Hot Topics
Satellite Symposium

Recent Observations in Surfactant Pharmacology: Translational Impact for Neonatal Care

Thomas H. Shaffer, MS.E., PhD
Professor of Pediatrics and Physiology
A.I. duPont Hospital for Children
Thomas Jefferson School of Medicine
Temple University School of Medicine

Jefferson. Nemours. Alfred I. duPont Hospital for Children

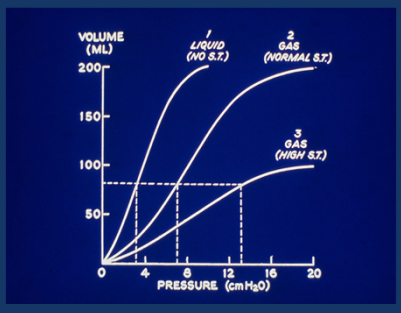
Disclosure

- I have disclosed the following financial relationship -
  - Discovery Laboratories, Inc. – Consultant

Background

- Kurt Von Neergaard (1929)

First Observations



Von Neergaard, 1929.

Background

- Kurt Von Neergaard (1929).
- Clements to Avery & Mead (1959) advanced the study of surface tension and tied this deficiency to RDS.
- Research on lung surface lining (surfactant) lead to a therapeutic intervention exogenous "surfactant replacement therapy (SRT)".
- Laboratories studied the impact of animal-derived surfactants, which contain surfactant protein (SP-B) and foreign proteins that are potentially immunogenic.
- Other investigators explored the use of synthetic surfactants (controlled formulation and stability; reduce possible inflammatory responses to animal-derived materials and improve production and product availability).

SP-B-B

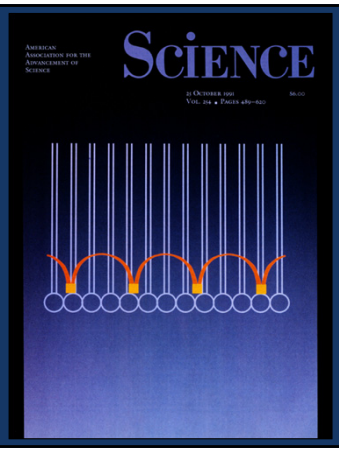
FPIPLPYCWLCRALIKRIQAMIPKGALAVAVAQVCRVVPL–
VAGGICQCLAERYSVILLDTLLGRMLPQLVCRLVLRCSMD

Simplified Peptide Structure

RYSVILLDTLLGRMLPQLVCRL
RLLLLLLLLRLLLLLLLLRLL RRRRRRRRRRR
DLLLLDLLLLDLLLLDLLLLD RLLRLLRLLLRLLRLLR
VAGGICDCLAERYSV FPIPLPYCWLRRAL
CRALIKRQAMIPKG KLLLLKLLLLK KLLLLKLLLLKLLLLK
KLLLLKLLLLKLLLLKLLLLKLLLLK LRLVLRCM

KLLLLKLLLLKLLLLKLLLLK KL4

C. Cochrane



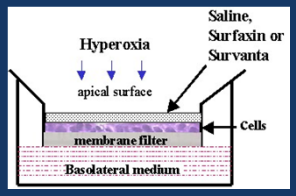
C. Cochrane

Preclinical Studies of Lucinactant (KL_4)

- Numerous preclinical studies have demonstrated that lucinactant has significant pharmacologic activity involving **pulmonary surface tension-lowering ability**, **improving lung function** and **oxygenation** comparable to commercially available pulmonary surfactants.
- Lucinactant has been shown to possess **anti-inflammatory** and **anti-microbial** activity, and is resistant to inhibition by plasma proteins and oxidants when compared with other surfactants .

Methods

- Human airway epithelial cell culture
  - Calu-3 monolayers
  - Air-liquid interface



- Treated with
  - Normal Saline
  - Lucinactant (Surfaxin®; Discovery Labs, Inc.)
  - Beractant (Survanta®; Abbott Labs, Inc.)

Zhu et al. Ped. Res. 64(2): 134, 2008.

Methods

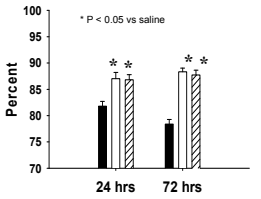
- Exposed to hyperoxia for 24 or 72 hrs
  - 60% O2
  - 5% CO2

- ASF collected for protein analysis
- Cells harvested for histology and viability analysis

Zhu et al. Ped. Res. 64(2): 154, 2008.

Physiologic Outcomes

Cell Viability



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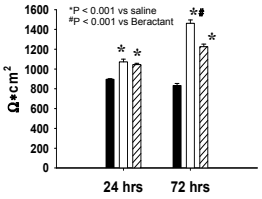
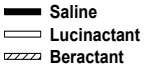
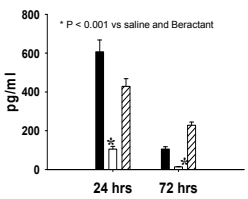




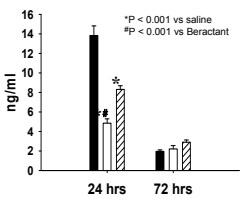
Zhu et al. Ped. Res. 64(2): 154, 2008

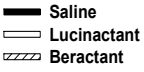
Inflammatory Mediators

IL-6



IL-8



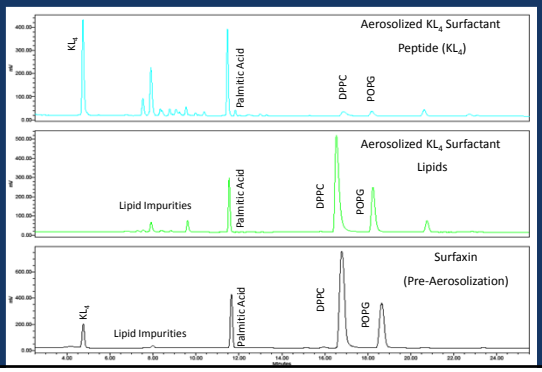


Zhu et al. Ped. Res. 64(2): 154, 2008.

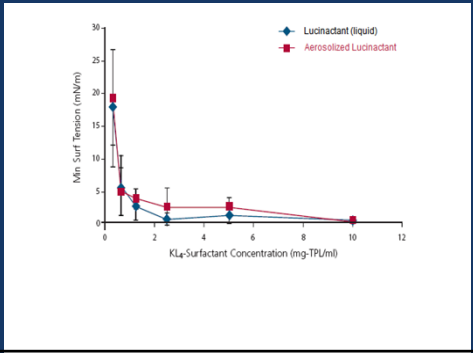
Aerosolized Lucinactant

- Initial aerosol delivery studies focused on *commercially available aerosol generators.*
- After testing of these devices in the first aerosol lucinactant study in humans, it became apparent that these *commercial devices were suboptimal.*
- Engineering efforts were refocused on an alternate aerosol generator capable of delivering *highly concentrated, aerosolized, active surfactant* to patients in sufficient amounts for an *efficacious response within a relatively short period of time.*
- These efforts led to novel aerosol generation technology, the capillary aerosol generator (CAG). Characterization of pre- and post-aerosolization of the drug showed that CAG aerosolized lucinactant *retained both its chemical composition* and *surface tension-lowering properties.*

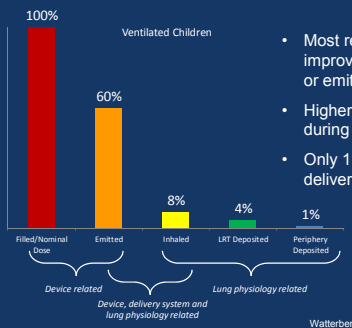
Aerosolized lucinactant chromatographic profiles - pre and post-aerosolization



Dilution curve on PBS pre and post-aerosolization



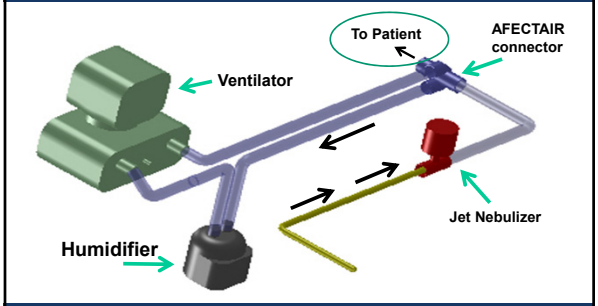
Delivery of Aerosolized Medication to Ventilated Patients is Currently Quite Inefficient



- Most research today is on improving aerosol generation, or emitted dose
- Higher losses of aerosol occurs during breathing cycle
- Only 1% of nominal dose is delivered to ventilated infants

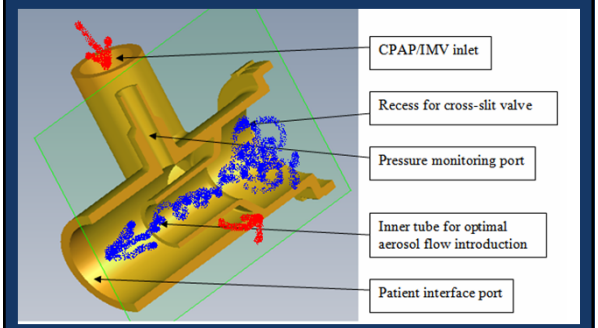
Watterberg K et al, *Pediatr Pulmonol 1991;10(2):136-41.*
Fok T et al, *Pediatr Pulmonol 1996;21:301-309.*
Mazela, Polin, Merritt, Arch *Perinat Med 2011;17(1):49-54*

AFECTAIR improves aerosol entrainment into the ventilator bias flow



Mazela et al. J Aerosol Med. 27(1):58-65, 2014.

AFECTAIR improves aerosol entrainment into the ventilator bias flow



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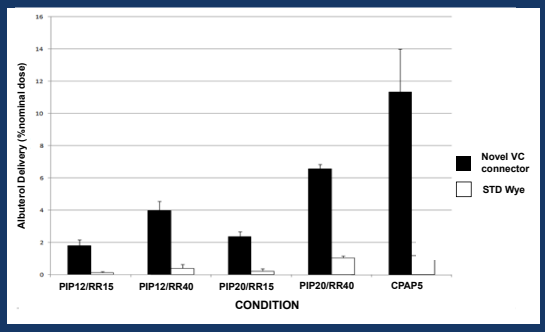
AFECTAIR improves aerosol entrainment into the ventilator bias flow



Mazela et al. J Aerosol Med. 27(1):58-65, 2014.

Aerosolized surfactants and RDS

Animal Models

Wagner et al, *Crit Care Med. 28:2540, 2000.*
Zimmermann et al. *Ped Pulmonol. 2010.*
Rey-Santano C et al, *EPAS 2012.*
Mielgo V et al, *EPAS 2012.*
Lampland et al. *Ped Pulmonol. 2013.*

Clinical

Donn & Sinha *Expert Opin Pharm 9(3): 2008.*
Finer et al. *J Aerosol Med & Pulmon Drug Del., 2010.*

Aerosurf ™

Wolfson et al., *Hot Topics Meeting 2010.*

Summary to Date:

Synthetic vs. Animal-Derived Surfactants

- Comparable surface tension activity.
- Controlled formulation consistency and stability.
- Improved production and product availability.
- Anti- inflammatory and antimicrobial activity.
- Resistant to inhibition by plasma proteins and oxidants when compared with other surfactants.
- Aerosol capability with non-invasive respiratory support.

Thank You!

Jefferson. Nemours. Alfred I. duPont Hospital for Children

Attempts to Minimize Invasiveness during the Acute Period: Where do we go from Here?

Jan Mazela

Poznan University of Medical Sciences, Poznan, Poland

Disclosure

- Consultant to Discovery Laboratories, Inc.
- Co-inventor of Afectair, aerosol delivery system owned by Discovery Laboratories, Inc.

- **Guidelines for ventilatory management**
- **Vent support – what we do?**
- **InSurE and LISA**
- **What is the bright future?**

Background

Neonatology

Consensus Guidelines

European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2010 Update

Surfactant therapy

Recommendations

(1) Babies with or at high risk of RDS should be given a natural surfactant preparation (A).

(2) Prophylaxis (within 15 min of birth) should be given to almost all babies of <26 weeks' gestation. Prophylaxis should also be given to all preterm babies with RDS who require intubation for stabilisation (A).

(3) Early rescue surfactant should be administered to previously untreated babies if there is evidence of RDS (A). Individual units need to develop protocols for when to intervene as RDS progresses depending on gestational age and prior treatment with antenatal steroids (D). Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for treatment of moderate to severe RDS (B).

(4) Consider immediate (or early) extubation to non-invasive respiratory support (CPAP or nasal intermittent positive pressure ventilation (NIPPV)) following surfactant administration provided the baby is otherwise stable (B).

CPAP therapy

Recommendations

(1) CPAP should be started from birth in all babies at risk of RDS, such as those <30 weeks' gestation who do not need MV, until their clinical status can be assessed (D).

(2) Short binasal prongs should be used rather than a single prong as they reduce the need for intubation and a pressure of at least 5 cm H_2O should be applied (A).

(3) The use of CPAP with early rescue surfactant should be considered in babies with RDS in order to reduce the need for MV (A).

MV therapy

Recommendations

(1) MV should be used to support babies with respiratory failure as this improves survival (A).

(2) Avoid hypocapnia as this is associated with increased risks of BPD and periventricular leucomalacia (B).

(3) Settings of MV should be adjusted frequently with the aim of maintaining optimum lung volume (C).

(4) Duration of MV should be minimised to reduce its injurious effect on lung (B).

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Effective Perinatal Intensive Care in Europe:
Translating knowledge into evidence-based practice

Neonatology

Consensus Guidelines

Neonatology 2013;103:353–368

Published online May 31, 2013

DOI: 10.1159/000349929

European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update

David G. Sweet[a] Virgilio Carnielli[b] Gorm Greisen[c] Mikko Hallman[d] Eren Ozek[e] Richard Plavka[f] Ola D. Saugstad[g] Umberto Simeoni[h] Christian P. Speer[i] Maximo Vento[k] Henry L. Halliday[l]

Surfactant therapy

Recommendations

(1) Babies with RDS should be given a natural surfactant preparation (A).

(2) A policy of early rescue surfactant should be standard but there are occasions when surfactant should be administered in the delivery suite, such as extremely preterm infants in whom the mother has not had antenatal steroids or those who require intubation for stabilization (A).

(3) Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies <26 weeks' gestation when FiO_2 requirements >0.30 and babies >26 weeks when FiO_2 requirements >0.40 (B).

(4) Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for treatment of RDS (A).

(5) Consider the INSURE technique. More mature babies can often be extubated to CPAP or nasal intermittent positive pressure ventilation (NIPPV) immediately following surfactant, and a clinical judgement needs to be made as to whether an individual baby will tolerate this (B).

CPAP therapy

Recommendations

(1) CPAP should be started from birth in all babies at risk of RDS, such as those <30 weeks' gestation who do not need MV, until their clinical status can be assessed (A).

(2) The system delivering CPAP is of little importance; however, the interface should be short binasal prongs or mask and a starting pressure of at least 6 cm H_2O should be applied (A). CPAP level can then be individualized depending on clinical condition, oxygenation and perfusion (D).

(3) CPAP with early rescue surfactant should be considered the optimal management for babies with RDS (A).

(4) A trial of NIPPV can be considered to reduce the risk of extubation failure in babies failing on CPAP; however, this may not offer any significant long-term advantages (A).

Mechanical Ventilation

Recommendations

(1) MV should be used to support babies when other methods of respiratory support have failed (B). Duration of MV should be minimized to reduce its injurious effect on the lung (B).

(2) Targeted tidal volume ventilation should be employed as this shortens duration of ventilation and reduces BPD (A).

(3) HFOV may be useful as a rescue therapy (B).

(4) When weaning from MV it is reasonable to tolerate a moderate degree of hypercarbia, provided the pH remains above 7.22 (B).

(5) Avoid hypocarbia as this is associated with increased risks of BPD and periventricular leukomalacia (B).

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1. Based on a meta-analysis of prophylactic surfactant versus CPAP as well as on other trials of more selective early use of surfactant versus CPAP not included in the meta-analysis, the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic or early surfactant therapy (Level of Evidence: 1).
2. Preterm infants treated with early CPAP alone are not at increased risk of adverse outcomes if treatment with surfactant is delayed or not given (Level of Evidence: 1).
3. Early initiation of CPAP may lead to a reduction in duration of mechanical ventilation and postnatal corticosteroid therapy (Level of Evidence: 1).
4. Infants with RDS may vary markedly in the severity of the respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care. Care for these infants is provided in a variety of care settings, and thus the capabilities of the health care team need to be considered.

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Effective Perinatal Intensive Care in Europe: Translating knowledge into evidence-based practice

Management of neonatal respiratory failure in Europe

Jan Mazela, Mercedes Bonet, Aurélie Piedvache, Ole Pryds, Patrick Truffert, Pierre-Henri Jarreau, Jennifer Zeitlin

on behalf of the EPICE Research Group

The 8th Congress of the EUROPEAN ACADEMY OF PAEDIATRIC SOCIETIES EAPS October 17-21, 2014, Barcelona, Spain — Accredited 33 CME Credits

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EPICE project

19 EU regions from 11 EU countries
Population based, prospective study with 2 year follow-up 2011-2012
All infants born between 22 and 31 weeks
Multidisciplinary teams:
obstetricians, pediatricians, epidemiologists, health care providers

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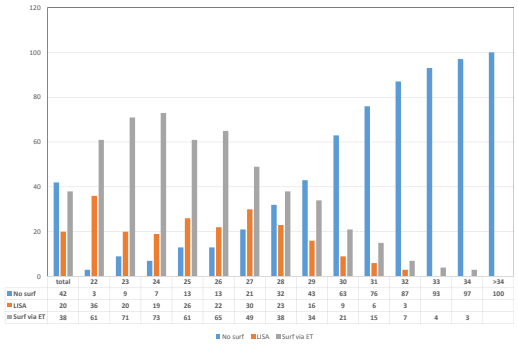
Effective Perinatal Intensive Care in Europe: Translating knowledge into evidence-based practice

Exogenous Surfactant Therapy

Surfactant administration



	total	22	23	24	25	26	27	28	29	30	31	32	33	34	>34
No surf	42	3	9	7	13	13	21	32	43	63	76	87	93	97	100
LISA	20	36	20	19	26	22	30	23	16	9	6	3			
Surf via ET	38	61	71	73	61	65	49	38	34	21	15	7	4	3	

No surf LISA Surf via ET

E. Herting *Early Human Development 2013; 89: 875–880*

Alternative Strategies for Surfactant Administration

- Kribs et al developed direct catheter SRT in Germany (MIST=LISA):
  - placed on Single Nasopharyngeal (SNP) Tube and CPAP or IMV
  - small feeding tube placed below the cords
  - surfactant instilled slowly in synchrony with breathing
- Dargaville et al in Australia has described using an angiocatheter #16 passed through the cords an instilling surfactant at 1-3 cm below the cords
- RCT LMA trial on going but generally available in infants > 1200 g (Roberts K et al….)

Kribs, A et al, *Acta Paediatr 2008; 97: 293*
Dargaville et al, *Neonatology 2012; 101: 326*

LISA = MIST

Method	Author, Year	Catheter	Magill Forceps Used?	Dose and Mode of Surfactant Delivery	Premedication
Cologne method	Kribs et al 2007 (25)	4- to 5-FG feeding tube	Yes	100 mg/kg Slow push, 1–3 min	Atropine, sedation, and analgesia (optional)
Hobart method	Dargaville et al 2011, 2013 (29) (30)	16-G Angiocath	No	100–200 mg/kg 3–4 boluscs, 15–30 sec	Sucrose
Take Care method	Kanmaz et al 2012 (31)	5-FG feeding tube	No	100 mg/kg Slow bolus, 30–60 sec	None
Karolinska method	Bohlin (unpublished)	5-FG × 30-cm catheter	No	Slow bolus, 30 sec	Atropine/fentanyl
SONSURE method	Aguar et al 2014 (32)	4-FG feeding tube	Yes	100 mg/kg Slow push, 1–3 min	Atropine

Aguar, M et al. **Minimally Invasive Surfactant Therapy: An Update** *Neoreviews 2014;15;e275*

LISA = MIST

Trial, Author, Year	Intervention and Comparator (n)	Gestation Range	Entry Criteria	Primary Outcome	Results of Primary Outcome	Other Findings
AMV trial Göpel et al 2011 (28)	I: LISA, Cologne method, 108 C: CPAP, 112	26–28 wk	<12 h after birth FiO_2 ≥0.30	Intubation day 2 or 3	28% vs 46% (NNT: 6; 95% CI: 3–20)	Intubation at any time: 33% vs 73% ($P < .001$) Median days on MV: 0 vs 2 Oxygen at 28 days: 30% vs 45% ($P = .032$)
Take Care trial, Kanmaz et al 2012 (31)	I: LISA, Take Care method, 100 C: INSURE, 100	<34 wk	FiO_2 ≥0.40	Intubation <72 h	30% vs 45% ($P = .02$)	Mean duration of nCPAP: 78 vs 116 h ($P = .1002$) Mean duration of MV: 33 vs 64 h ($P = .006$) BPD: 20% vs 10% ($P = .009$)
NINSAPP trial, Kribs et al 2013 (unpublished)	I: LISA, Cologne method, 107 C: Intubation and surfactant, 104	23–26 wk	FiO_2 ≥0.30 or Silverman score ≥5	Survival without BPD	Pending	Pending

Aguar, M et al. **Minimally Invasive Surfactant Therapy: An Update** *Neoreviews 2014;15;e275*

Where is caffeine???

BMC Pediatrics

STUDY PROTOCOL **Open Access**

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

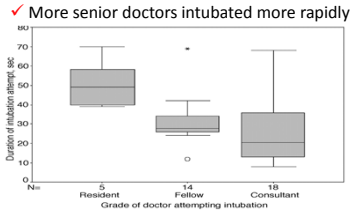
Peter A Dargaville[1,2*], Camille Omar F Kamlin[3,4,5], Antonio G De Paoli[1], John B Carlin[6,7], Francesca Orsini[6], Roger F Soll[8] and Peter G Davis[3,4,5]

Intubation still required…

Endotracheal Intubation Attempts During Neonatal Resuscitation: Success Rates, duration and Adverse Effects

✓62% of intubations were successful; consultants (86%), fellows (78%) & residents (24%).

✓ More senior doctors intubated more rapidly



- 49% of infants deteriorated during intubation attempts.
- SpO_2 fell by ≥ 10% in 12/25
- HR fell by ≥ 10% in 4/25

O'Donnell CPF et al *Pediatr. 117 No. 1 January 2006, pp. e16-e21*

Aerosolized surfactants – clinical studies

The only study utilized single naso-pharyngeal (SNP) tube for CPAP and aerosol delivery

	Surfactant	*Method*	*Population*	*Outcome*
Jorch G	Alveofact®	Jet nebulizer 150 mg x 2 SNP tube CPAP	28-35 wks	A-a O_2 gradient, PCO2 & Silverman score improved
Arroe M	Exosurf®	Side stream nebulizer prongs CPAP	23-36 wks	No significant benefits
Berggren E	Curosurf®	Jet nebulizer IF CPAP	27-34 wks	No significant benefits
Finer N	Aerosurf®	Aeroneb Pro® prongs CPAP	28-32 wks	Procedure safe

QUESTION: Was the right patient interface used?
QUESTION: Was the right nebulizer used?

Mazela et al, *Curr Opin Pediatr 2007; 19: 155*

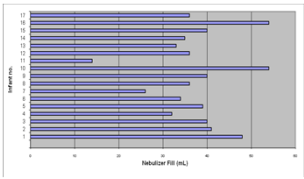
Multicenter pilot study of aerosolized KL_4 surfactant delivered via nCPAP (KL_4-CPAP-01 Phase 2A)

- Results:

Adverse Experiences During Initial Aerosol Dosing

	Number of Patients (N=17)	Percentage
Oxygen desaturation	9	52.9
Pallor	1	5.9
Bradycardia	0	0
Hypotension	0	0
Gastric distension	0	0
Nasal irritation	1	5.9
Skin irritation	1	5.9
Apnea	5	29.4

Average nebulizer dispensed volume per treatment /infant.



- Treatment safe – no SAE related to dosing
- No need for intubation related to treatment
- Nebulizer showed significant device to device variability in output rate – need to develop more reliable aerosol generator

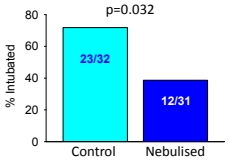
Finer N, et al. *J Aerosol Med Pulm Drug Del 2010;23:1-7.*

Cure*N*eb study

- Moderately preterm infants (29^0 – 33^6), n=64 with FiO_2 = 0.22-0.3, < 4h of life
  - Poractant alfa (Curosurf, Chiesi)
    - 200 mg/kg 1st Dose (nominal during ~20 min.)
    - 100 mg/kg 2nd Dose if required after 12 h
- VM (Pari *e*-Flow, PARI) nebuliser combined with bubble CPAP via face mask

Significant reduction in CPAP failure in 1st 72 h

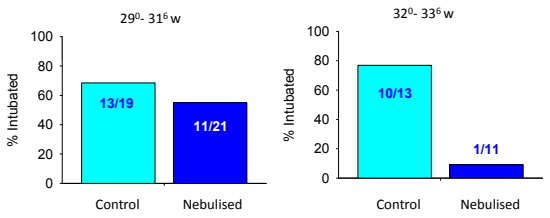
RR: 0.563 (0.341 to 0.929) p=0.032



Pillow J, Minocchieri S, et al. PAS 2013

CureNeb study

Primary Outcome: Failed CPAP in 1st 72 h



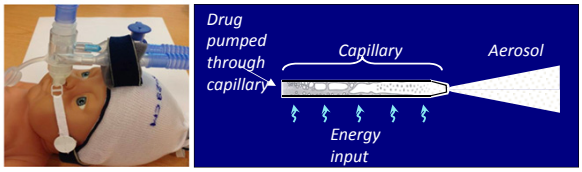
RR: 0.860 (0.399 to 1.854)
p=0.984

RR: 0.118 (0.178 to 0.784)
p=0.004

Pillow J, Minocchieri S, et al. PAS 2013

Ongoing clinical study phase II and III

- 26-32 wga on nCPAP:
  - Treatment group:
    - CAG with Afectair® for aerosol generation and delivery
    - KL4 surfactant
  - Control group: initial CPAP with standard approach



Take Home…

- Perinatal factors such as: cesarean section, presence of preeclampsia, low gestational age and Apgar score below 7 identify infants likely to experience nCPAP failure. When adjusted for center and region prenatal steroids and CPAP experience play a role as well
- INSURE is not influencing effectiveness of nCPAP when used as a rescue mode
- When using less invasive surf administration give Caffeine Citrate first!
- Bright future – aerosolized surfactant administration with optimized nebulizer, delivery system and patient interface

New Directions: Respiratory Support in Neonates

Martin Keszler, M.D.
Professor of Pediatrics
Brown University
Women and Infants Hospital of Rhode Island

The Following Industry Relationships are Germane to my Participation/Presentation

Draeger Medical Inc.	Consultant, Research Grant, Lecture Honoraria
Discovery Laboratories, Inc.	Chair, Medical Advisory Board
Medipost America	Member of Scientific Advisory Board

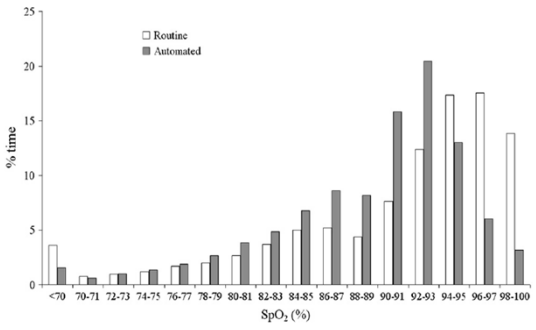
Rationale for Closed Loop Automatic Control

- NB respiratory function is labile
- Human response to perturbations is:
  - Inconsistent
  - Intermittent
  - Subject to bias
  - But adaptable and intelligent
- Automated systems are:
  - Consistent
  - Continuous
  - Objective
  - But rote, do not adapt and subject to artifact

Modalities of Closed Loop Control

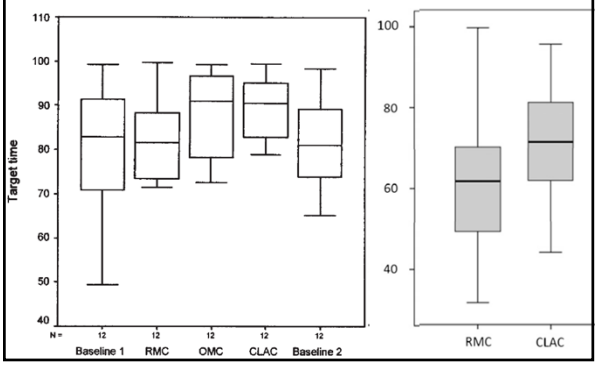
- Automated FiO_2 control
- Mandatory Minute Ventilation (MMV)
- Neutrally Adjusted Respiratory Assist (NAVA)
- Proportional Assist Ventilation (PAV)
- Volume targeted ventilation
  - VG
  - PRVC
  - VTV

Closed Loop O_2 Control Claure, et al, J Pediatr 2009



Closed Loop Automated FiO_2 Control

Urschitz, et al, AJRCCM 2004; Hallenberger, et al Pediatrics 2014



New Directions: Respiratory Support in Neonates

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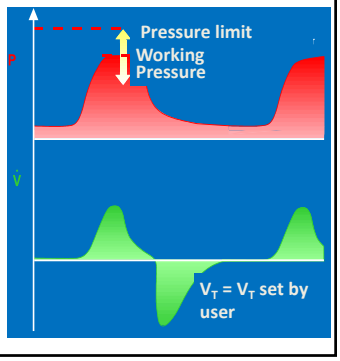
Volume Guarantee
Principles of Operation

The PIP ("working pressure") is servo-regulated within preset limits ("pressure limit") to achieve V_T that is set by the user.

Regulation of PIP is in response to exhaled V_T to minimize artifact due to ETT leak. Breath terminates if 130% of TV_T reached



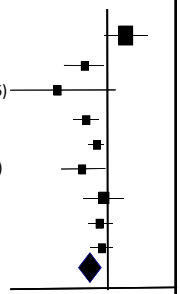
Benefits of VG

- **Maintenance of (relatively) constant tidal volume**
- **Prevention of volutrauma and hypocapnia due to:**
  - Surfactant administration
  - Lung volume recruitment
  - Clearance of lung fluid
- **Automatic lowering of pressure support level during weaning**
- **Compensation for variable respiratory drive**
  - stabilization of tidal volume and minute ventilation due to changes of respiratory drive (periodic breathing)

PLV vs. VTV Meta-analysis: Duration of MV

Peng, et al, *ADC-FNN 2014*

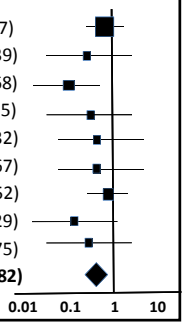
Study	VTV	PLV	MD 95% CI
D'Angio 2006	28±24	24±23	3.6 (-3.1, 10.3)
Guven 2013	3.0±7	6.9±8	-3.9 (-7.4, -0.5)
Keszler 2014	4.5±7	15±18	-11.1 (-24.8, 2.6)
Lista 2014	8.8±3	12.3±3	-3.5 (-5.1, -1.9)
Liu 2011	4.8±1	6.5±2	-1.7 (-2.5, -0.9)
Piotrowski 1997	6.7±5	13±15	-6.3 (-12.9, 0.3)
Singh 2016	8.4±13	9.7±14	-1.3 (-6.8, 4.2)
Sinha 1997	5.1±3	6.7±6	-1.6 (-4.0, 0.8)
Zhou 2007	9.3±2	9.8±2	-0.5 (-2.1, 1.1)
Total	**8.7±7.5**	**11.5±5.6**	**-2.0 (-3.1, -0.9)**



PLV vs. VTV Meta-analysis: BPD

Peng, et al, *ADC-FNN 2014*

Study	VTV	PLV	RR 95% CI
D'Angio 2006	27/93	32/92	0.83 (0.55-1.27)
Duman 2012	3/23	7/22	0.41 (0.12-1.39)
Guven 2013	2/42	9/30	0.16 (0.04-0.68)
Keszler 2014	2/9	5/9	0.40 (0.10-1.55)
Lista 2014	3/30	4/23	0.57 (0.14-2.32)
Nafday 2005	2/16	4/18	0.56 (0.12-2.67)
Singh 2016	16/57	17/52	0.86 (0.49-1.52)
Sinha 1997	1/25	6/25	0.17 (0.02-1.29)
Zhou 2007	2/15	5/15	0.40 (0.09-1.75)
Total	**58/310**	**89/286**	**0.61 (0.46-0.82)**

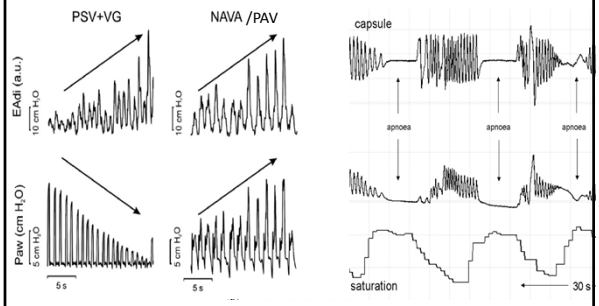


PLV vs. VTV MAA: Other Outcomes

Peng, et al, *ADC-FNN 2014*

Outcome	No. of Studies	No. of Subjects	RR (95% CI) or Mean diff (95%CI)
Any IVH	11	759	0.65 (0.42-0.99)
Cystic PVL	7	531	0.33 (0.15-0.72)
Grade 3-4 IVH	11	707	0.55 (0.39-0.79)
Pneumothorax	8	595	0.46 (0.25-0.86)
Any hypocapnia	2	58	0.56 (0.33-0.96)
Failure of assigned mode	4	405	0.64 (0.43-0.94)
Length of suppl. Oxygen (d)	2	133	-1.68 (-2.5to-0.88)

VG vs. NAVA/PAV and Extreme Periodic Breathing



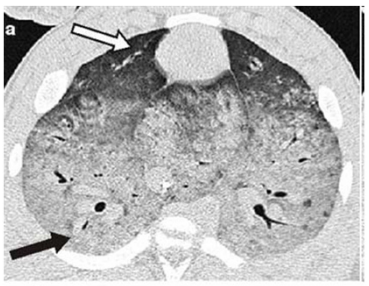
Owen, et al, *ADC 2010*

The benefits of VTV can not be realized without ensuring that the tidal volume is evenly distributed throughout an "open lung"!!!

Compliant chest wall
Limited muscle strength
C-section/ absence of labor
Fluid filled lungs
Respiratory depression

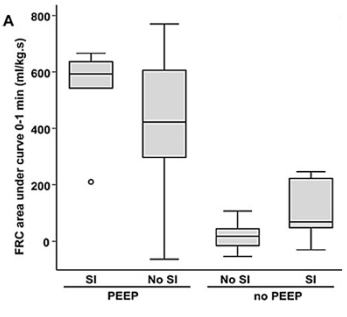
Impaired ability to establish FRC

Where does the air go with PPV?



SI in preterm rabbits

te-Pas, et al, *Pediatr Res 2009*



RCT of SI + PEEP vs PEEP

te Pas, et al, Pediatrics 2007

	SI + PEEP n=104	PEEP n=103	P value
Intubated in DR	17%	36%	0.002
Length of RS (d)	2.7 [0.5-10]	4.3 [0.5-20]	0.01
>1 dose of Surf	10%	21%	0.02
Survival	98%	96%	0.4
BPD	22%	34%	0.05
IVH 3-4/PVL	9%	8%	0.4

New Directions: Respiratory Support in Neonates

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Sustained Lung Inflation in DR: 25 cm H_2O for 15 s

Lista, et al, *Neonatology 2010*

	SLI group (n = 89)	Control group (n = 119)	p
INSURE	14 (16)	3 (3)	0.001
Mechanical ventilation	45 (51)	90 (76)	<0.0001
duration, days	5 ± 11	11 ± 19	0.008
Exclusive NCPAP	44 (49)	29 (24)	<0.0001
Surfactant	40 (45)	73 (61)	0.027
O_2 therapy	89 (100)	119 (100)	N/A
duration, days	21 ± 27	31 ± 31	0.016
Postnatal steroids	9 (10)	30 (25)	0.010
Pneumothorax	8 (9)	10 (8)	0.920
PDA	24 (27)	29 (24)	0.791
BPD	6 (7)	25 (25)	0.004
Grade 3–4 IVH	1 (1)	5 (4)	0.372
PVL	4 (4)	11 (9)	0.299

Italian Multicenter RCT

Lista, et al, *PAS 2014*

	Control (N=143)	SI (N=148)	P	Adjusted OR(95% CI)
Birth weight (g)	894±247	893±241	NS	
GA (wk)	26.8±1.2	26.8±1.1	NS	
MV in 1st 72h - no.(%)	93 (65)	79 (53)	0.04	0.57 (0.33-0.96)
Surfactant – no. (%)	110 (77)	109 (74)	0.52	0.88 (0.50-1.56)
Any MV – no. (%)	98 (69)	88 (59)	0.11	0.68 (0.41-1.13)
BPD – no. (%)	50 (35)	57 (39)	0.42	1.14 (0.78-1.69)
Death – no. (%)	12 (8)	17 (11)	0.40	1.39 (0.66-2.93)
Ptx - no.(%)	2 (1)	9 (6)	0.06	4.57 (0.97-21.50)

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Sustained inflation to Aerate Infants' Lungs (SAIL) Trial

PIs: H. Kirpalani, M. Keszler
P. Davis, S. Ratcliffe
Co Is: J. Davis, S. Donn, N. Finer, H. Hummler, R. Steinhorn, G. Lista, A. tePas

Stay tuned!
Results in 4 years ☺