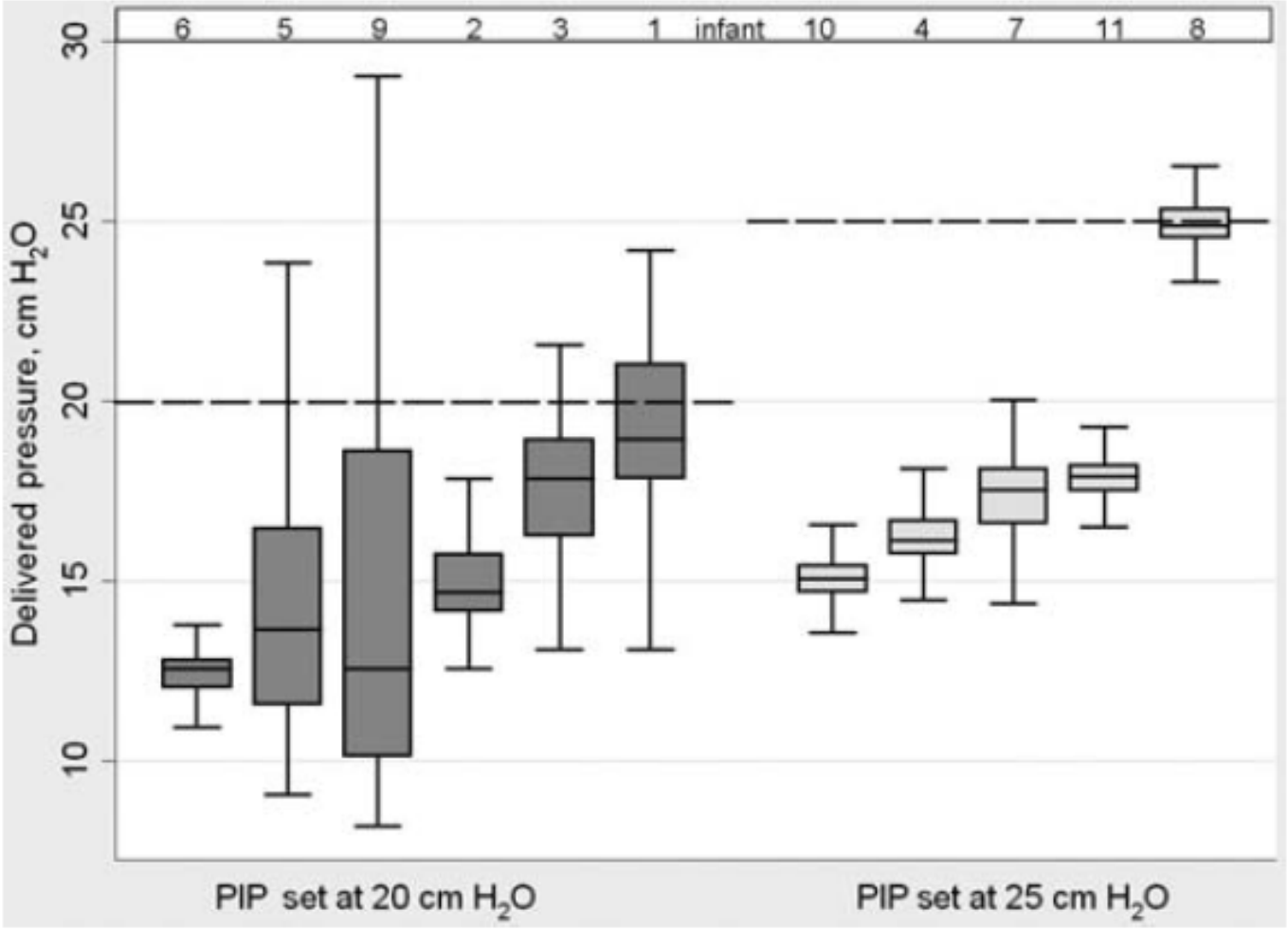
Influence of inspiratory time length

Jardin B and Sant'Anna, E-PAS 2012

Desafios com VNI

- Falta de sincronização
- Presença de escapes
- Patência das vias aéreas superiores

Variabilidade da PIP transmitida

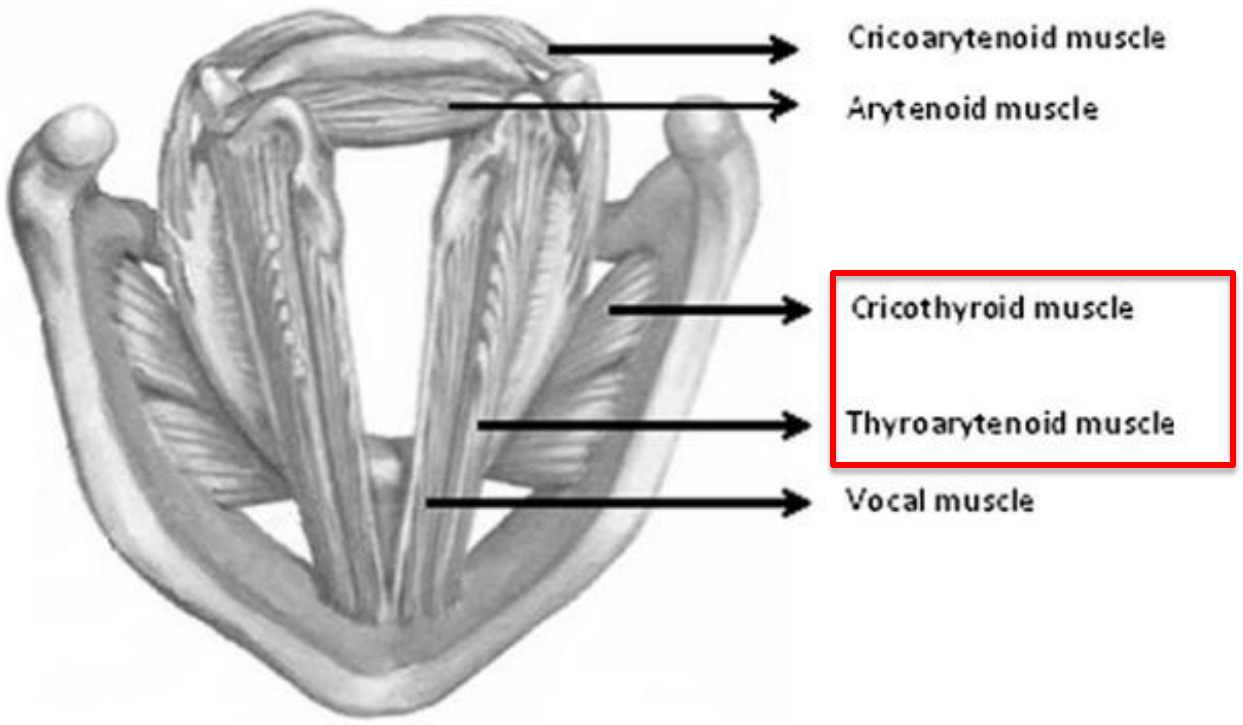


Owen L, *Arch D Child* 2010

Desafios com VNI

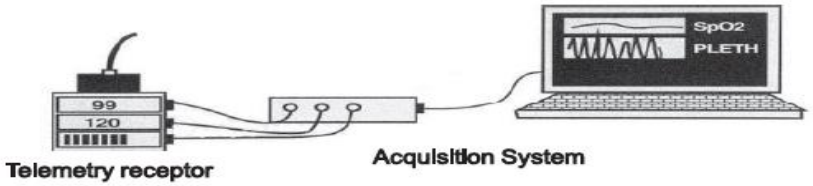
- Falta de sincronização
- Presença de escapes
- Patência das vias aéreas superiores

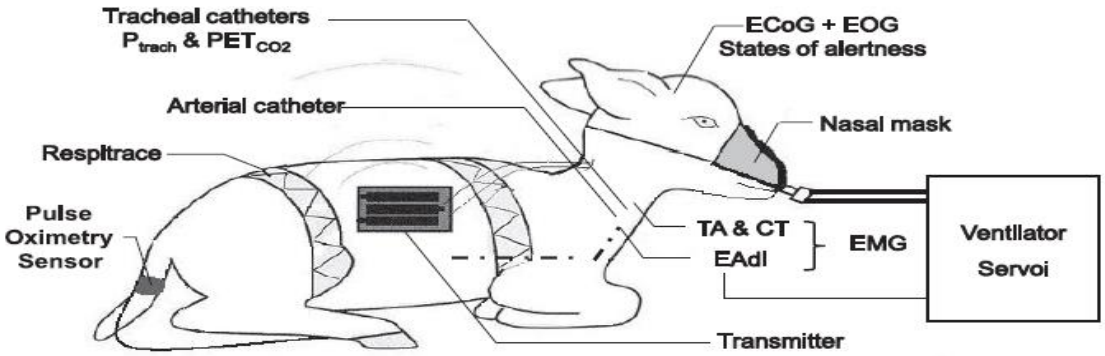
- A faringe e a laringe são estruturas predominantemente musculares e que portanto podem alterar a patência das VAS



Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs

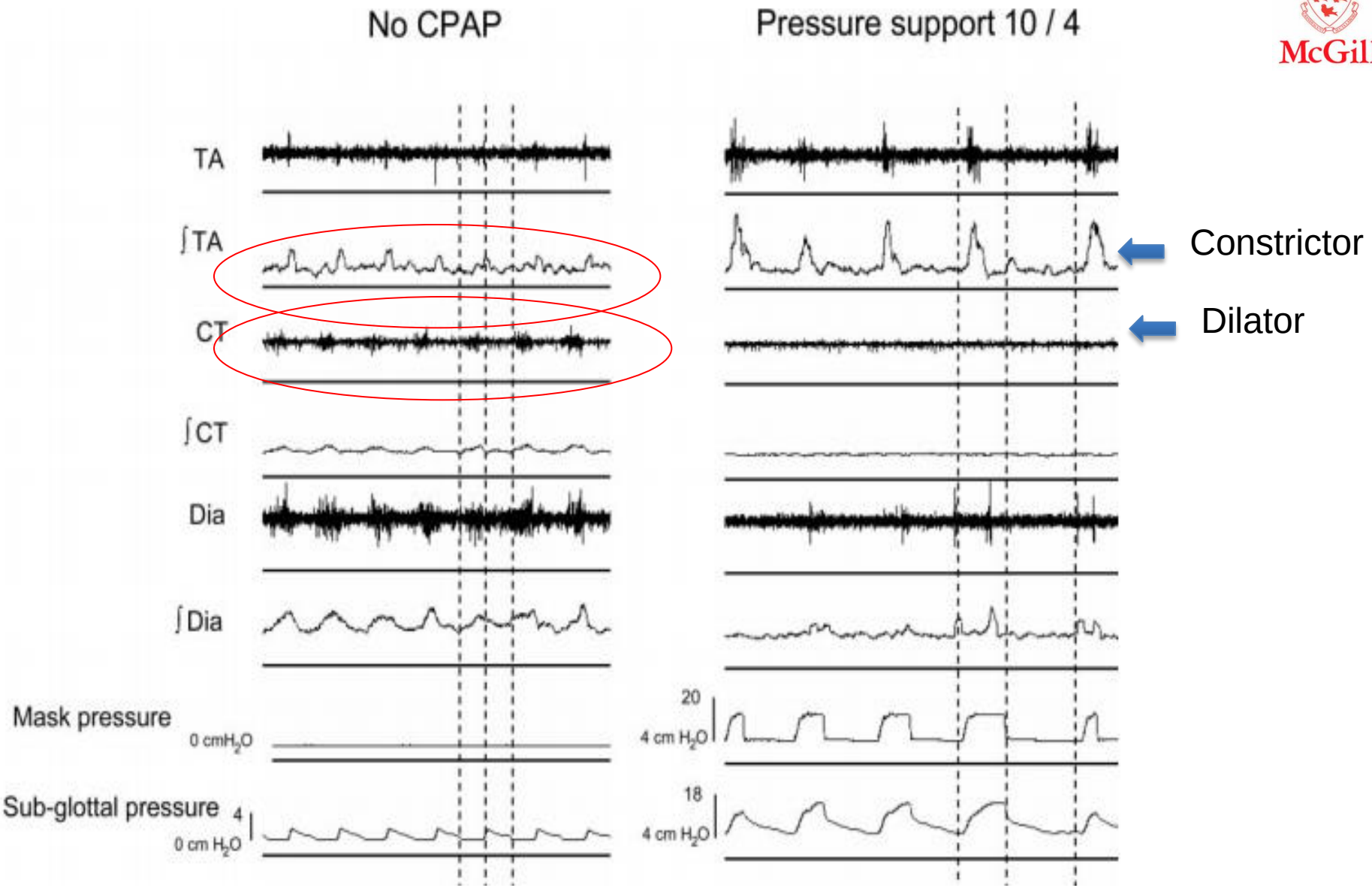
Mohamed Amine Hadj-Ahmed,[1] Nathalie Samson,[1] Marie Bussières,[2] Jennifer Beck,[3] and Jean-Paul Praud[1,2]





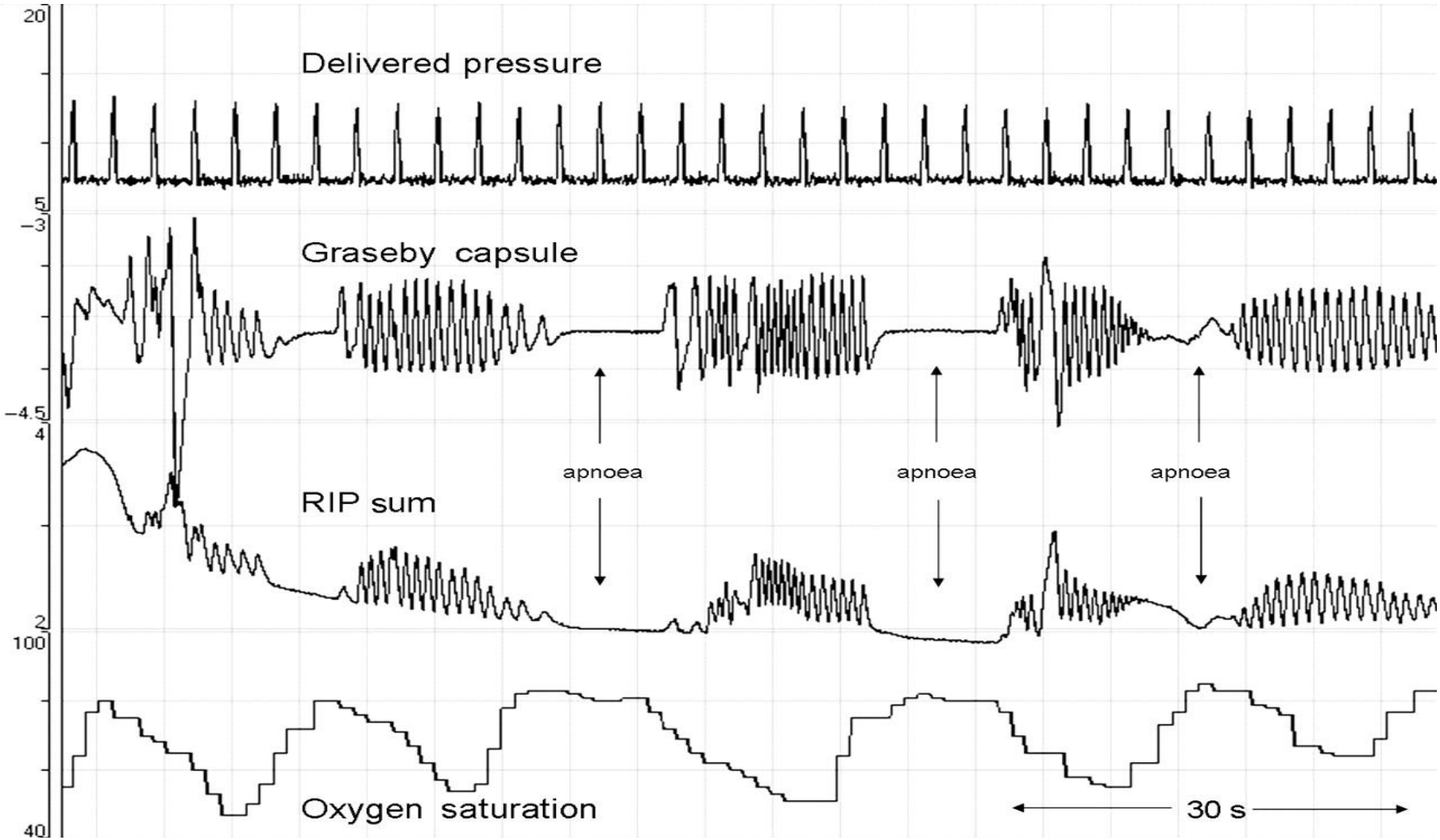
Ovelhas – sem sedação

J. Applied Physiol, 2012



Moreau-Bussiere F, JAP 2007

VNI e apnéia



Owen L, ADC Fetal & Neo Ed 2010

CPAP ou VNI ???

SDR

- Apenas 2 estudos incluíram RNs < 30 sem de IG, que são os aqueles tem maiores chances de falhar CPAP

- Somente 1 desses estudos teve poder suficiente para avaliar qualquer diferença em relação a incidência de DBP

  – IG media = 26 sem: VNI = 38% vs CPAP = 37%

  – Nenhum diferença na duração do suporte ventilatório, ou sobrevida sem DBP

AAP Fetus and Newborn Committee 2017

AAP Fetus and Newborn Committee 2017

McGill

CONCLUSÃO:

- Os dados analisados não demonstram a superioridade da VNI (sincronizado ou não) sobre CPAP no manejo dos RNs com SDR

- Mais pesquisas são necessárias para que se possa recomendar VNI como melhor do que CPAP no tratamento da SDR ou apnéia

Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants (Review)

Lemyre B, Laughon M, Bose C, Davis PG

Mortality

1.3.2 No surfactant treatment before enrollment

Armanian 2014	2	44	1	54	2.0%	2.45 [0.23, 26.18]
Bisceglia 2007 (1)	0	42	0	46		Not estimable
Kirpalani 2013	3	95	4	90	9.2%	0.71 [0.16, 3.09]
Kugelman 2007 (2)	0	43	0	41		Not estimable
Meneses 2011	22	100	26	100	58.1%	0.85 [0.52, 1.39]
Wood 2013	0	60	2	60	5.6%	0.20 [0.01, 4.08]
Subtotal (95% CI)		**384**		**391**	**74.9%**	**0.82 [0.52, 1.30]**
Total events	27		33			

Heterogeneity: Chi² = 1.71, df = 3 (P = 0.63); I² = 0%

Test for overall effect: Z = 0.84 (P = 0.40)

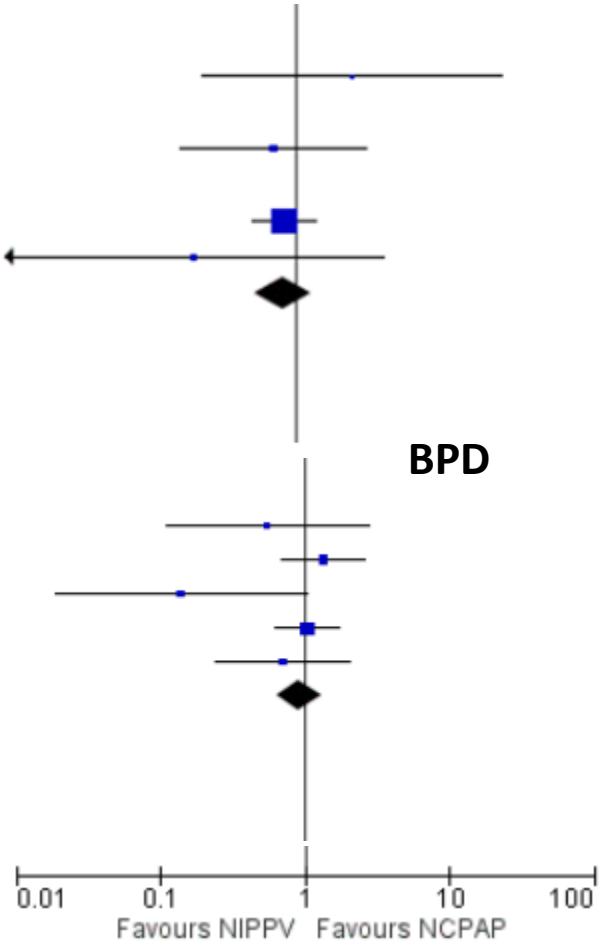
BPD

1.4.2 No surfactant treatment before enrollment

Bisceglia 2007 (1)	2	42	4	46	5.0%	0.55 [0.11, 2.84]
Kirpalani 2013	17	87	12	85	15.8%	1.38 [0.70, 2.72]
Kugelman 2007	1	43	7	41	9.3%	0.14 [0.02, 1.06]
Meneses 2011	22	83	20	80	26.5%	1.06 [0.63, 1.79]
Wood 2013	5	60	7	60	9.1%	0.71 [0.24, 2.13]
Subtotal (95% CI)		**315**		**312**	**65.8%**	**0.92 [0.64, 1.32]**
Total events	47		50			

Heterogeneity: Chi² = 5.61, df = 4 (P = 0.23); I² = 29%

Test for overall effect: Z = 0.45 (P = 0.65)



2017

CPAP ou VNI?

- Taxas de óbito ou sobrevida sem DBP – semelhantes
- Intervalo de confiança de 95%:

Esse achados levantam a questão quanto ao uso corrente e disseminado de VNI

NEJM – NIP trial 2013

CPAP ou VNI ???

VNI vs CPAP após extubação

	Respiratory Failure	Reintubation
Number of studies	9 randomized trials	10 randomized trials
Studies Design		
Risk of Bias	**serious**	**serious**
Inconsistency	not serious	not serious
Indirectness	not serious	not serious
Imprecision	**serious**	**serious**
Others	none	none
Number of Patients		
NIPPV	200/69 3 (28.9%)	199/693 (28.7%)
CPAP	283/67 5 (41.9%)	266/675 (39.4%)
Effect		
Relative	RR 0.70 (0.60 to 0.81)	RR 0.74 (0.64 to 0.85)
Absolute	13 fewer per 100 (8 to 17 fewer)	10 fewer per 100 (6 to 14 fewer)
Quality	**++ Low**	**++ Low**
Importance	CRITICAL	CRITICAL

L'Hôpital de Montréal pour enfants
The Montreal Children's Hospital
Centre universitaire de santé McGill
McGill University Health Centre

Ferguson KN et al JAMA Peds, 2016

Problemas metodológicos

- Ao se usar VNI utiliza-se uma pressão média nas vias aéreas MAIOR do que se usa com CPAP

- VNI vs CPAP com a mesma pressão média nunca foi testado

VNI sincronizado?

Is synchronised NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A randomised cross-over trial

Camilla Gizzi,[1] Francesco Montecchia,[2] Valentina Panetta,[3] Chiara Castellano,[1] Chiara Mariani,[1] Maristella Campelli,[1] Paola Papoff,[4] Corrado Moretti,[4] Rocco Agostino[1]

Table 2 Desaturation (≤80%) and bradycardia (≤80 bpm) events per hour of artefact-free recording time (n=19)

	Mode of ventilation				SNIPPV (p)†	
	SNIPPV	NIPPV	NCPAP	p Value*	vs NIPPV	vs NCPAP
Desaturations and/or bradycardias	2.9 (0.75–6.8)	6.1 (3.1–9.4)	5.9 (2–10.3)	<0.001	0.009	<0.001
Desaturations ≤80%	2.9 (0.5–7.2)	6.1 (2.9–9.4)	5 (1.2–10.1)	<0.001	0.059	0.046
Bradycardias ≤80 bpm	0 (0–0.48)	0 (0–0.52)	0.24 (0–1.4)	0.025	1.000	0.195

Data are expressed as median (IQR).
*Friedman test.
†After Bonferroni adjustment.
NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; SNIPPV, synchronised NIPPV.

NAVA não invasivo

- VNI sincronizado

NIV-NAVA

- O paciente controla:
  - Tempo inspiratório
  - Tempo expiratório
  - Pressão de inflação

- Não depende da pressão ou fluxo nas vias aéreas para ativar respirador, portanto não é afetado pela presença de escapes

Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs

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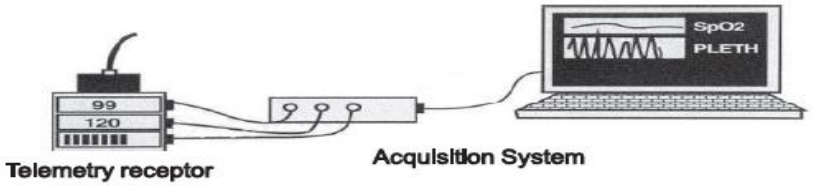
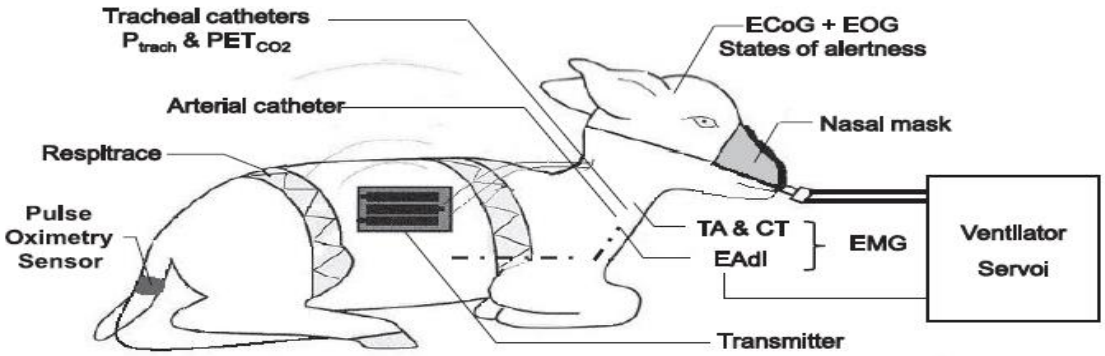


Ovelhas – sem sedação



NIV-NAVA não induziu atividade inspiratória de fechamento da glote

J. Applied Physiol, 2012

Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs

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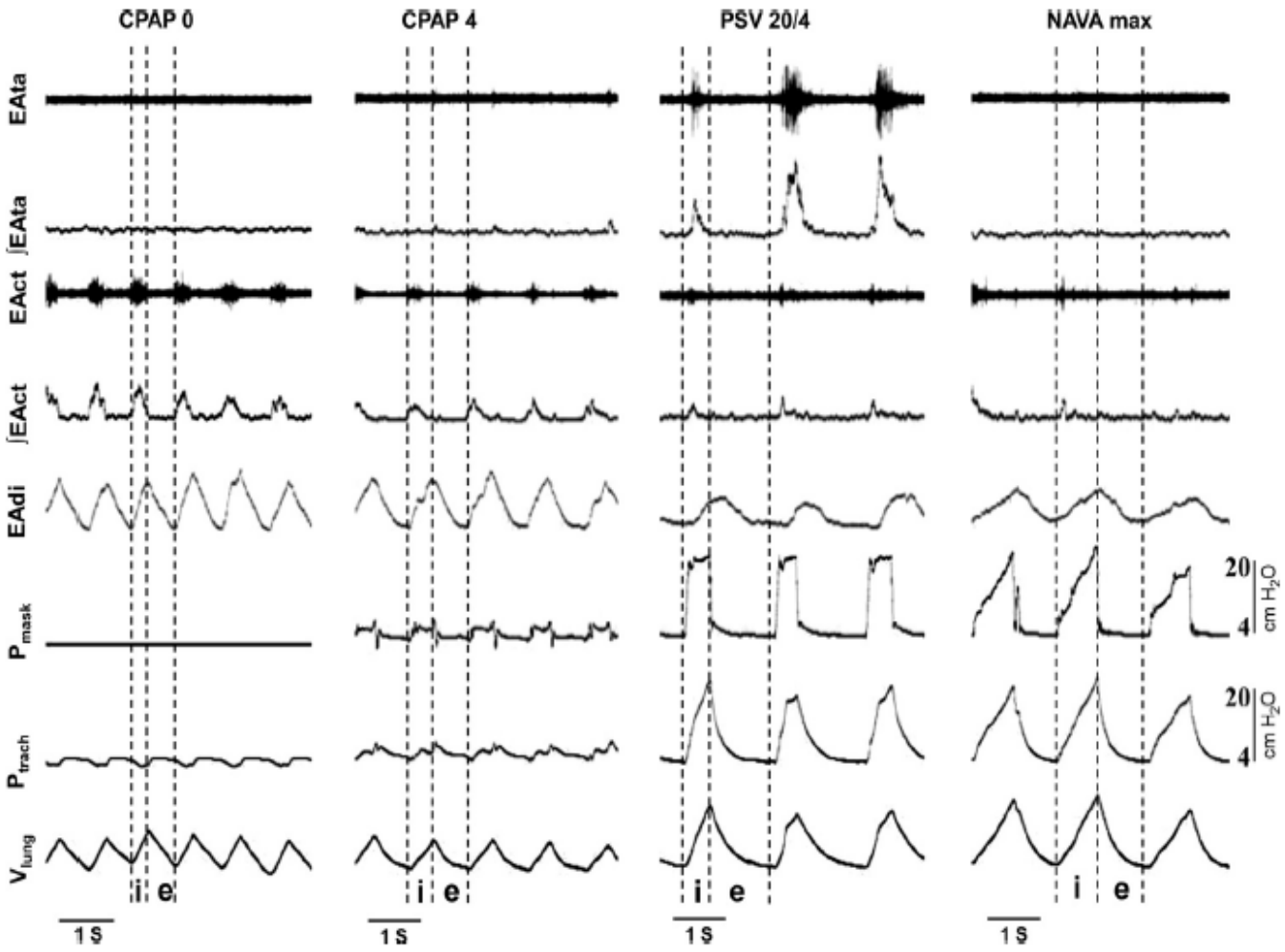


Constrictor

Dilatador

J. Applied Physiol, 2012

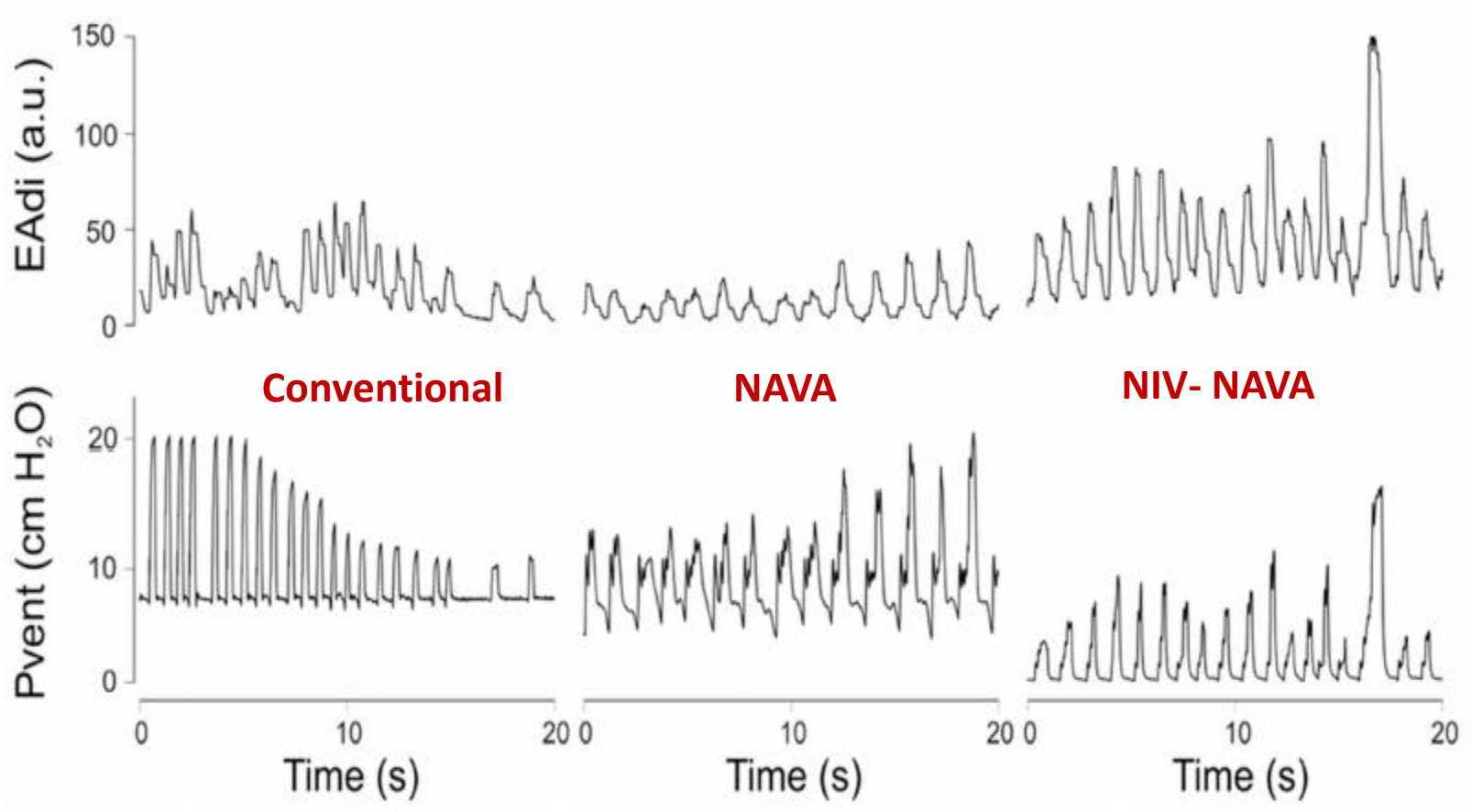
NIV-NAVA – Estudo Clínico

- 7 RNs de baixo peso imediatamente após extubação

- Sincronia entre paciente-ventilador não foi afetada pela presença de escapes grandes

Beck et al. Pediatric Research. 2009

NIV-NAVA



Beck et al. Pediatric Research. 2009

Tipos de suporte não invasivo

BiPAP

VNI

NIV-NAVA

VAFn

VAF nasal

- Pouco dados clínicos sobre eficácia ou segurança
- Usado em alguns lugares na prática clínica
- Europa: 30 de 172 (17%) NICUs [Fischer et al, Eur J Pediatr, 2015].
- Canadá: 4 UTINs em Ontario reportaram uso em 52 em RNs [Mukerji et al, Am J Perinatol, 2015]

REGULAR ARTICLE

Survey of noninvasive respiratory support practices in Canadian neonatal intensive care units

Amit Mukerji (mukerji@mcmaster.ca)[1], Prakesh S. Shah[2], Sandesh Shivananda[1], Wendy Yee[3], Brooke Read[4], John Minski[5], Ruben Alvaro[5], Christoph Fusch[1], for the Canadian Neonatal Network Investigators*

30 level III NICUs - 28 (93%) responded

Table 1 Utilisation of various NRS modes at Canadian NICUs and per cent of each NRS use that is policy driven

NRS Mode	Use, %	Policy use, %
CPAP	100	75
Biphasic CPAP	79	68
NIPPV	54	60
NIHFV	18	80
HFNC	89	36

CPAP = Continuous positive airway pressure; HFNC = High-flow nasal cannula; NIHFV = Noninvasive high-frequency ventilation; NIPPV = Nasal intermittent positive pressure ventilation; NRS = Noninvasive respiratory support.

Acta Paediatr. 2017

Possíveis vantagens da VAFn

1. VAFn não precisa de sincronização [Carlo WA, 2000]

2. Estudos de bancada: eliminação efetiva de CO_2 [Mukerji et al 2013; Czernick et al, 2012]

3. Dados de animais: ↓ inflamação pulmonar e ↑ alveolarização vs VM [Null et al, 2014]

Neonatal bench study – nHFOV

- VAFn têm condicionamento do gás pior quando comparado com CPAP

- Efeitos colaterais – secreções altamente viscosas and obstrução das vias aéreas – quando usada em baixa frequência e altas amplitudes
  - Lavagem de CO_2 foi demonstrada efetiva em frequências de 6 a 8 Hz e amplitude de 30 cmH_2O [Mukerji et al, Neonatology. 2013]

Original article

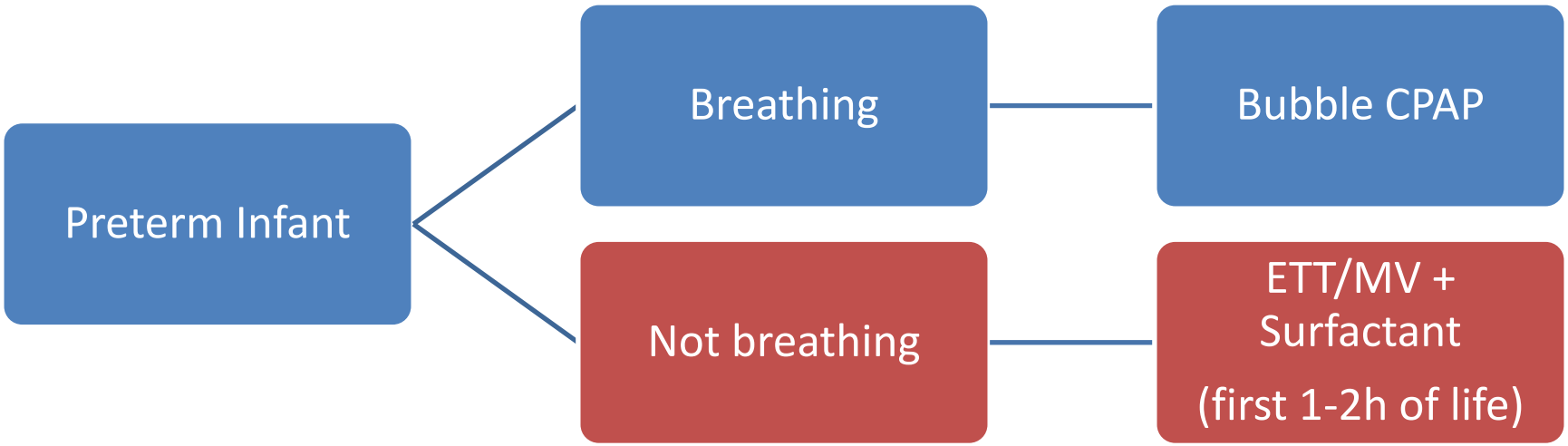
Non-invasive high-frequency oscillatory ventilation in preterm infants: a randomised controlled cross-over trial

Daniel Klotz[1], Hendryk Schneider[1], Stefan Schumann[2], Benjamin Mayer[3], Hans Fuchs[1]

Author affiliations + University of Freiburg, Germany

- 26 RNs com 27± 2 sem IG após extubação ou tratamento com MIST
- **Interventions:** 4 h VAFn e 4 h nCPAP
  - Desfecho: pCO_2 4 h
  - Secundarios: apnéia e bradicardia, FR, FC, dor ou desconfort, MAP, FiO_2 e falha do suporte não invasivo
- **Results**:
  - pCO_2 semelhantes (p=0.33)
  - Sem diferenças em todos os desfechos secundários
  - nHFOV terminada prematuramente em 5 casos (19%) por falha do tratamento (p=0.051)

Abordagem prática na SP

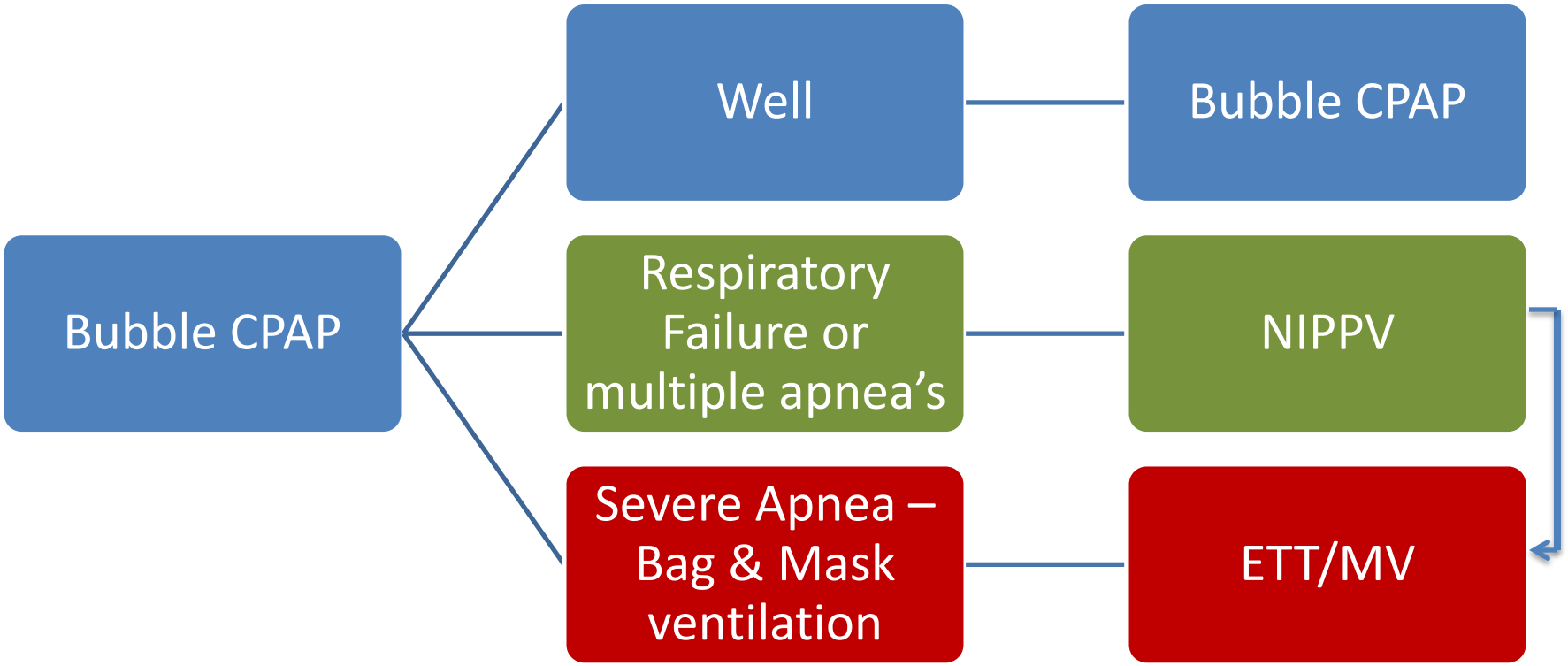




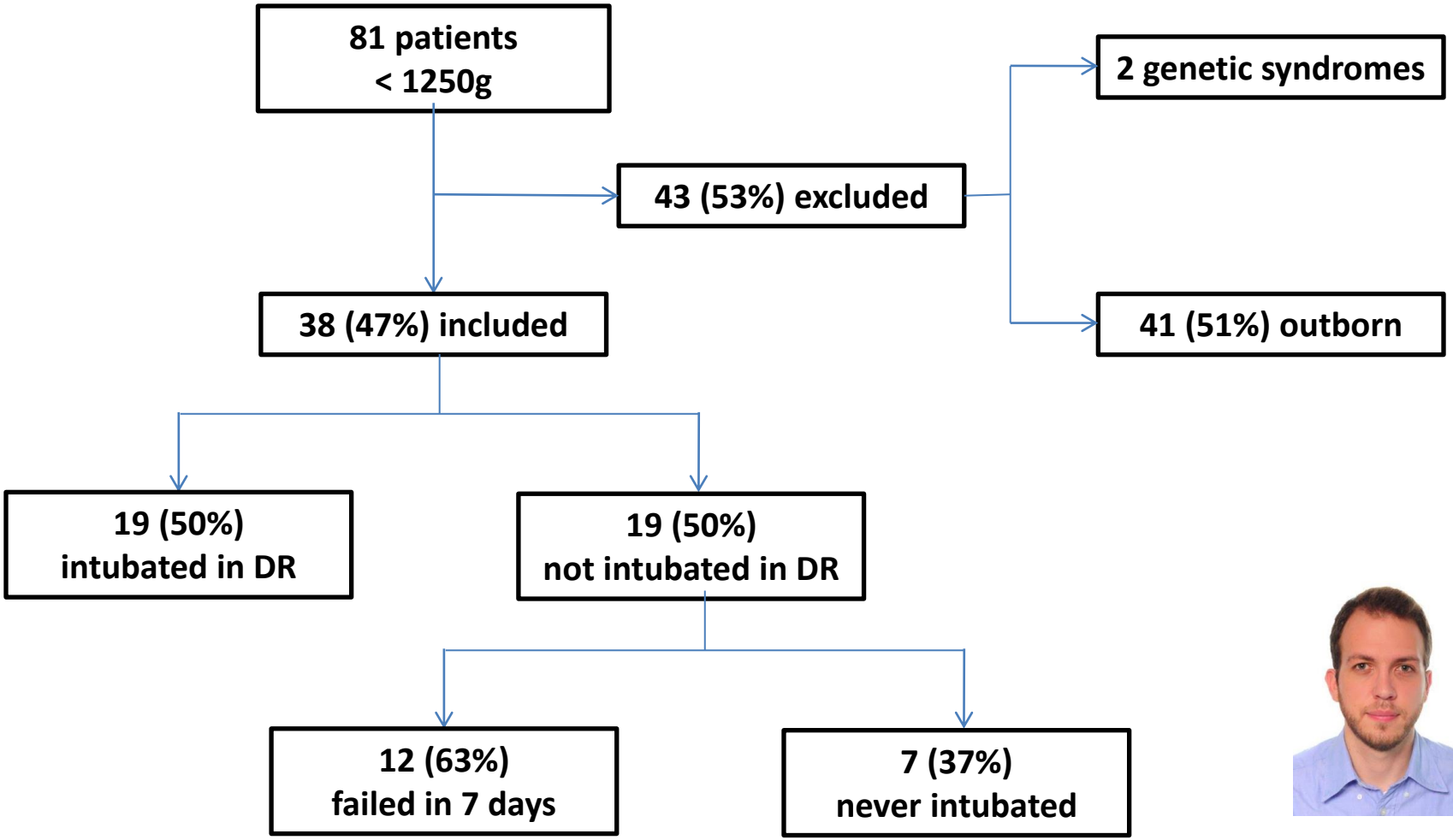
TEAM INDIGO


Giraffe
OmniBed

Practical Approach in the NICU

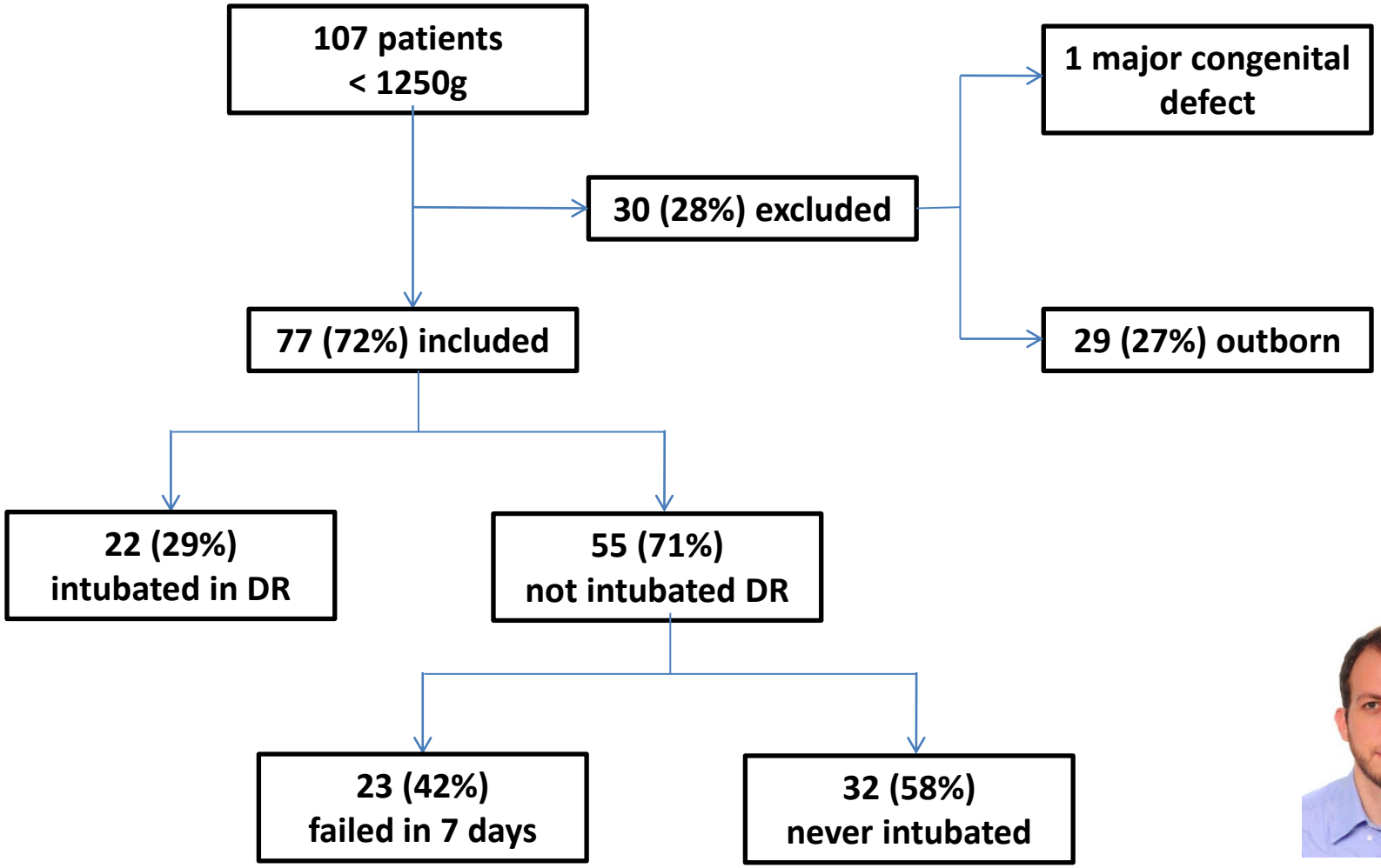


Early CPAP - Year 1: 2015-2016



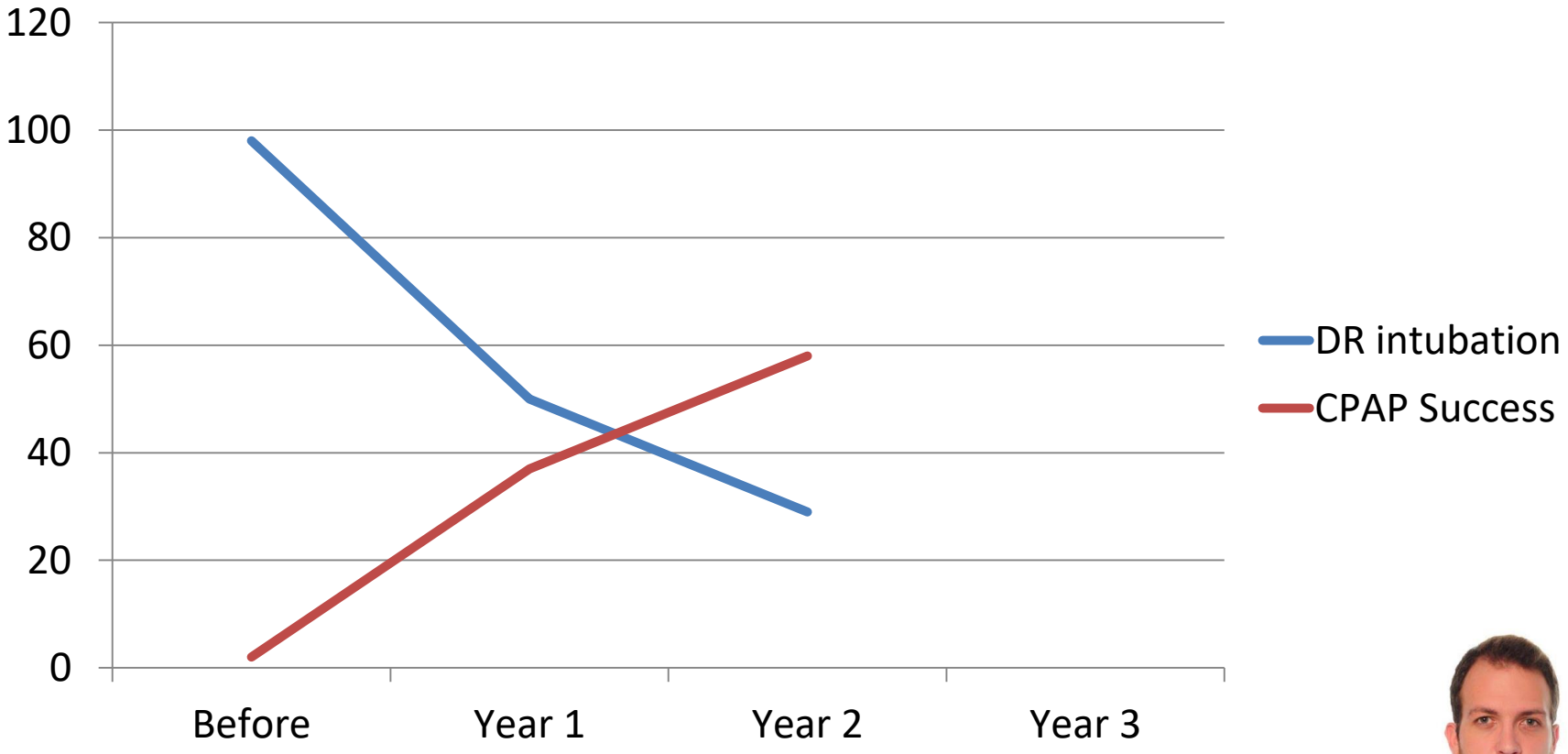
Caio Barbosa

Early CPAP - Year 2: 2016-2017



Caio Barbosa

MCH – NICU Experience



Caio Barbosa

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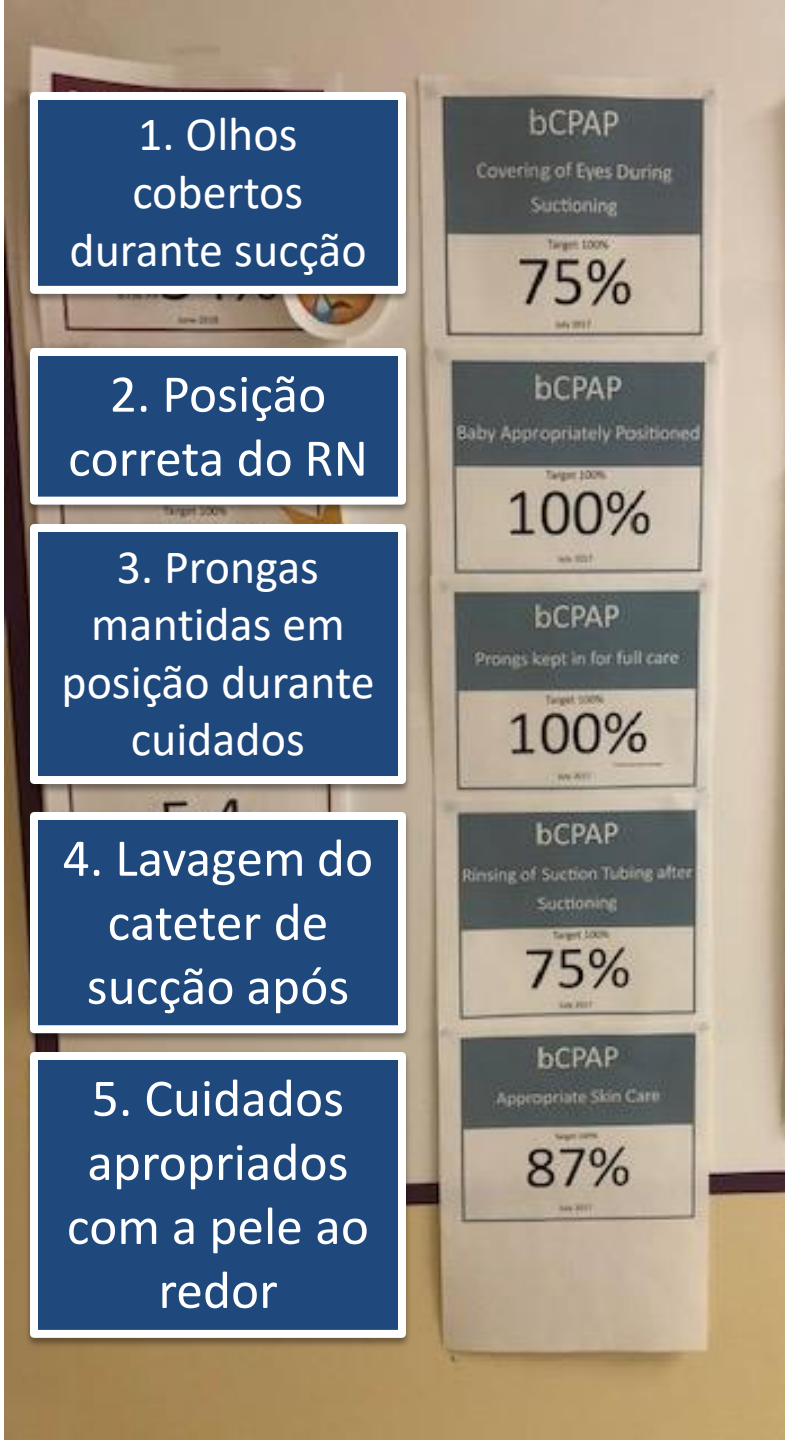
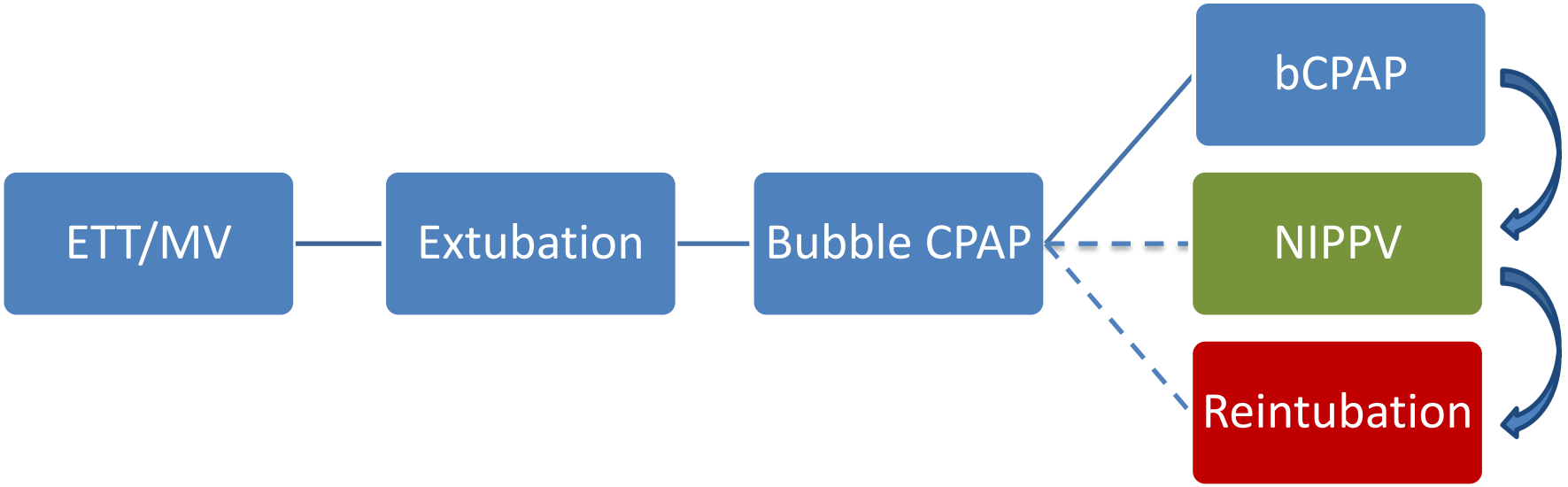
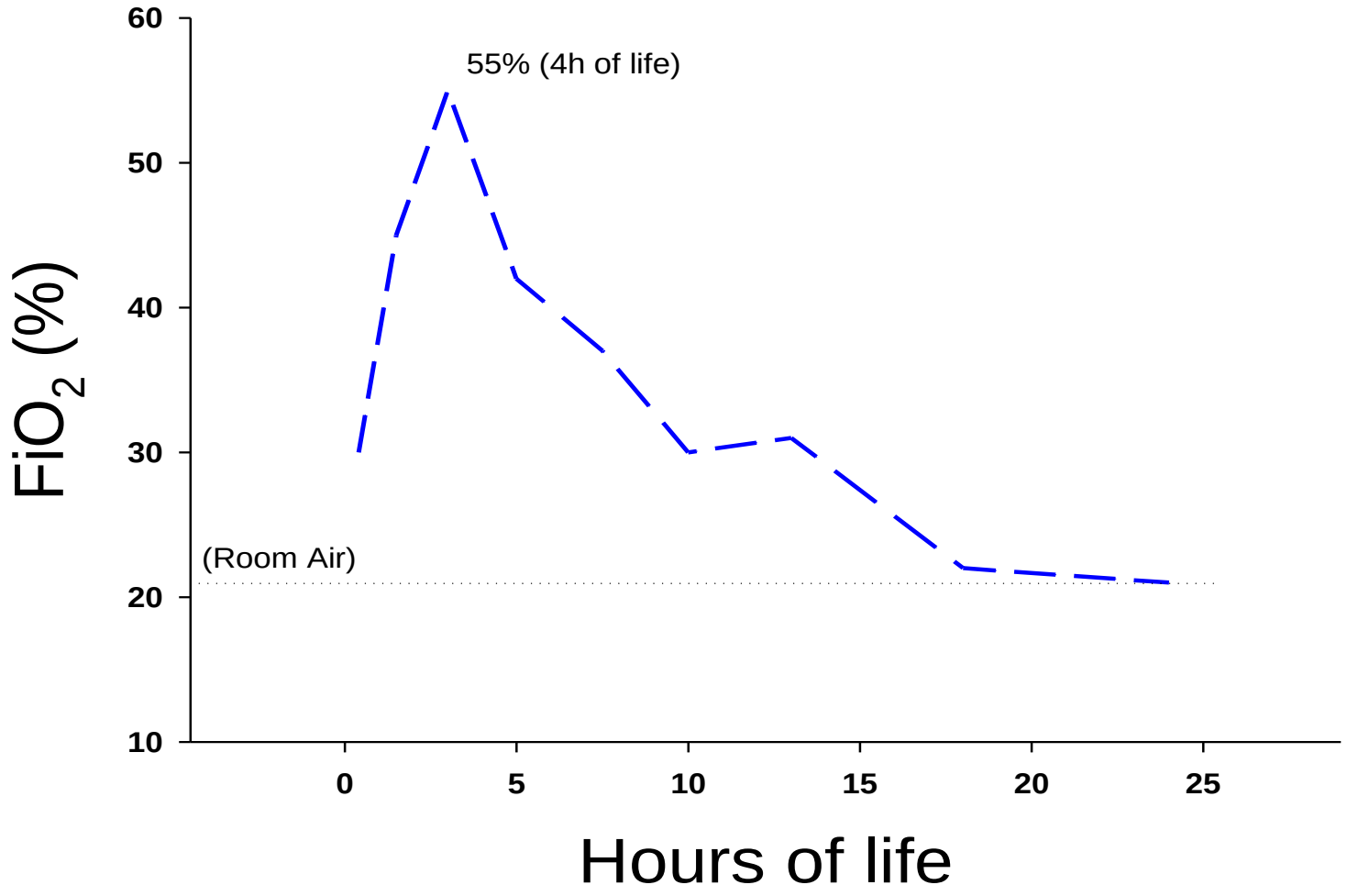
NICU Quality Improvement Board
bCPAP
75%
bCPAP
100%
bCPAP
100%
bCPAP
75%
bCPAP
87%
NEONATAL ROUNDS


1. Olhos cobertos durante sucção
2. Posição correta do RN
3. Prongas mantidas em posição durante cuidados
4. Lavagem do cateter de sucção após
5. Cuidados apropriados com a pele ao redor
bCPAP
Covering of Eyes During Suctioning
75%
bCPAP
Baby Appropriately Positioned
100%
bCPAP
Prongs kept in for full care
100%
bCPAP
Rinsing of Suction Tubing after Suctioning
75%
bCPAP
Appropriate Skin Care
87%

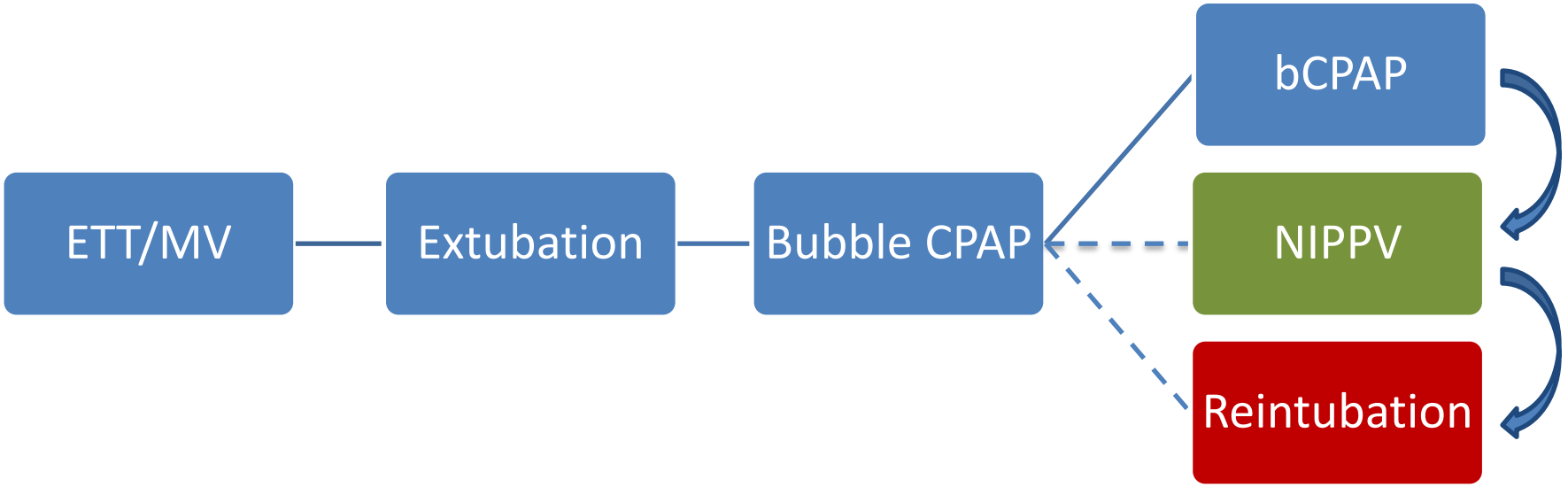
Practical Approach Postextubation



FiO_2 – evolução nas primeiras 24 h de vida



Practical Approach Postextubation



Thanks ! Obrigado!!!

Obrigado pela atenção

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Surfactante sem intubação?

- Técnicas diferentes de instilação

Non randomized trials

First Author	Type of study	Number of LISA-patients	Reference	Mean results
Kribs	Observational, single centre	29	Paediatr Anaesth 2007; 17:364-9	Lower mortality, less IVH>II°, less PIE compared to historical control
Kribs	Observational, single centre	150	Acta Paediatr 2008; 97:293-8	Less CPAP failure after introduction of method, lower mortality in infants with CPAP success regardless whether with or without surfactant
Kribs	Observational, multi-centre	319	Klin Paediatr 2010; 222:13-7	Lower prevalence of mechanical ventilation, less BPD compared to "standard care"
Dargaville	Observational, single centre	25	Arch Dis Child Fetal Neonatal Ed 2011; 96:F243-8	Increase of SpO2 after the procedure, reduction of FiO2 and CPAP pressure
Porath	Observational, Follow-up	31	Acta Paediatr 2011; 100:352-9	No differences in outcome at early school age compared to historical control
Mehler	Observational, single centre	164	Acta Paediatr 2012; 101:1232-9	Improved survival and reduced morbidity in infants with a gestational age below 26 weeks after introduction of the procedure

Non randomized trials

First Author	Type of study	Number of LISA-patients	Reference	Mean results
Dargaville	Feasibility study	61	Arch Dis Child Fetal Neonatal 2013; 98:F122-6	Increase of SpO2 after the procedure, reduction of FiO2 and CPAP pressure
Klebermass-Schrehof	Observational, single centre	224	Neonatology 2013; 103:252-8	lower mortality after introduction of LISA, esspecially in infants with a gestational age 23+0 - 25+6, less IVH, less severe IVH, less cystic PVL but more ROP and severe ROP, more PDA,less Death or BPD
Aguar	Observational, single centre	44	Acta Paediatr 2014; 103: 229-33	Procedure is feasibily without differences in any observed outcome compared to INSURE
Canals Candela	Observational single centre	19	An Pediatr (Barc) 2015 S1695-4033	Procedure is feasible without adverse events, less intubation during the first 72 hours of life compared to historical control
Göpel	Matched pairs from German neonatal network	1103	Acta Paediatr 2015; 104:241-6	Lower rates of mechanical ventilation and BPD
Krajewski	Observational single centre	26	J Matern Fetal Neonatal Med 2015; 10:1161-4	Procedure is feasible and is associated with less intubation and mechanical ventilation compared to INSURE

Original Investigation

Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants
A Randomized Clinical Trial

Angela Kribs, MD; Claudia Roll, MD; Wolfgang Göpel, MD; Christian Wieg, MD; Peter Groneck, MD; Reinhard Laux, MD; Norbert Teig, MD; Thomas Hoehn, MD; Wolfgang Böhm, MD; Lars Welzing, MD; Matthias Vochem, MD; Marc Hoppenz, MD; Christoph Bührer, MD; Katrin Mehler, MD; Hartmut Stützer, PhD; Jeremy Franklin, PhD; Andreas Stöhr, PhD; Egbert Herting, MD; Bernhard Roth, MD; for the NINSAPP Trial Investigators

Table 2. Primary Outcome and Predefined Secondary Outcomes

Characteristic	Group, No. (%)		Absolute Risk Reduction (95% CI)	*P* Value[a]
	Intervention (n = 107)	Control (n = 104)		
Survival without BPD[b]	72 (67.3)	61 (58.7)	8.6 (−5.0 to 21.9)	.20
Death	10 (9.3)	12 (11.5)	2.2 (−11.5 to 15.6)	.59
Surviving infants with BPD	25 (23.4)	31 (29.8)	7.9 (−6.6 to 22.1)	.19
Survival without major complications[c]	54 (50.5)	37 (35.6)	14.9 (1.4 to 28.2)	.02[a]
Mechanical ventilation[d]				
All infants	80 (74.8)	103 (99.0)[e]	24.3 (16.2 to 33.8)	<.001
Gestation, wk				
23	14/15 (93.3)	9/9 (100.0)	6.7 (−26.6 to 33.5)	>.99
24	24/26 (92.3)	30/31 (96.8)	4.5 (−9.9 to 22.3)	.59
25	24/31 (77.4)	41/41 (100.0)	22.6 (9.4 to 41.1)	.002
26	18/35 (51.4)	23/23 (100.0)	48.6 (30.3 to 66.0)	<.001

Table 3. Surfactant and Other Drug Treatment

Characteristic	Group, No. (%)		P Value[a]
	Intervention (n = 107)	Control (n = 104)	
Surfactant			
No. of surfactant applications per infant, median, (IQR) [range]	1 (1-2) [1-9]	1 (1-2) [0-7]	.67[b]
Cumulative surfactant doses per infant, median (IQR), mg	200 (145-300)	191 (145-260)	.54[b]
During application			
Bradycardia	12 (11.2)	3 (2.9)	.029
SpO_2 <80%	60 (56.1)	27 (26.0)	<.001
≥2 Attempts needed for successful application	29 (27.1)	28 (27.0)	.98
Medical closure of duct			.89[c]
Only indomethacin meglumine	42 (39.3)	42 (40.3)	
Only ibuprofen	36 (33.6)	31 (29.8)	
Indomethacin and ibuprofen	1 (0.9)	2 (1.9)	
Respiratory stimulants			
Caffeine	105 (98.1)	99 (95.2)	.28

JAMA Peds, 2015

Intubação nas primeiras 72h

LISA technique

	Surfactant	Columbia	CPAP
26 weeks	42%	32%	42%
27 weeks	29%	13%	48%
28 weeks	17%	8%	45%

MIST technique

	Surfactant	Columbia	CPAP
25-28 weeks (72h)	32%	27.6%	68%
25-28 weeks (any)	53%		73%

June 1999-2002

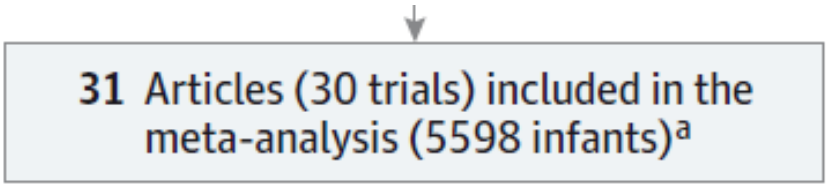
JAMA | Original Investigation

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

Tetsuya Isayama, MD, MSc; Hiroko Iwami, MD; Sarah McDonald, MD, FRCSC, MSc; Joseph Beyene, PhD

McGill

Qual a melhor estratégia respiratória não invasiva para prevenir óbito/DBP nas primeiras 24 de vida, em RNs com respiração espontânea com SDR?



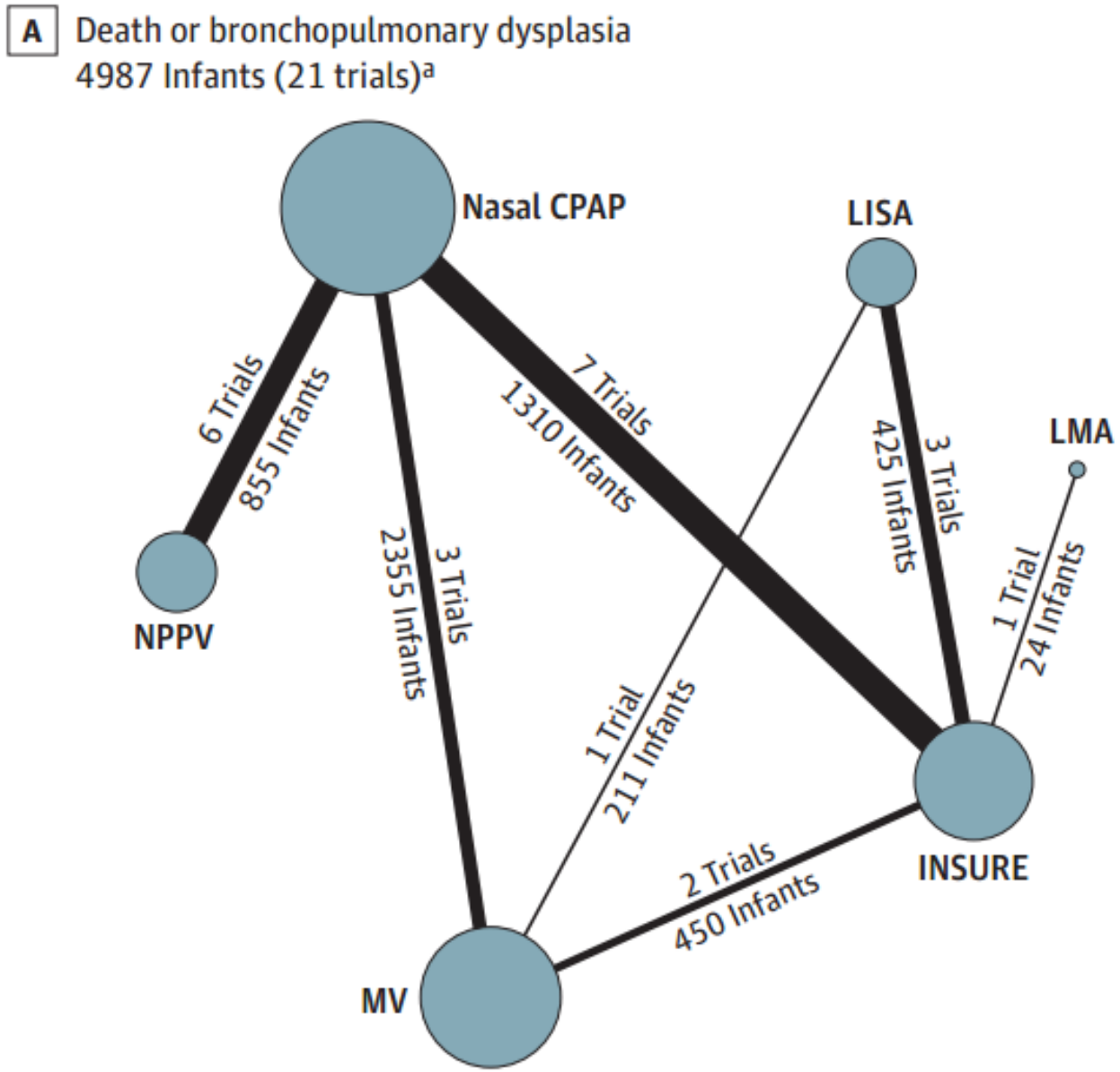
1. CPAP
2. INSURE
3. Administração de surfactante menos invasivo
4. VNI
5. Surfactante nebulizado
6. Administração de surfactante via mascara laríngea
7. Ventilação mecânica

Qualidade da Evidência

- **34 comparações diretas para os desfechos primários e secundários**

- Qualidade da evidência foi classificada como baixa:
  - Risco sério de viés em 10 comparações
  - Risco sério de heterogeneidade em 10 comparações
  - Risco sério ou muito sério de imprecisão em todas 34 comparações

- A amostra da meta-análise não atingiu o número ideal na maioria das comparações (31 de 34) resultando em baixo scores de evidência por imprecisão


A
Death or bronchopulmonary dysplasia
4987 Infants (21 trials)a
Nasal CPAP
LISA
LMA
NPPV
MV
INSURE
6 Trials
855 Infants
3 Trials
2355 Infants
7 Trials
1310 Infants
1 Trial
211 Infants
3 Trials
425 Infants
1 Trial
24 Infants
2 Trials
450 Infants

JAMA, 2016

CONCLUSÃO E RELEVÂNCIA

Entre pré-termos, o uso de LISA foi associado com a menor chance do desfecho óbito/DBP com 36 sem de IG

ACHADOS LIMITADOS:

1. **Baixa qualidade de evidência em geral**
2. **Falta de robustez nos estudos com qualidade alta**

Noninvasive surfactant delivery

- As evidências atuais para uso de técnicas não invasivas de administrar surfactante são limitadas

- Varios métodos usados (LMA, LISA, MIST, aerolized)

- Sem dados de resultados a longo prazo e avaliações de custo/benefício

STUDY PROTOCOL Open Access

McGill

The OPTIMIST-A trial: evaluation of minimally-invasive surfactant therapy in preterm infants 25–28 weeks gestation

Peter A Dargaville[1,2*], Camille Omar F Kamlin[3,4,5], Antonio G De Paoli[1], John B Carlin[6,7], Francesca Orsini[6], Roger F Soll[8] and Peter G Davis[3,4,5]

- > 30 centers and to be completed by end-2017
- n = 606 infants
- Eligible: CPAP and requiring $FiO_2 \geq 0.30$ at ≤ 6 h
  - Exogenous surfactant (200 mg/kg poractant alfa) via the Hobart method
  - Sham treatment

STUDY PROTOCOL Open Access

The OPTIMIST-A trial: evaluation of minimally-invasive surfactant therapy in preterm infants 25–28 weeks gestation

Peter A Dargaville[1,2*], Camille Omar F Kamlin[3,4,5], Antonio G De Paoli[1], John B Carlin[6,7], Francesca Orsini[6], Roger F Soll[8] and Peter G Davis[3,4,5]

- Intubation criteria :
  - $FiO_2 \geq 0.45$, unremitting apnea or persistent acidosis
- Primary outcome: **composite of death or physiological BPD**
- Secondary outcomes:
  - Death
  - Major neonatal morbidities
  - Duration of all modes of respiratory support and hospitalisation
  - Safety of the method
  - Outcome at 2 years

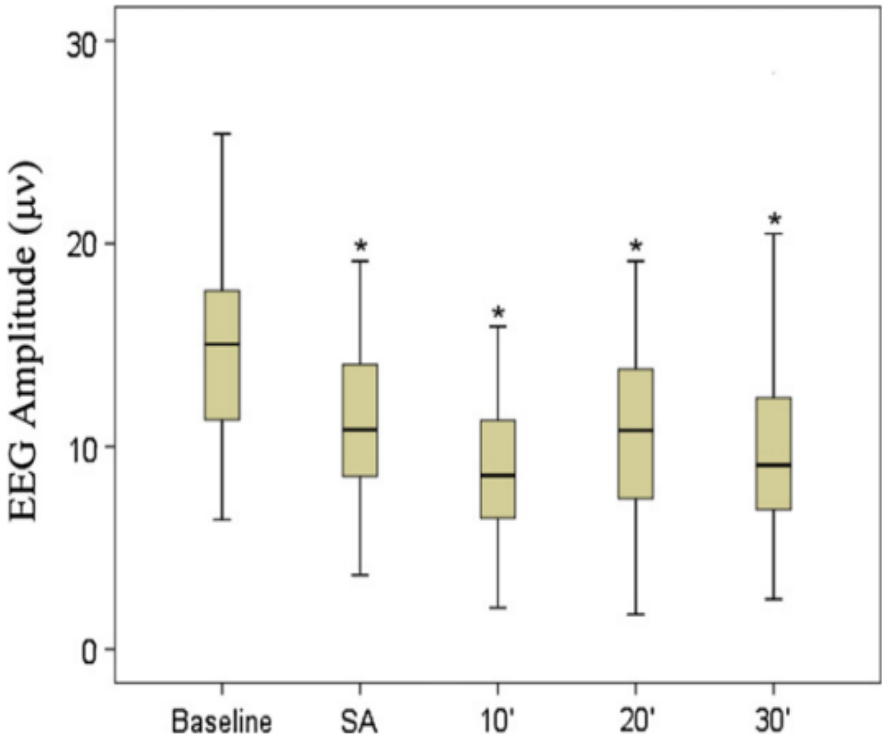
Effects of Endotracheal Intubation and Surfactant on a 3-Channel Neonatal Electroencephalogram

Carl E. Shangle, MD[1], Richard H. Haas, MB, BChir[2], Florin Vaida, PhD[3], Wade D. Rich, RRT, CCRC[1], and Neil N. Finer, MD[1]

18/29 RNs (62%) mostraram traçados de supressão no EEG após administração de surfactante (P # .008).

% recebeu premedicação para intubação endotraqueal

Administração de surfactante tem um potencial de alterar os sinais do EEG

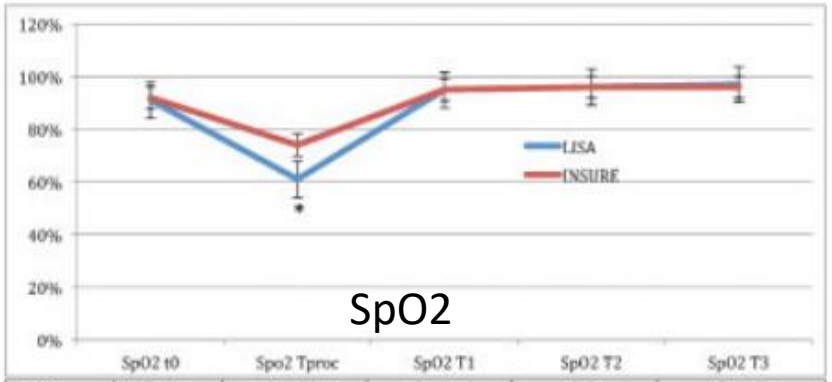


Change of Cerebral Oxygenation during Surfactant Treatment in Preterm Infants: "LISA" versus "InSurE" Procedures

Giovanna Bertini[1] Caterina Coviello[1] Elena Gozzini[1] Tommaso Bianconi[1] Cecilia Bresci[1] Valentina Leonardi[1] Carlo Dani[2]

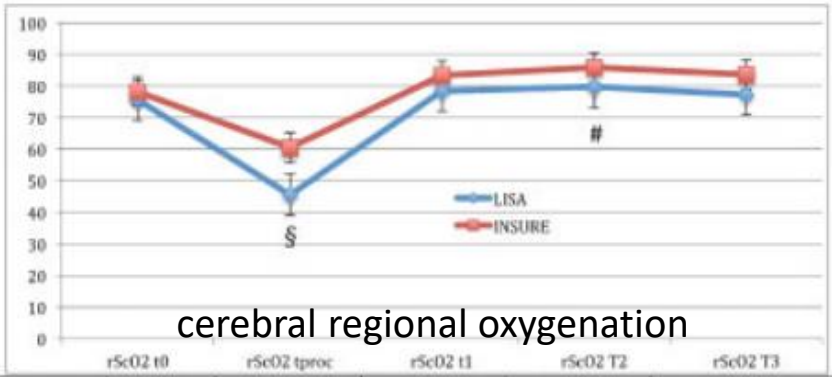
20 premature infants:

- 10 in the LISA group
- 10 in the INSURE group



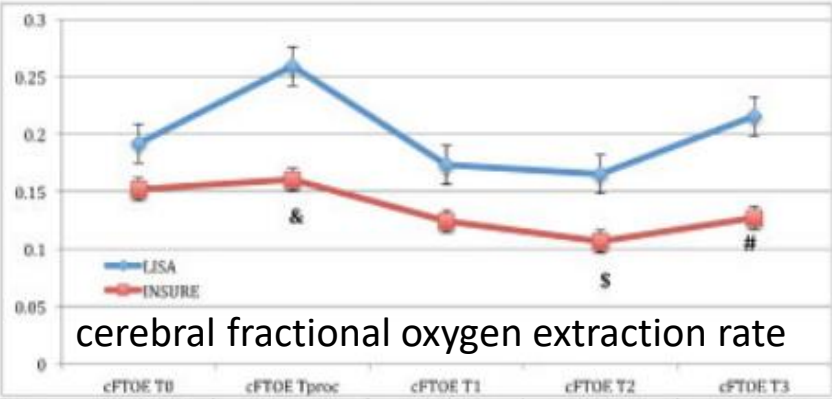
SpO2

	SpO2 t0	Spo2 Tproc	SpO2 T1	SpO2 T2	SpO2 T3
LISA	91±2.7	61±10.8	95± 2.2	96±2	97± 2.4
INSURE	92±1.3	74± 4.2	95± 2.5	96±2.5	96± 2.6



cerebral regional oxygenation

	rSc02 t0	rSc02 tproc	rSc02 t1	rSc02 T2	rSc02 T3
LISA	75.6±7.9	45.5±10.7	78.4± 7.1	79.7±7.3	77.2± 5.6
INSURE	78.1±7.1	60.5± 13	83.2± 8.3	85.8±7	83.6± 6.3



cerebral fractional oxygen extraction rate

	cFTOE T0	cFTOE Tproc	cFTOE T1	cFTOE T2	cFTOE T3
LISA	0.19±0.07	0.25±0.14	0.17± 0.07	0.16±0.07	0.21± 0.08
INSURE	0.15±0.07	0.16± 0.10	0.12± 0.08	0.10±0.06	0.12± 0.07

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Neuropediatrics 2017

Cafeína Precoce

- Aumento no uso de cafeína logo após o nascimento:
  - Estudos fisiológicos → melhora no V_T, V_E e atividade diafragmática
  - Associações entre uso precoce e ↓ DBP em análises secundárias de estudos clínicos

A pilot randomized trial of high-dose caffeine therapy in preterm infants

Christopher McPherson[1,2], Jeffrey J. Neil[3], Tiong Han Tjoeng[4], Roberta Pineda[5,6] and Terrie E. Inder[2]

Methods: 74 RNs prematuros (≤ 30 wk GA)

Treatment : dose ataque nas primeiras 24 h de vida

- Alta (80 mg/kg)
- Padrão (20 mg/kg)

Manutencao = 5mg/kg

Primary outcomes: RMN e teste de DNPM a termo (corrigido) e com 2 anos de vida

Table 3. Brain injury

	High-dose caffeine ($n = 37$)	Standard-dose caffeine ($n = 37$)	*P* value
Cerebellar hemorrhage, *n* (%)[a]	10 (36)	3 (10)	0.03
Focal unilateral	2 (7)	1 (3)	
Focal bilateral	4 (14)	1 (3)	
Extensive unilateral	3 (11)	0	
Extensive bilateral	1 (4)	1 (3)	
Death or cerebellar hemorrhage, *n* (%)[b]	17 (49)	8 (23)	0.03

[a]Diagnoses based on magnetic resonance images at term equivalent age obtained in 28 high-dose infants and 30 standard-dose infants. [b]Analysis includes infants who died

Neurobehavioral testing

Incidência alta de hipertonicidade e alterações do exame neurológico

L'Hôpital de Montréal pour enfants
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Centre universitaire de santé McGill
McGill University Health Centre

Mc Pherson C et al, Ped Research 2015

Early High- Dose Caffeine Increases Seizure Burden in Extremely Preterm Neonates: A Preliminary Study

	High Dose n=37	Standard Dose n=37	p
Convulsões (%)	58	40	0.1
Duração das convulsões (seg)	170.9	48.9	0.1

Vesoulis ZA, et. al., J. Caffeine 2016

Early Caffeine Prophylaxis and Risk of Failure of Initial Continuous Positive Airway Pressure in Very Low Birth Weight Infants

Ravi M. Patel, MD, MSc[1,2], Kanecia Zimmerman, MD, MPH[3], David P. Carlton, MD[1,2], Reese Clark, MD[4], Daniel K. Benjamin, PhD[5], and P. Brian Smith, MD, MHS, MPH[3]

- 366 NICUs - Pediatrix Medical Group entre 2000 e 2014
- PN <1500 g

Precoce = D0
Rotina = D1-6

- Exclusão:
  1. Nascido em outro hospital
  2. Obito na 1a semana vida
  3. 5-min Apgar <3
  4. Duração da hospitalização ?
  5. Não fez cafeína
  6. VM ou surfactante começou no dia do nascimento
  7. Sem informação sobre suporte respiratório no dia do nascimento

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Early Caffeine Prophylaxis and Risk of Failure of Initial Continuous Positive Airway Pressure in Very Low Birth Weight Infants

Ravi M. Patel, MD, MSc[1,2], Kanecia Zimmerman, MD, MPH[3], David P. Carlton, MD[1,2], Reese Clark, MD[4], Daniel K. Benjamin, PhD[5], and P. Brian Smith, MD, MHS, MPH[3]

Table II. Study outcomes

	Early caffeine N = 4528	Routine caffeine N = 6605	aOR* or IRR‡ (95% CI)
Primary outcome evaluated during the first postnatal wk			
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)
Secondary outcomes evaluated during the first postnatal wk			
Maximal FiO_2 >0.3*	1209 (27%)	2119 (32%)	1.05 (0.94, 1.17)
Days of CPAP‡	3 [1, 6]	2 [1, 4]	1.02 (0.99, 1.05)

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Early Caffeine Prophylaxis and Risk of Failure of Initial Continuous Positive Airway Pressure in Very Low Birth Weight Infants

Ravi M. Patel, MD, MSc[1,2], Kanecia Zimmerman, MD, MPH[3], David P. Carlton, MD[1,2], Reese Clark, MD[4], Daniel K. Benjamin, PhD[5], and P. Brian Smith, MD, MHS, MPH[3]

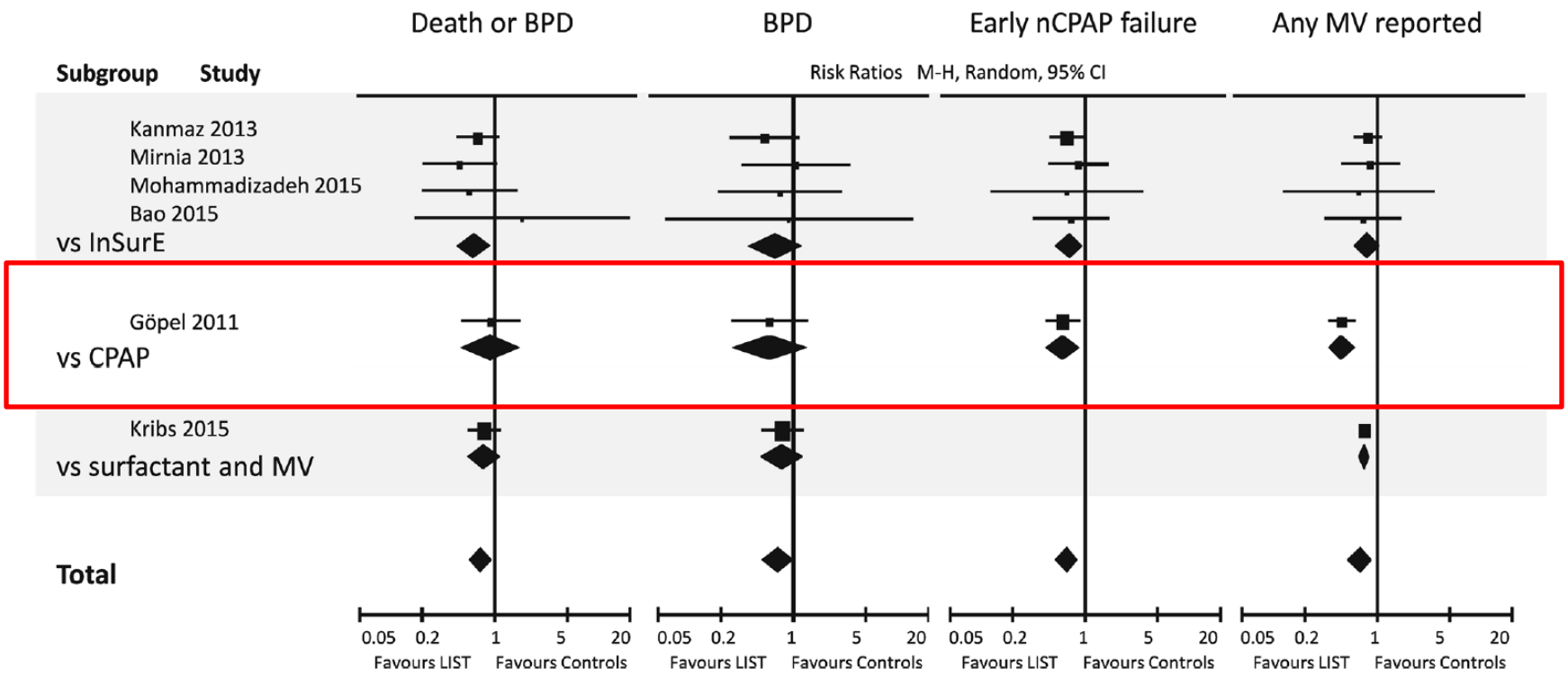
Table IV. Primary study outcome by subgroups

	Early caffeine N = 4528	Routine caffeine N = 6605	Stratified aOR* (95% CI)
Primary outcome evaluated during the first postnatal wk			
CPAP failure by GA subgroups†			
<28 wk	290/963 (30%)	220/716 (31%)	0.87 (0.65, 1.17)
≥28 wk	700/3565 (20%)	1156/5889 (20%)	1.13 (1.00, 1.29)
CPAP failure by birth weight subgroups‡			
<1000 g	367/1282 (29%)	318/1089 (29%)	0.91 (0.72, 1.16)
≥1000 g	623/3246 (19%)	1058/5516 (19%)	1.13 (0.99, 1.29)

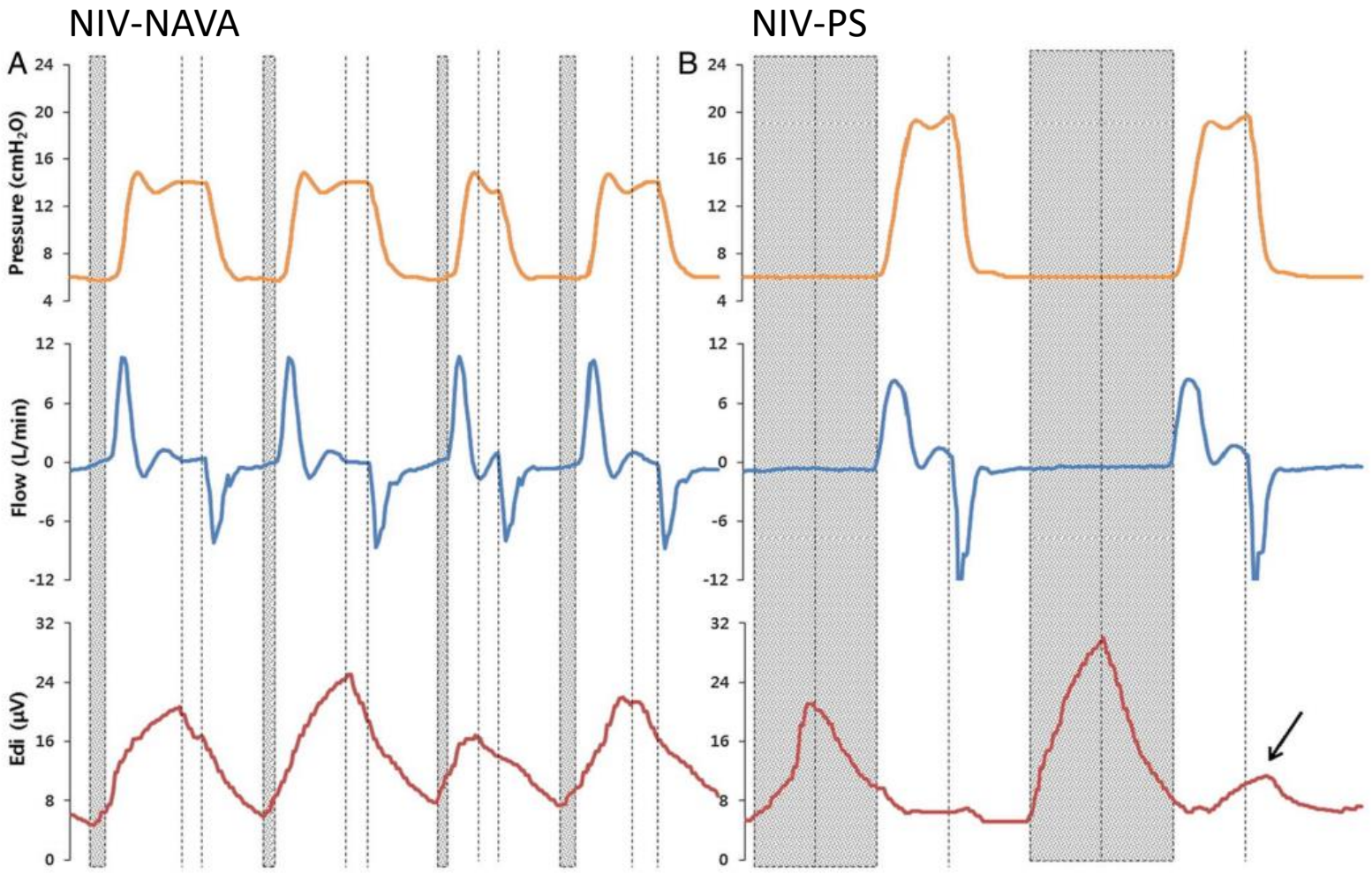
Questões em aberto

- Melhor dose e idade de começar para atingir resultados ótimos?

- Nenhum estudo prospectivo sobre efeitos da cafeína sobre DBP ou PCA como desfechos primários


Death or BPD
BPD
Early nCPAP failure
Any MV reported
Subgroup
Study
Risk Ratios M-H, Random, 95% CI
Kanmaz 2013
Mirnia 2013
Mohammadizadeh 2015
Bao 2015
vs InSurE
Göpel 2011
vs CPAP
Kribs 2015
vs surfactant and MV
Total
0.05 0.2 1 5 20
Favours LIST
Favours Controls

Baby girl born: GA = 29^{+4} wk / BW = 1305 g
Studied: PCA = 32^{+6} wk (23 dol) / CW = 1600 g



Dark area = trigger delay and arrow = ineffective effort