Peridosing Effects of Surfactant Administration: Treating the Lung Without Harming the Brain

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Disclosure Statement

Dr. Blood's laboratory has performed preclinical testing of lucinactant (Surfaxin®) for Discovery Laboratories, Inc.

Objectives

- Determine factors that determine the uniformity of surfactant distribution within the lung.
- Identify the effects of surfactant administration on various physiological parameters (brain perfusion and oxygenation).
- Relate the factors which determine pulmonary surfactant distribution to peridosing physiological effects.

Introduction

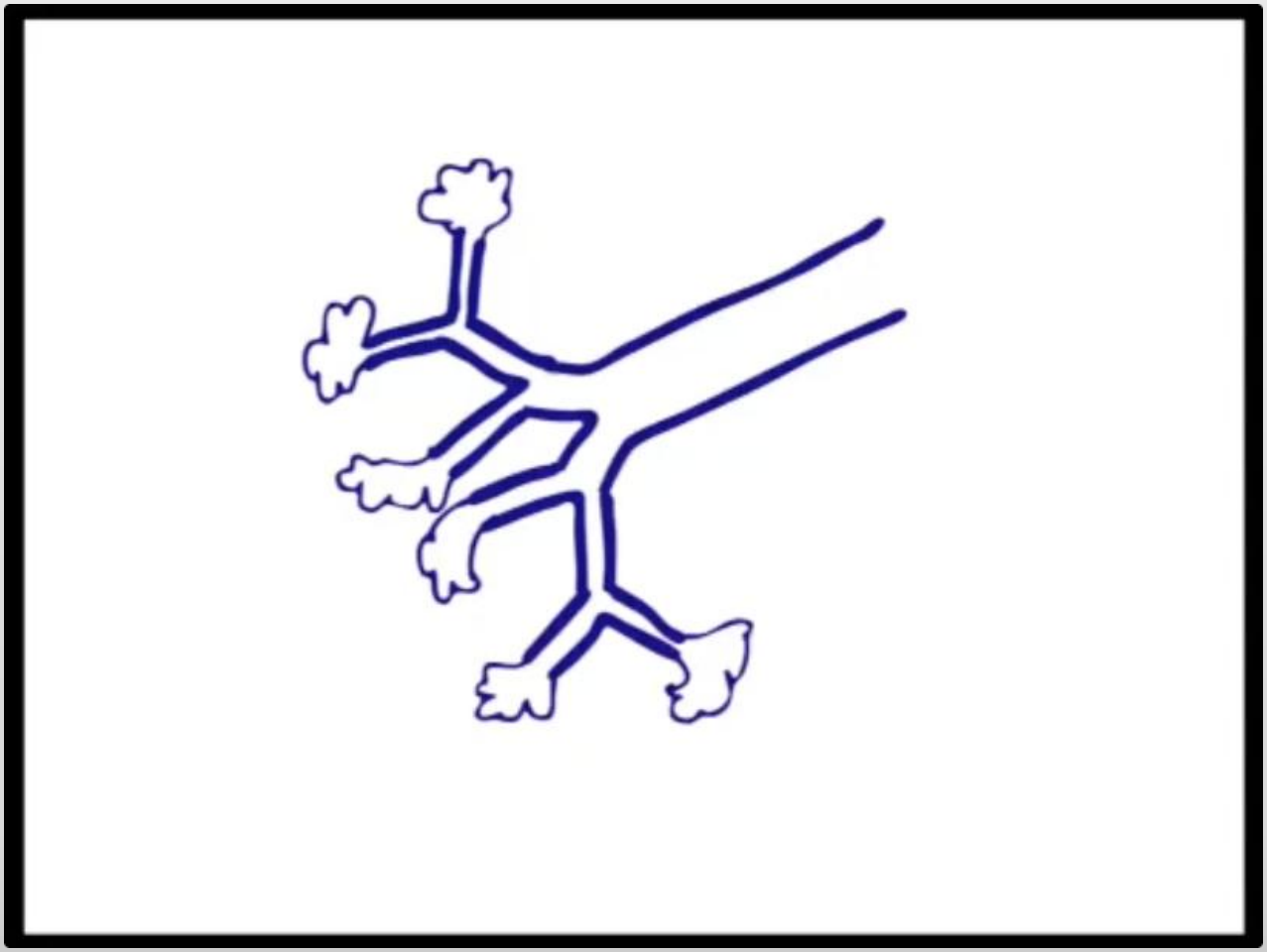
- One goal of surfactant replacement therapy is to achieve uniform distribution of the surfactant throughout the lung
- Uneven distribution can result in:
  - Volutrauma and barotrauma in the alveoli that receive the surfactant
  - Underutilization of untreated alveoli

Factors Affecting Surfactant Distribution

- Volume instilled
- Rate of instillation
- Surfactant composition and viscosity
- Gravity (infant positioning)
- Ventilation parameters
- Maintenance of positive airway pressure

Espinosa and Kamm. *J Appl Physiol.* 1999;86:391-410.

Two Phases of Surfactant Distribution



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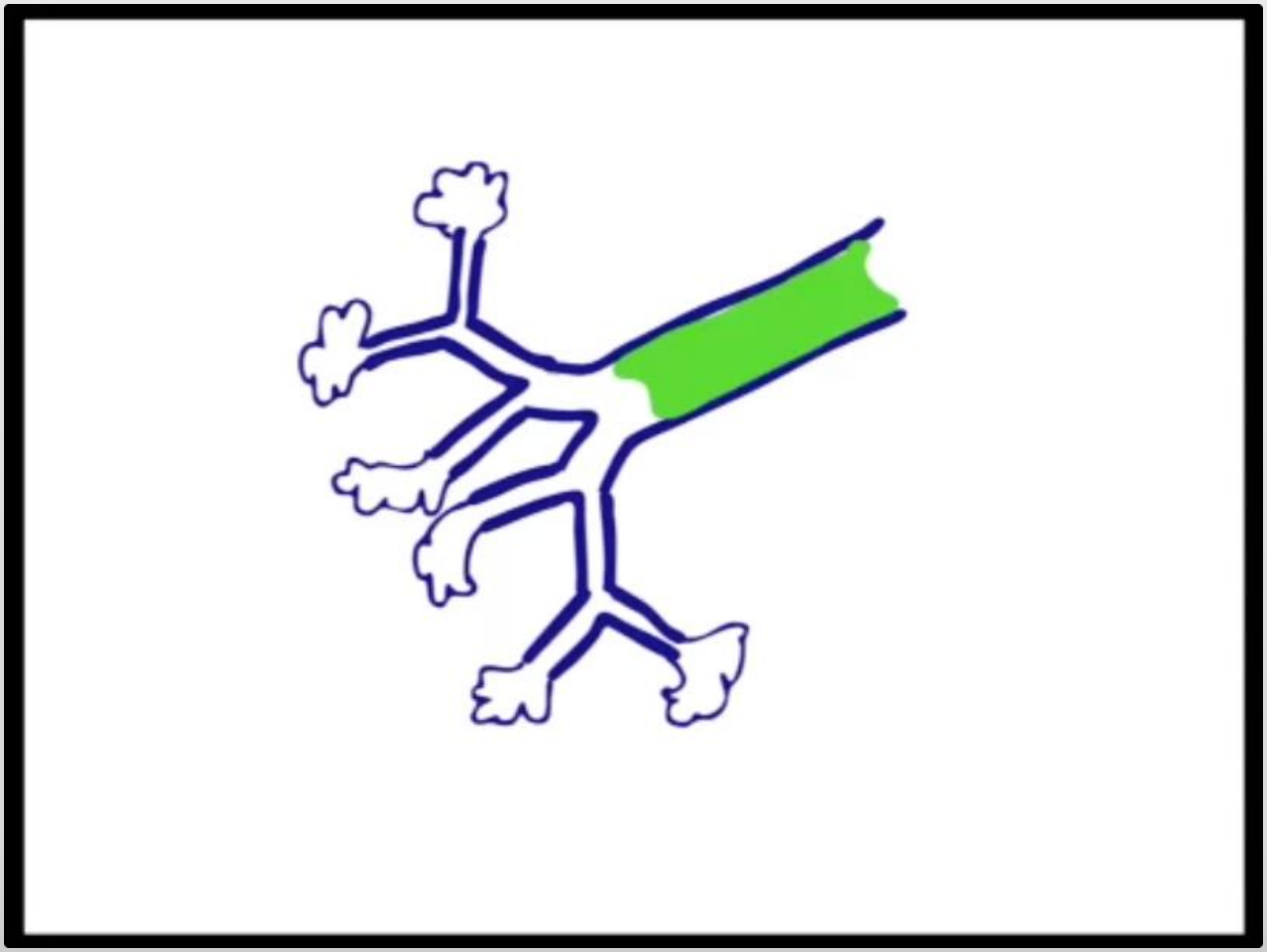

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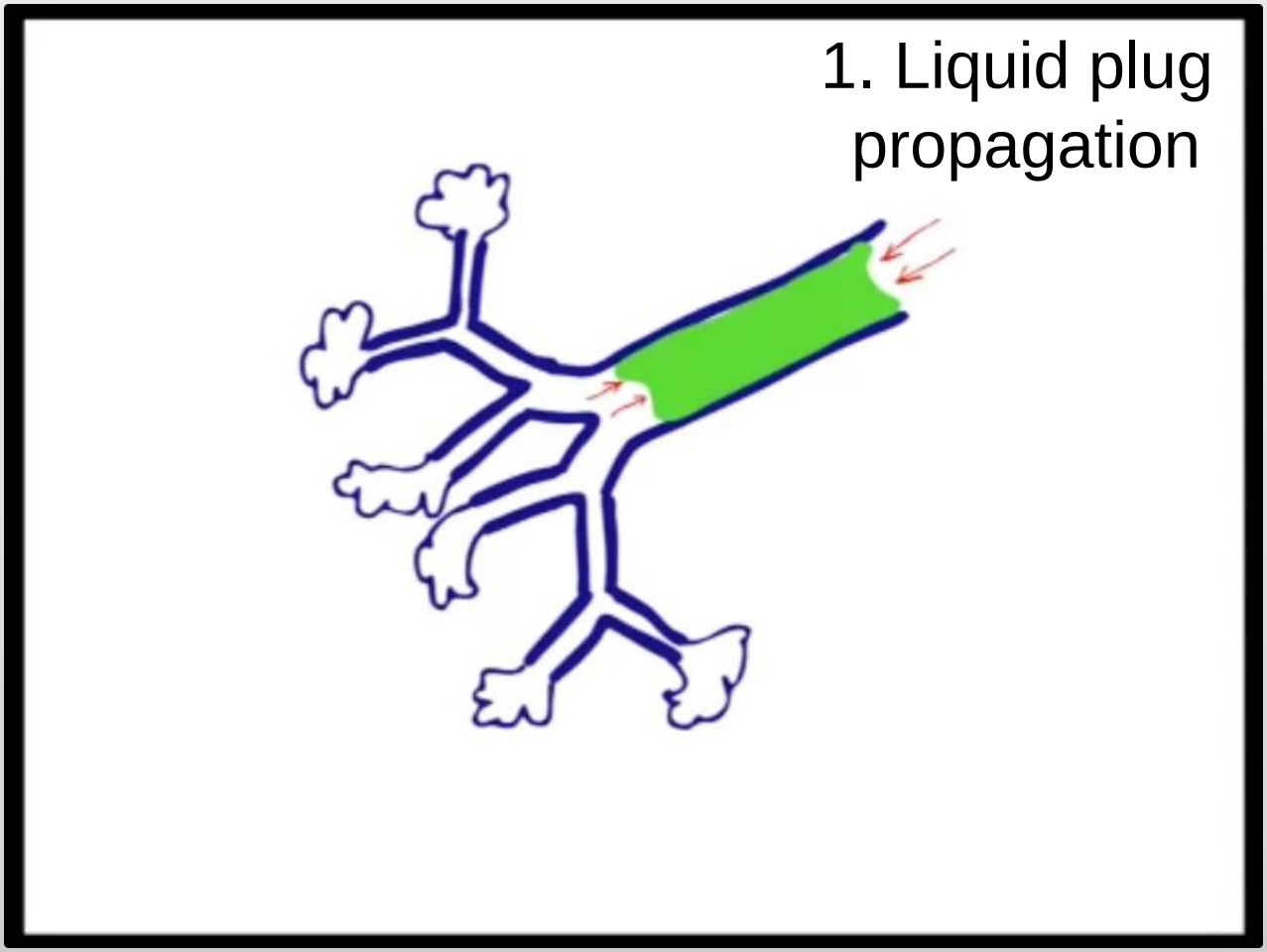

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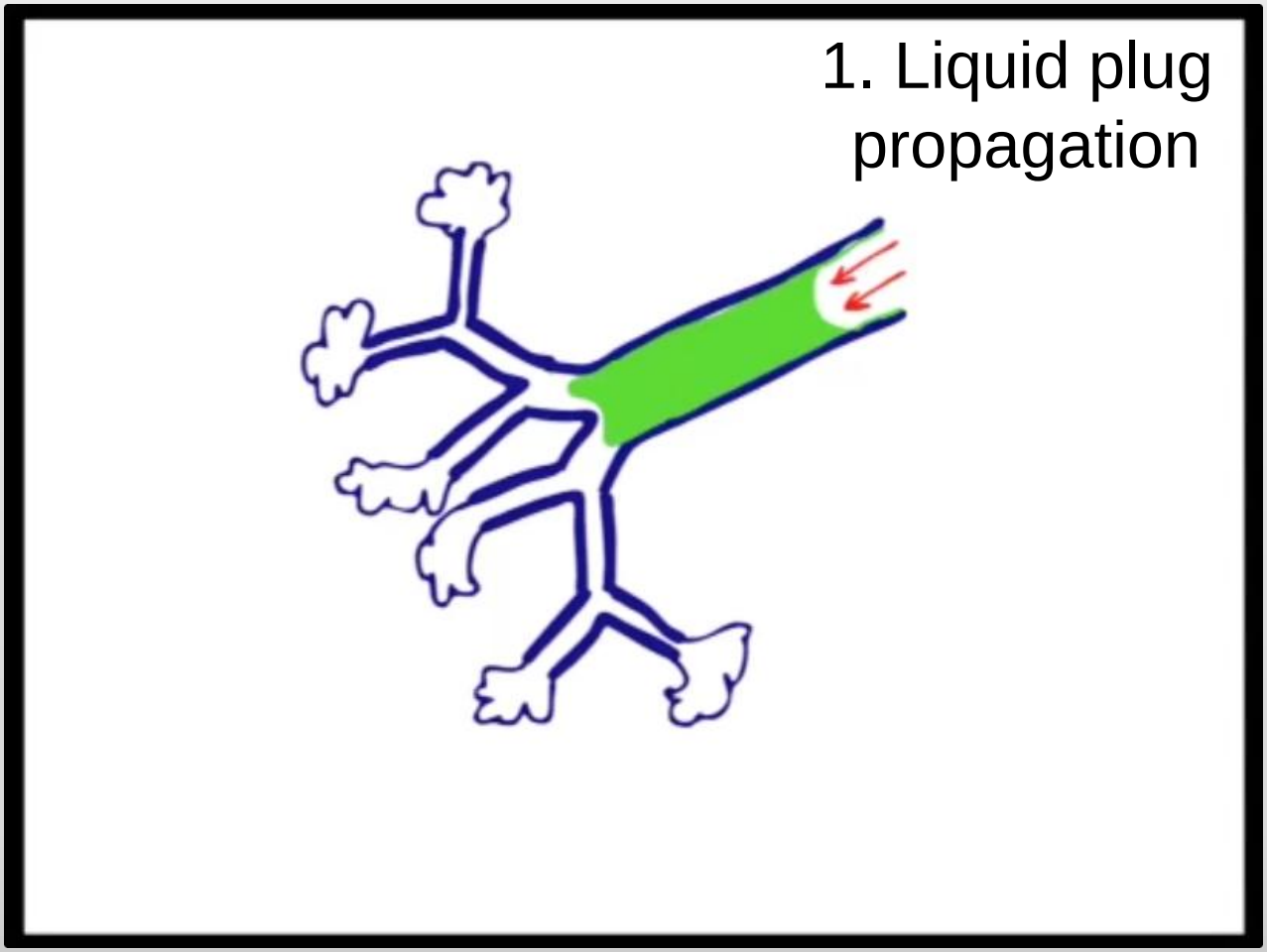

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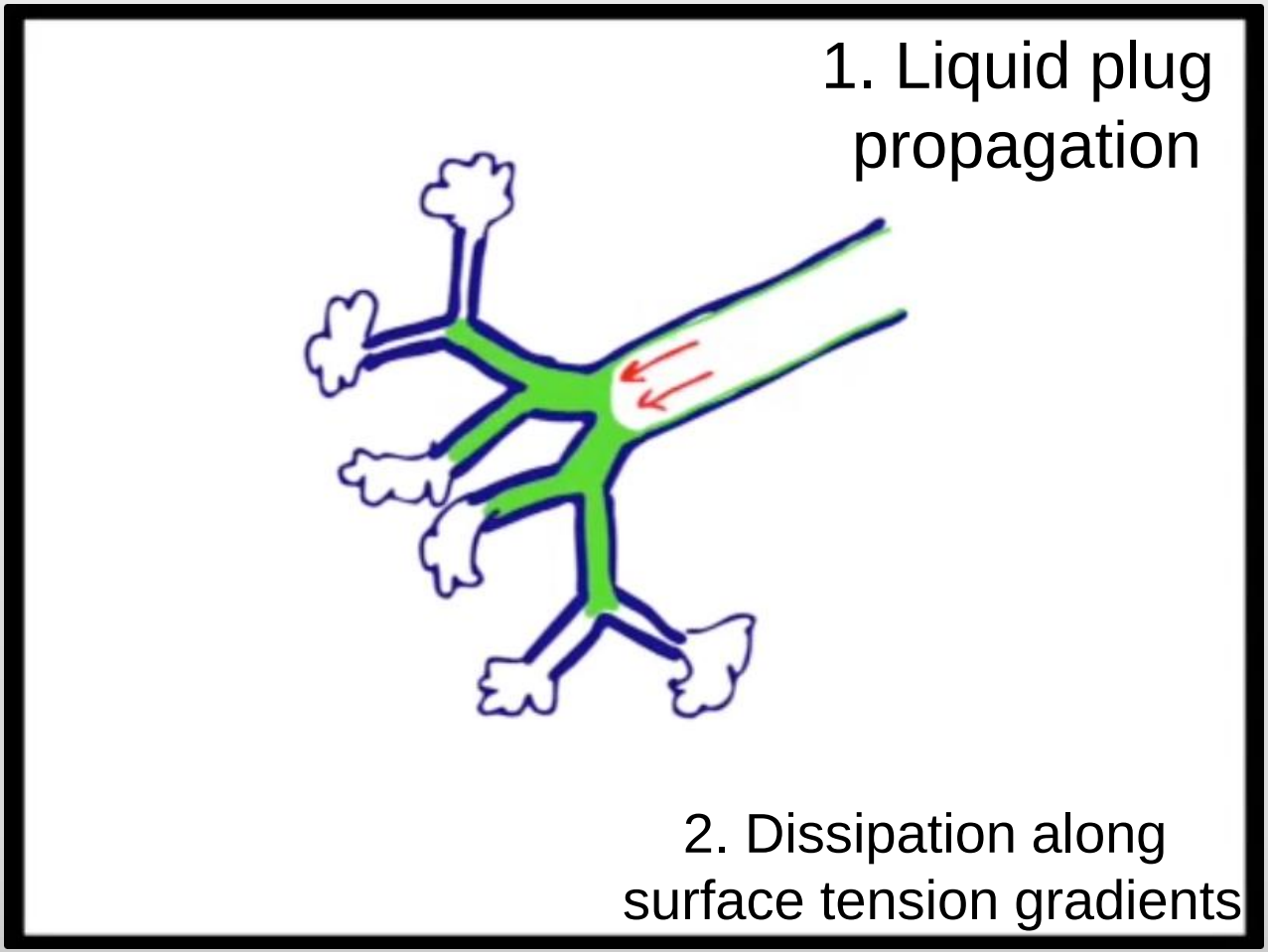

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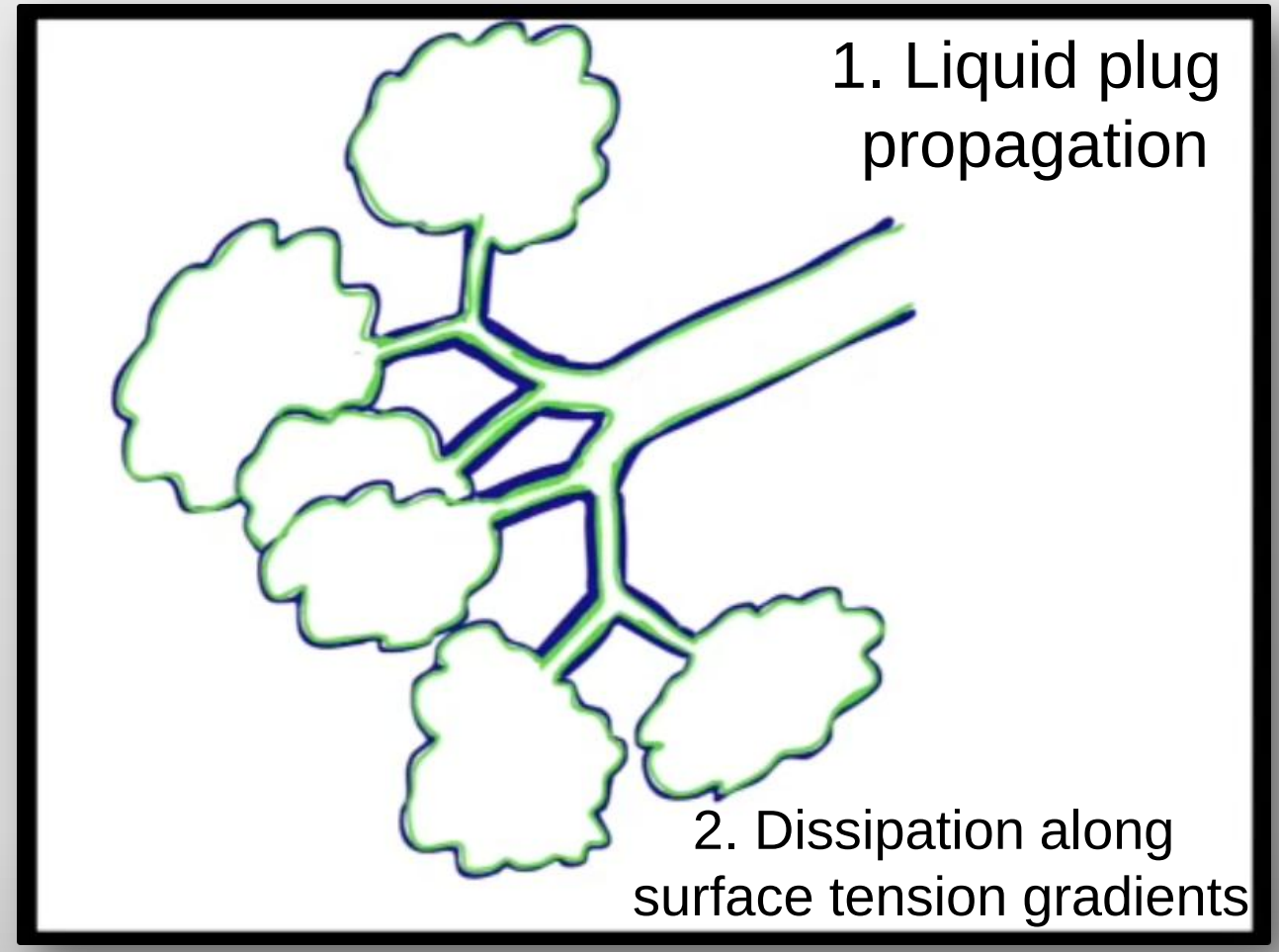
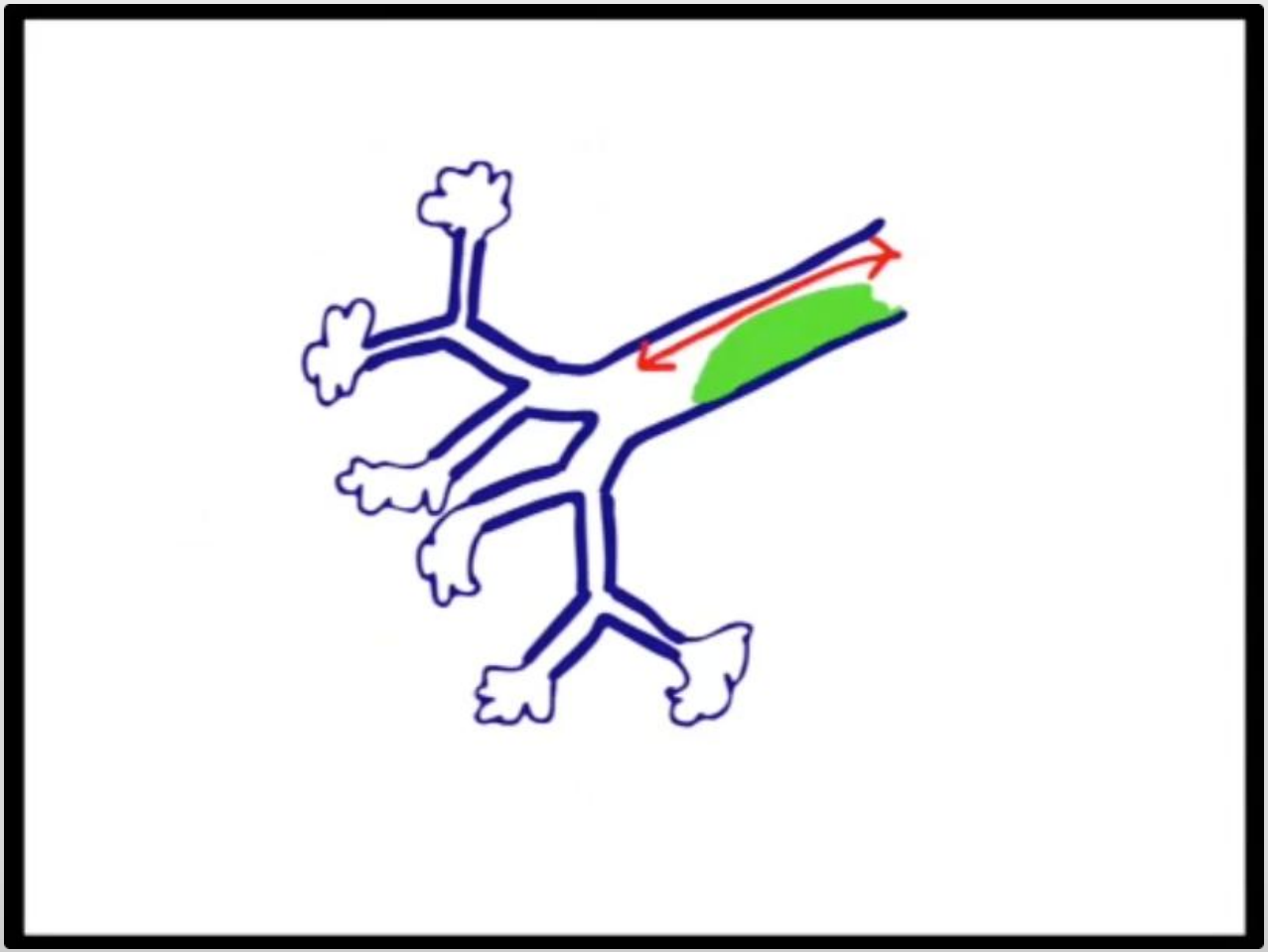


Lack of Liquid Plug



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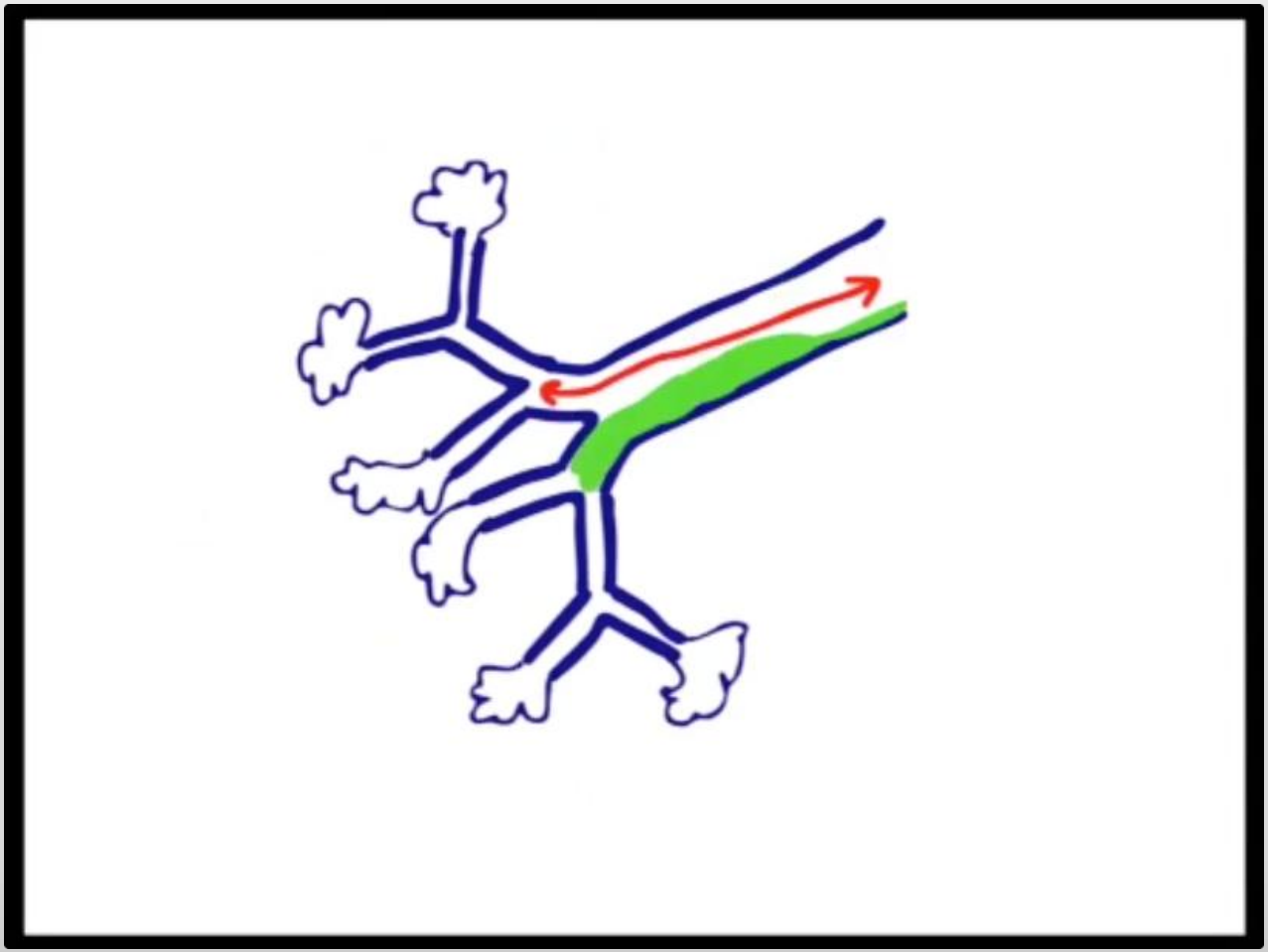

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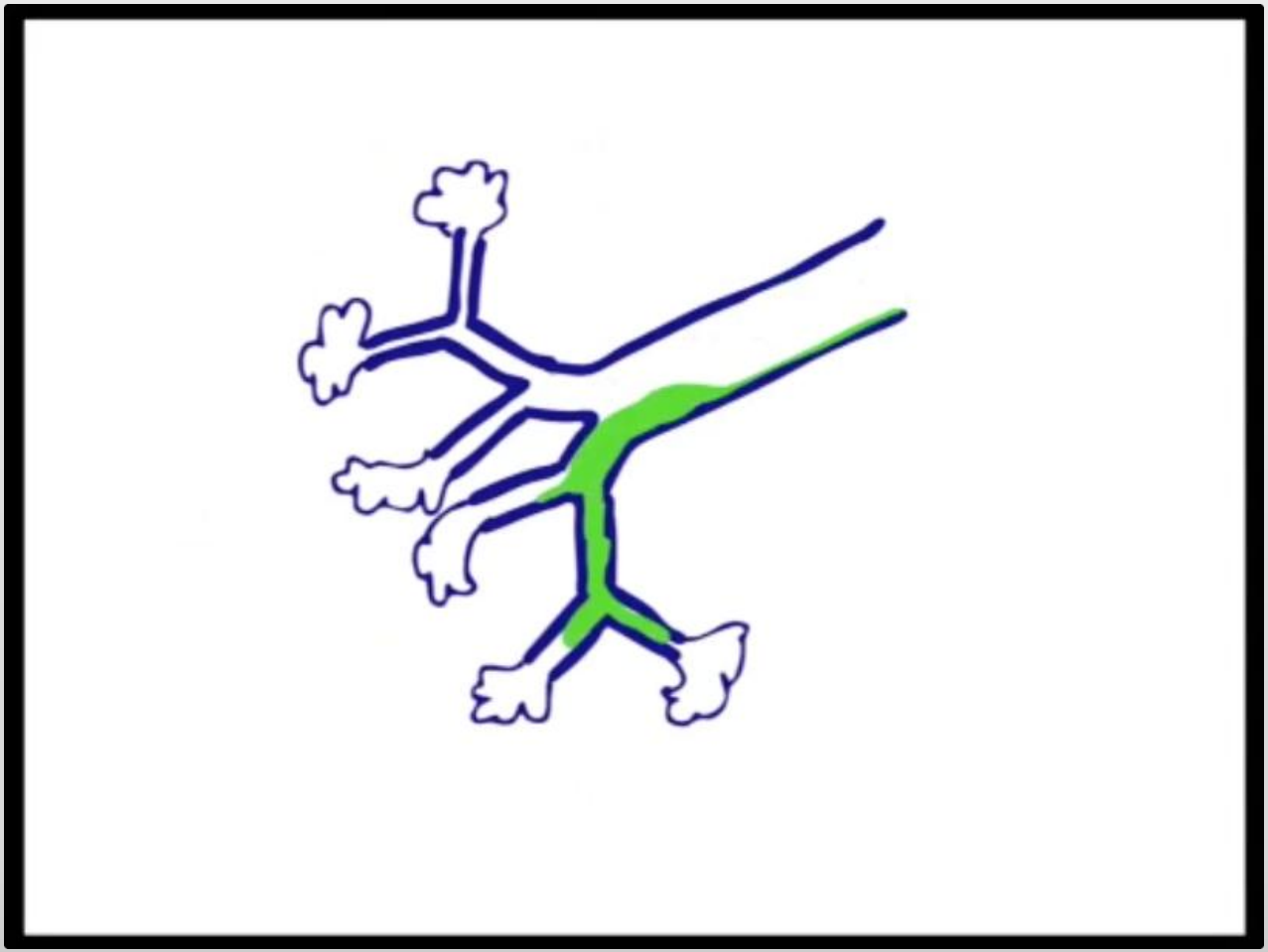

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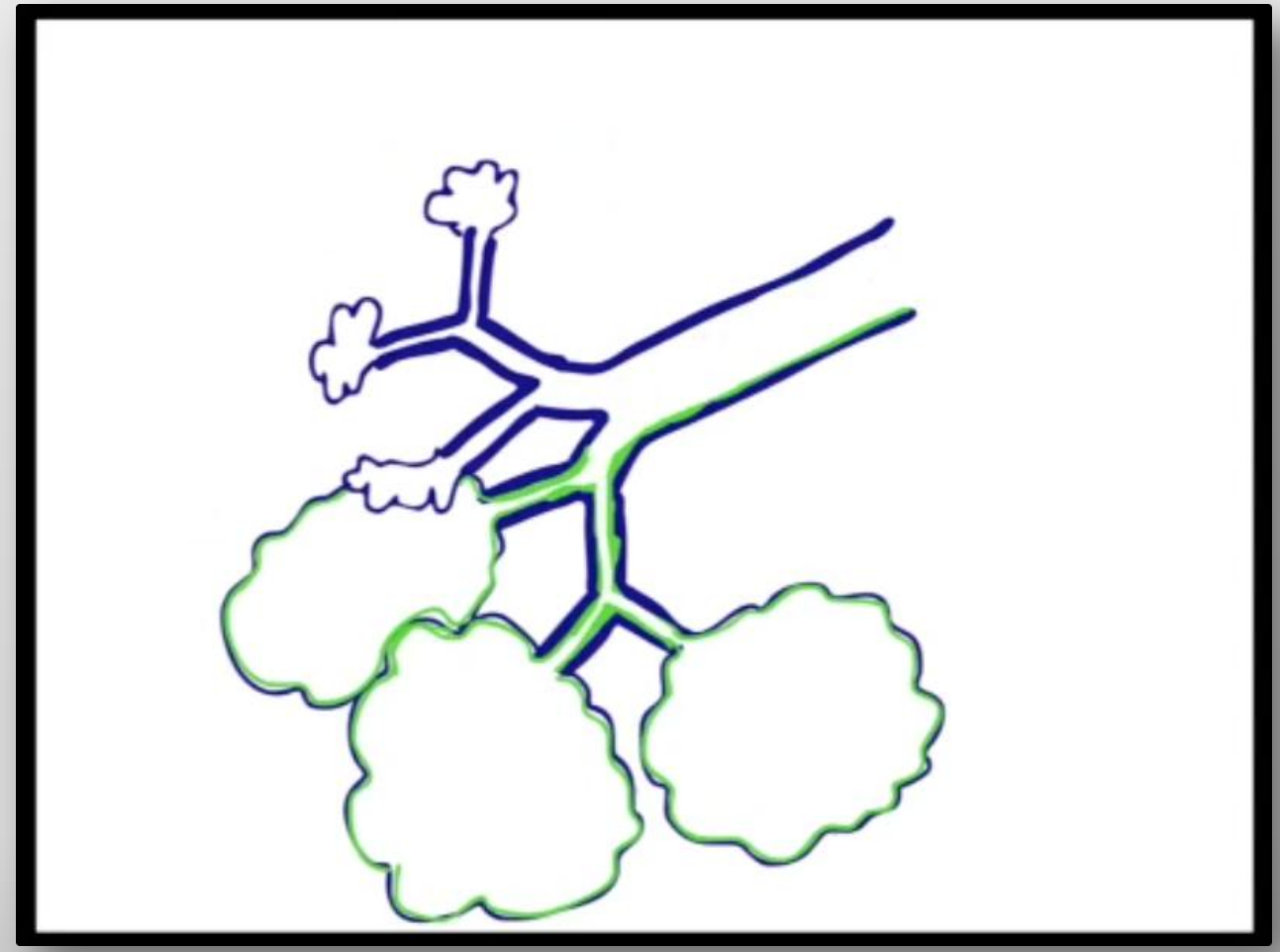
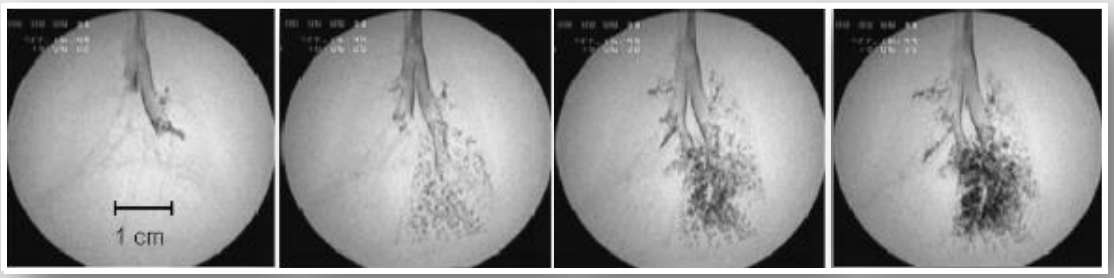


Effect of Tracheal Liquid Plug

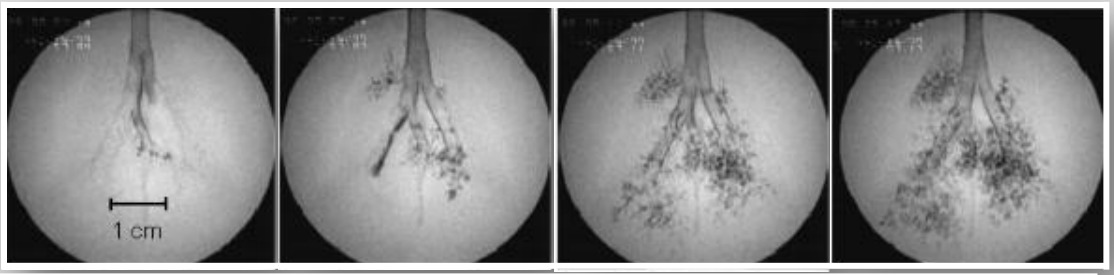
- Isolated rat lungs
- Surfactant + radiopaque tracer
- Continuous X-ray video
- Instillation w/ or w/out tracheal liquid plug

No tracheal liquid plug



1st breath 3rd breath 6th breath 10th breath

Tracheal liquid plug



1st breath 3rd breath 6th breath 10th breath

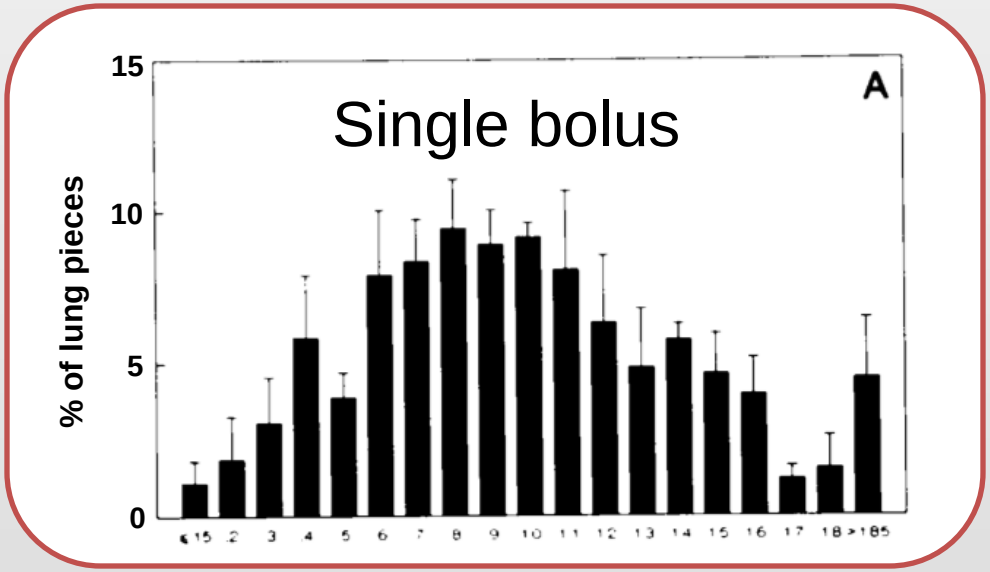
Cassidy et al. *J Appl Physiol*. 2001;90:1955-1967.

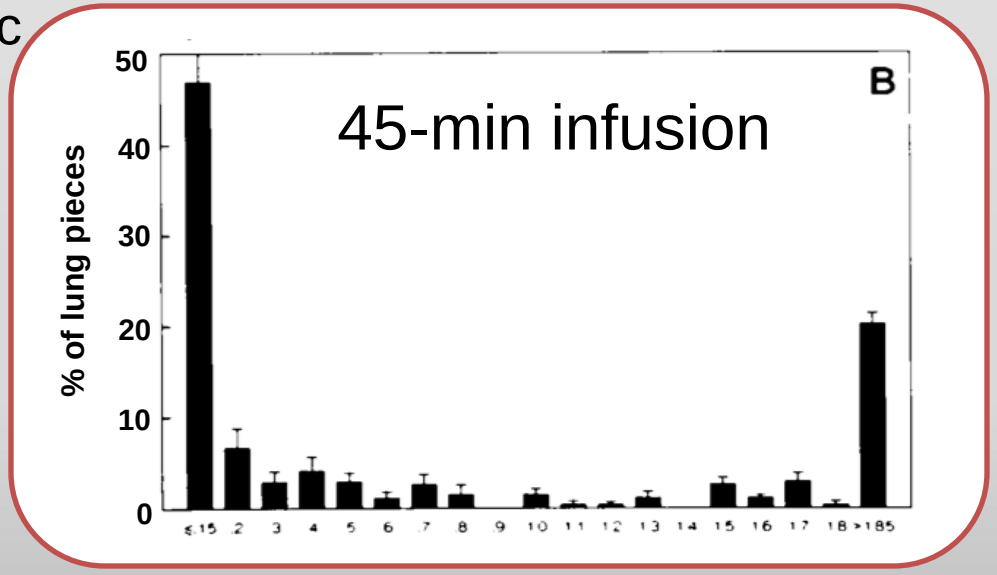
Current Doses and Protocols

	Survanta® (beractant)	Curosurf® (poractant alfa)	Infasurf® (calfactant)	Surfaxin® (lucinactant)
Total phospholipid	100 mg/kg	200 mg/kg	105 mg/kg	174 mg/kg
Total volume	4 ml/kg	2.5 ml/kg	3 ml/kg	5.8 ml/kg
Number of aliquots	4	2	2	4
Volume/aliquot	1 ml/kg	1.25 ml/kg	1.5 ml/kg	1.45 ml/kg
Position	Head and foot inclinations, right and left side dependence	No inclination, right and left side dependence	No inclination, position to right and left dependence AFTER instillation	Head inclination, right and left side dependence
Ventilation	Manual ventilation	40-60 breaths/min	Small bursts with each breath	Mechanical ventilation; PEEP 4-5 cm H_2O

Effect of Instillation Rate

- Intact adult rabbits
- poractant alfa
- Single bolus = 4 ml/kg over 10 sec
- Infusion = 4 ml/kg over 45 min

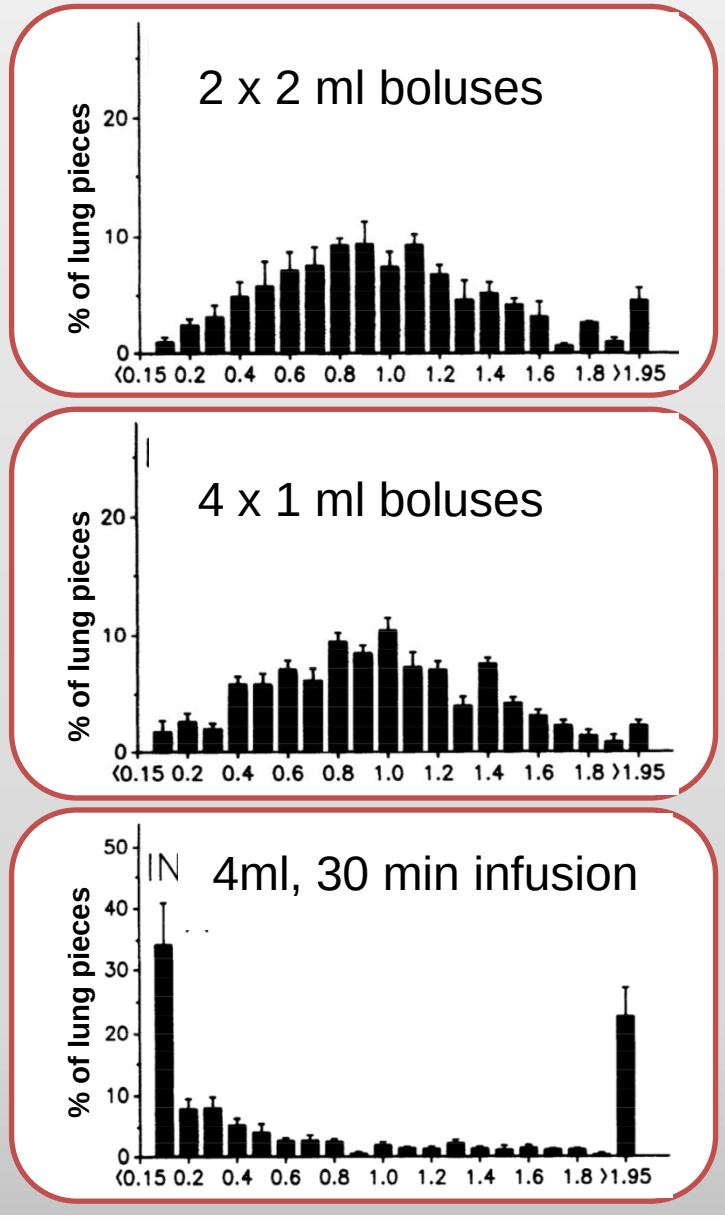




Segerer et al. *Ped Res.* 1993;34(4):490-494.

Effect of Bolus Volume

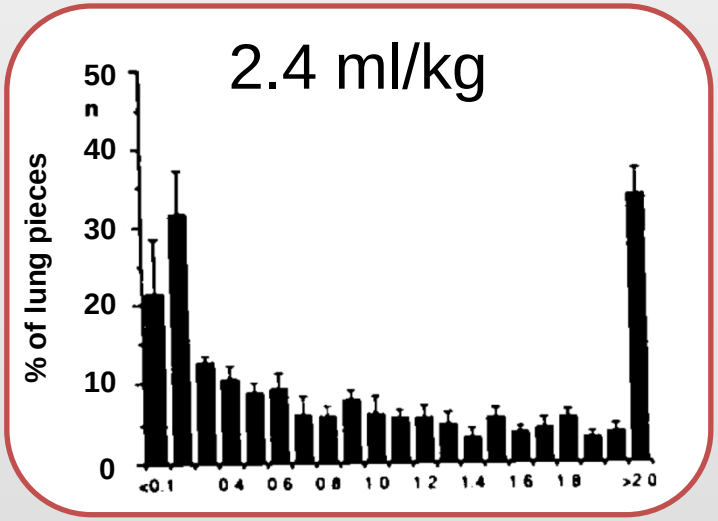
- Intact preterm lambs
- Repositioned right/left side between each bolus
- 100 mg/kg beractant

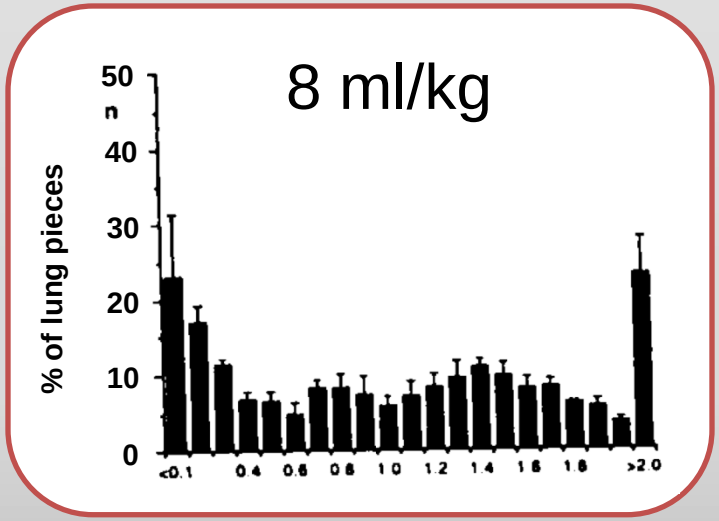


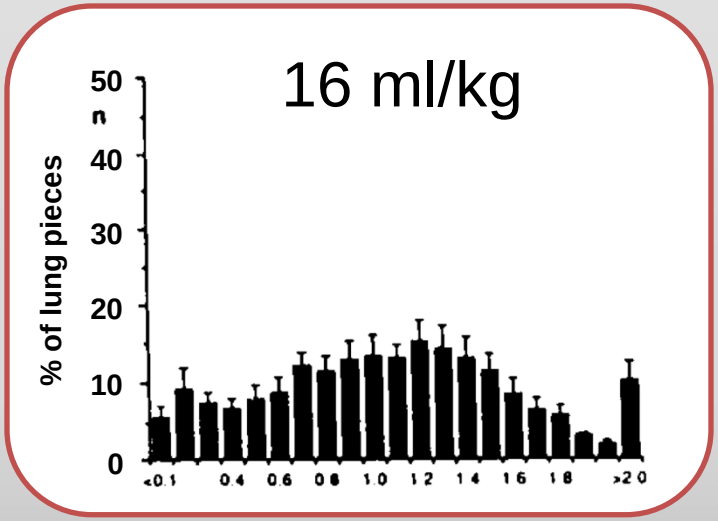
Ueda et al. *J Appl Physiol*. 1994;76(1):45-55.

Effect of Volume

- Intact adult rabbits
- 100 mg/kg bovactant
- Single bolus



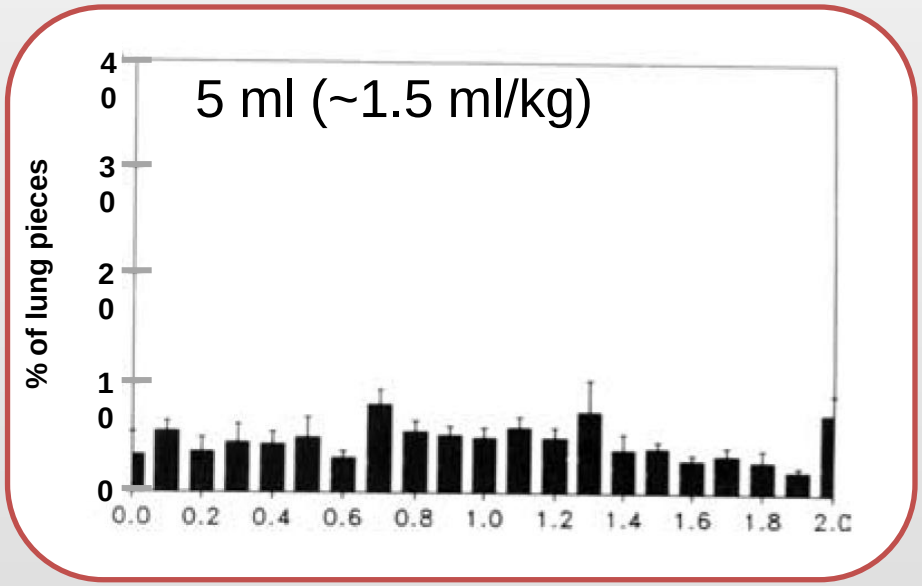


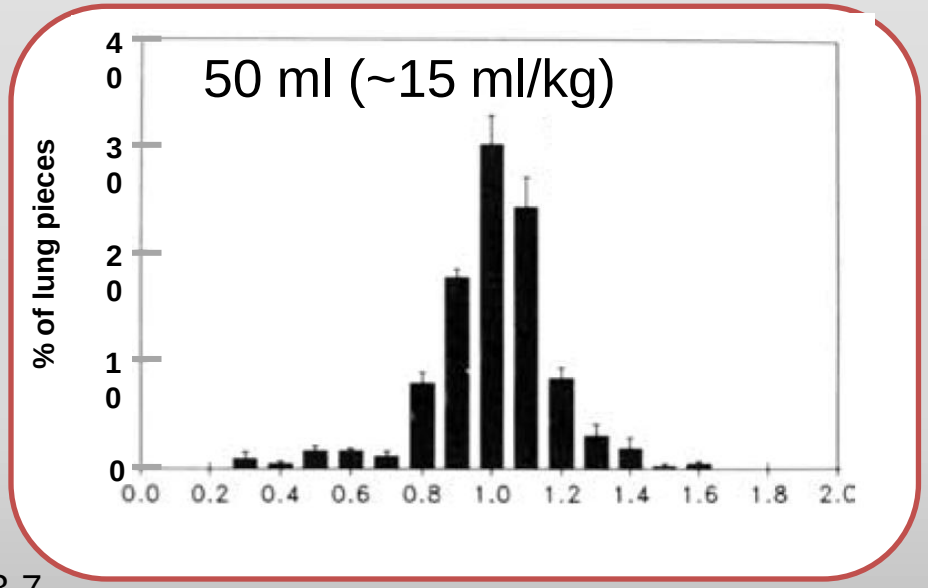


Van der Bleek et al. *Ped Res.* 1993;34:2,154-158.

Effect of Volume

- Intact adult rabbits
- Bovine surfactant
- 5 ml dose was 0.5 ml every 2 min for 20 min
- 50 ml dose was 2.5 ml every 2 min for 40 min

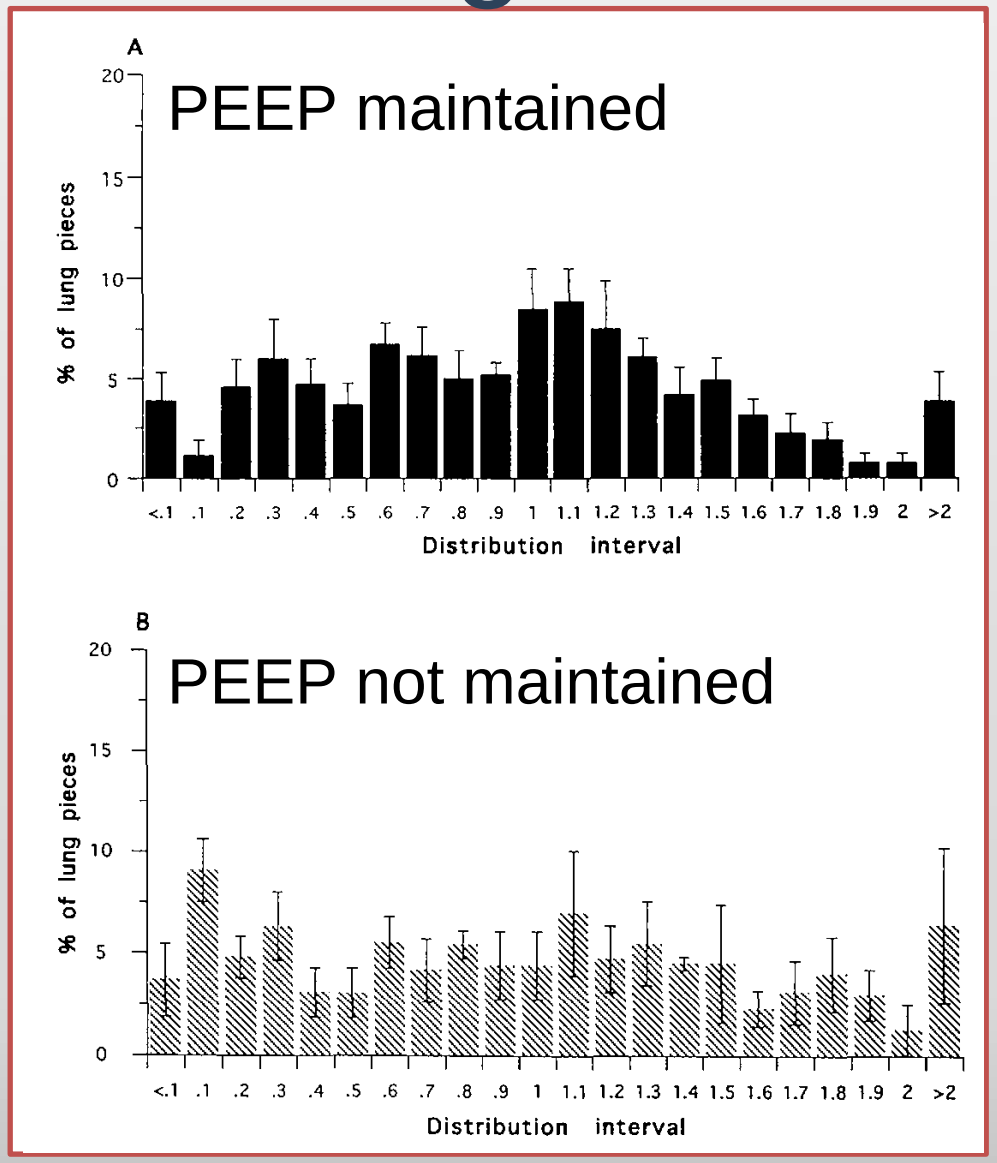




Gilliard et al. *Am Rev Respir Dis*. 1990 Mar;141(3):743-7.

Effect of Maintaining PEEP

- Premature rhesus newborns
- 200 mg of radiolabeled lucinactant
- Two boluses of 2.5 ml/kg
- With or without Bodai adapter to maintain PEEP



Merritt et al. *Ped Res*. 1995;38(2):211-217.

So Then More Is Better, Right?

Wait a sec…
What about acute effects on cerebral perfusion?

Possible Acute Effects of Surfactant on Cerebral Perfusion

- Transient hypercapnia-induced cerebral vasodilation
- Pulmonary vasodilation
  - Left-to-right shunt → Cerebral steal effect
- Increased lung volume → decreased venous return
- Pharmacologic
  - Vasoactive components in surfactant affect systemic/cerebral vascular tone?

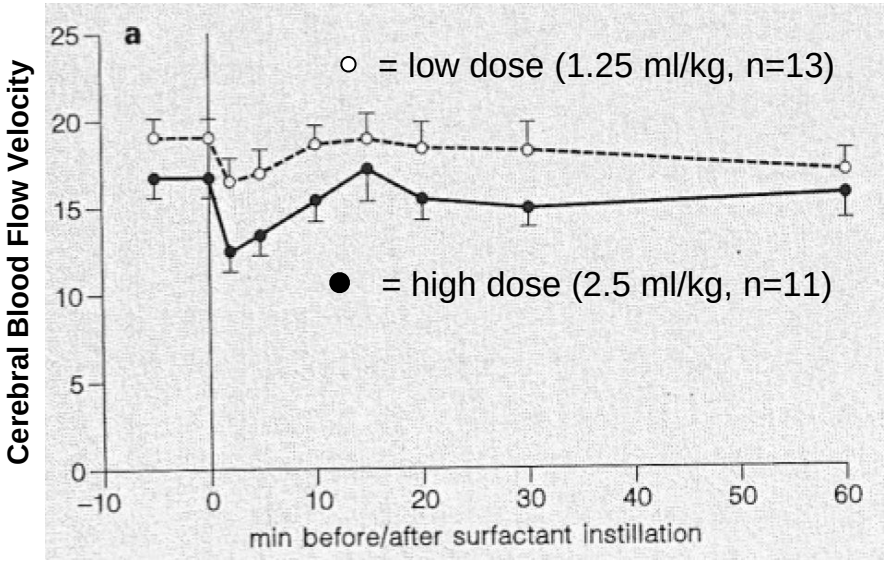
Acute Effects of Poractant Alfa on Blood Pressure and Cerebral Perfusion

	Increase	Decrease	No change
Mean Arterial Blood Pressure	0	4	5
Cerebral Blood Flow Velocity	1	4	3
Cerebral Oxygenation Status (NIRS)	1	0	3

See supplemental table in Terry et al. *Ped Res.* 2010,68(3):193-198.

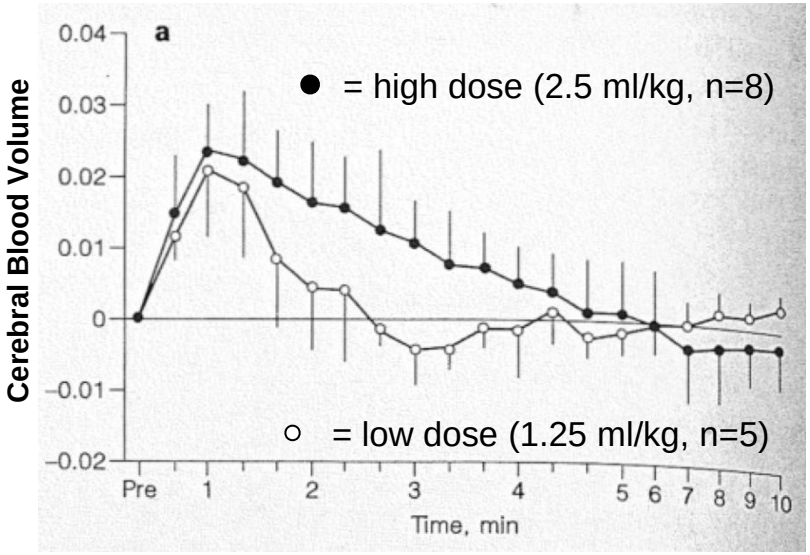
Low vs. High Dose Poractant

Internal carotid blood flow velocity



(Doppler ultrasound)

Change in cerebral blood volume



(Near infrared spectroscopy)

Rey et al. *Biol Neonate.* 1994;66:16-21.

Dorrepaal et al. *Biol Neonate.* 1993;64:193-200.

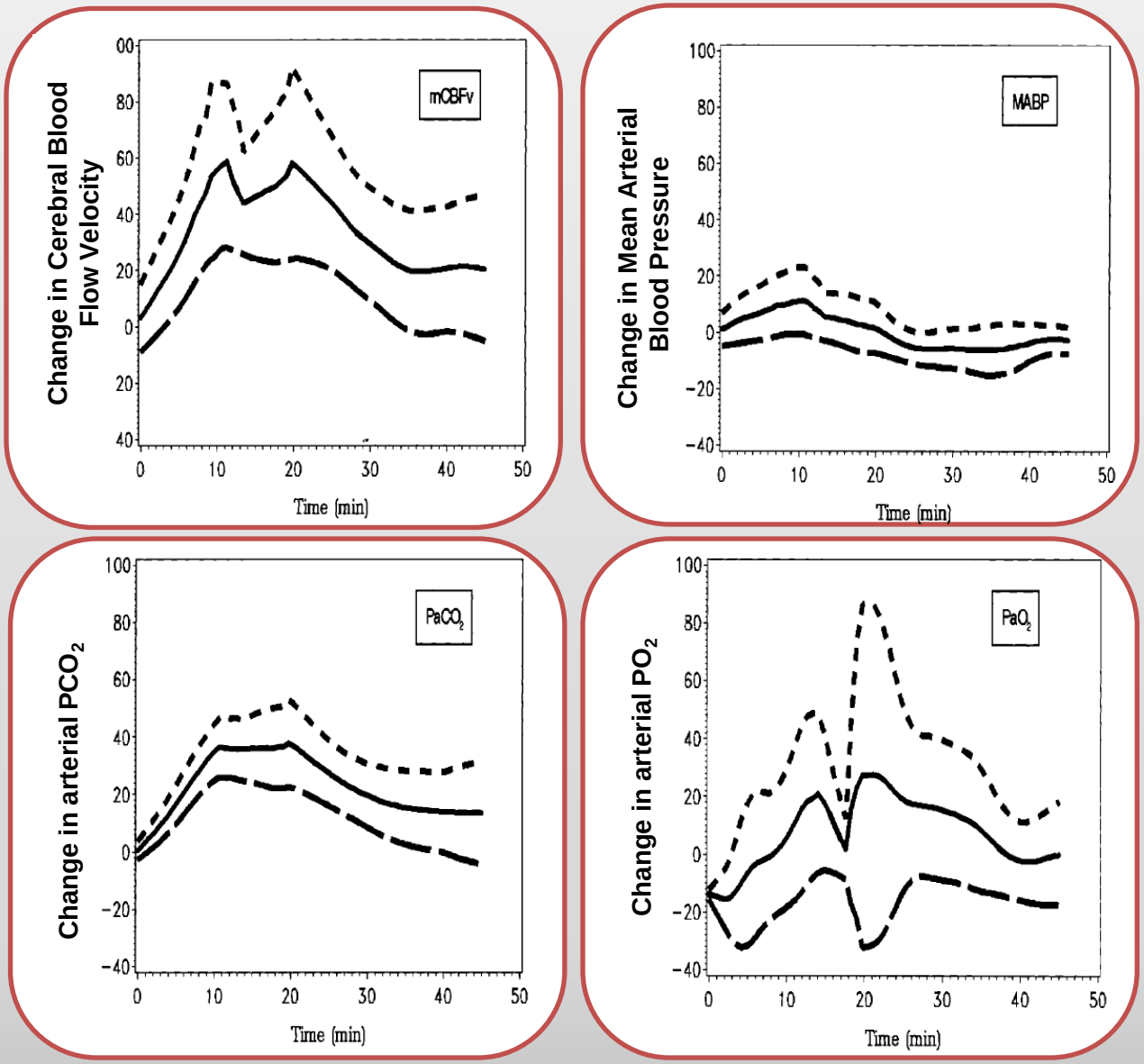
High vs. Low Dose Poractant

- Infants received initial doses of 100 mg/kg (n=1069) or 200 mg/kg (n=1099)
- No difference in incidence of intraventricular hemorrhage (16.0% in low dose vs 16.6% in high dose)
- High dose group had better oxygenation at 1, 12, and 36 hours

Halliday et al. *Arch Dis Child.* 1993;38:276-280.

Effect on Cerebral Perfusion- Beractant (4 ml/kg)

14 newborn infants



Kaiser et al. *J Pediatr.* 2005;144:809-814.

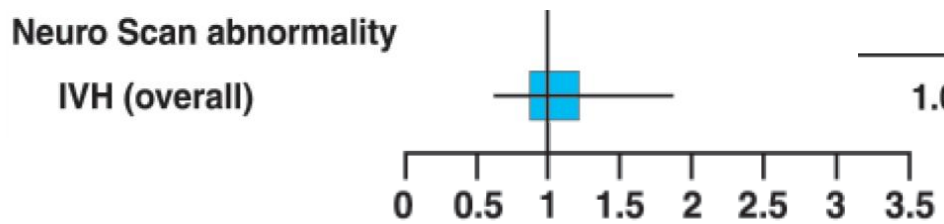
Multicenter Comparisons of Surfactants With Varying Dose Volumes

Poractant (2.5 ml/kg) vs. Beractant (4 ml/kg)

Table 2 Outcomes by Groups as Randomized and for the Subgroup ⩽32 wk

Outcome	Poractant Alfa 100 mg/kg (n = 96)	Poractant Alfa 200 mg/kg (n = 99)	Beractant 100 mg/kg (n = 98)
IVH grade III–IV	9 (9%)	8 (8%)	9 (9%)
Infants ⩽ 32 wk	**(n = 85)**	**(n = 95)**	**(n = 90)**
IVH grade III–IV	8 (9%)	7 (7%)	8 (9%)

Poractant (2.5 ml/kg) vs. Lucinactant (5.8 ml/kg)



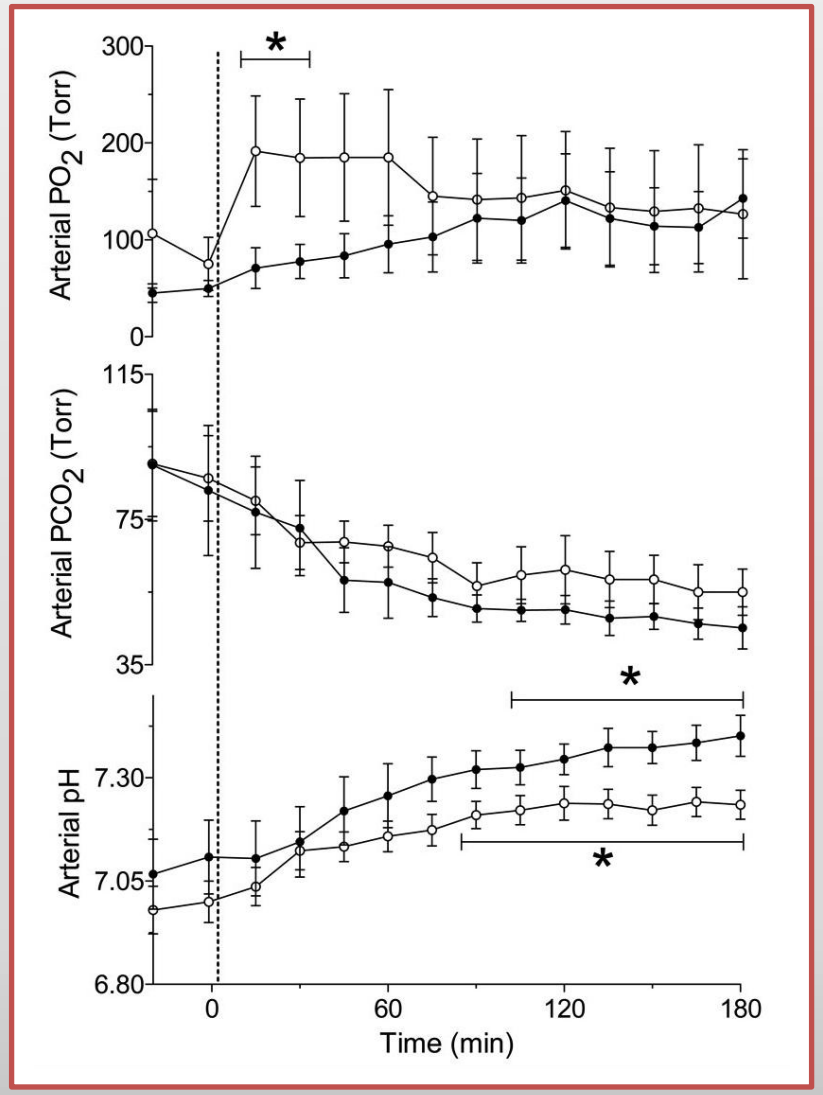
	Odds Ratio (95% CI)	Lucinactant Rate (%)	Poractant Rate (%)	*P* Value
Neuro Scan abnormality				
IVH (overall)	1.06 (0.55, 2.02)	38.7	37.9	0.87

Ramanathan et al. *Am J Perinatol*. 2004;21:3,109-119.

Sinha et al. *Pediatrics.* 2005;115:1030-1038.

Low Volume vs. High Volume (Poractant vs. Lucinactant)

- ○ Low Volume (poractant- 2.5 ml/kg)
- ● High Volume (lucinactant- 5.8 ml/kg)



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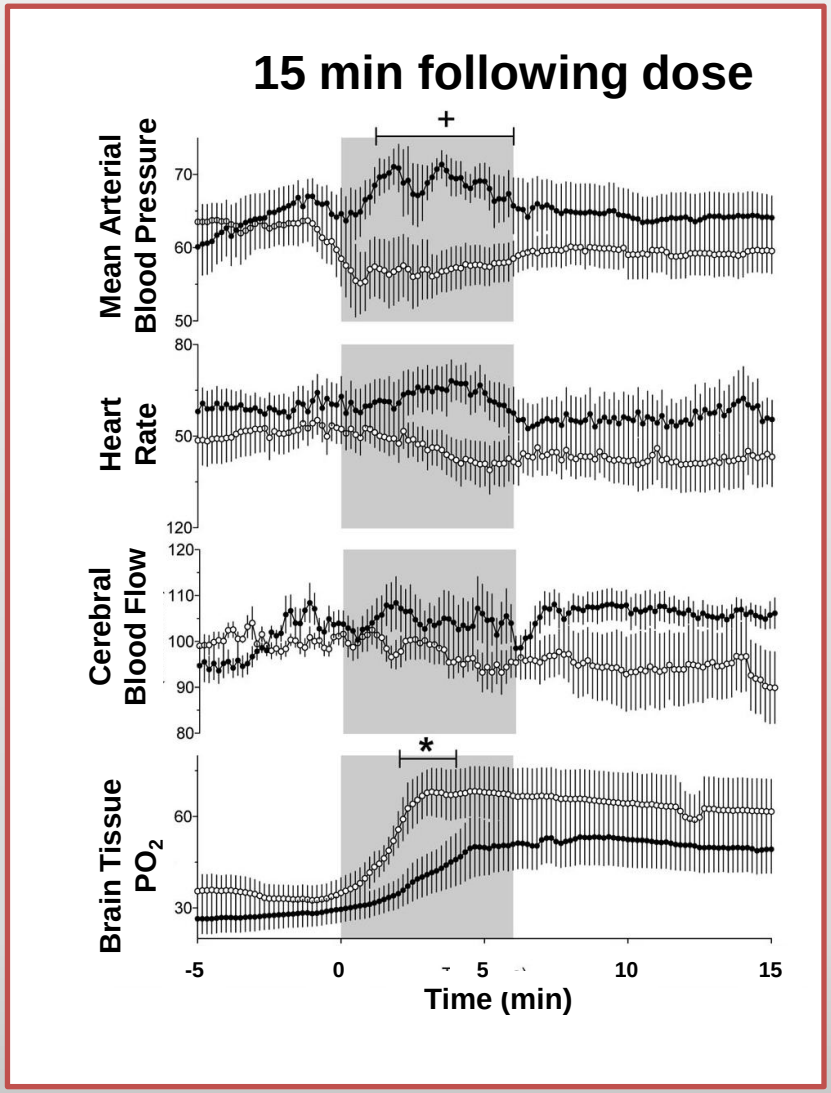

6 preterm lambs
(n= 6 per group)

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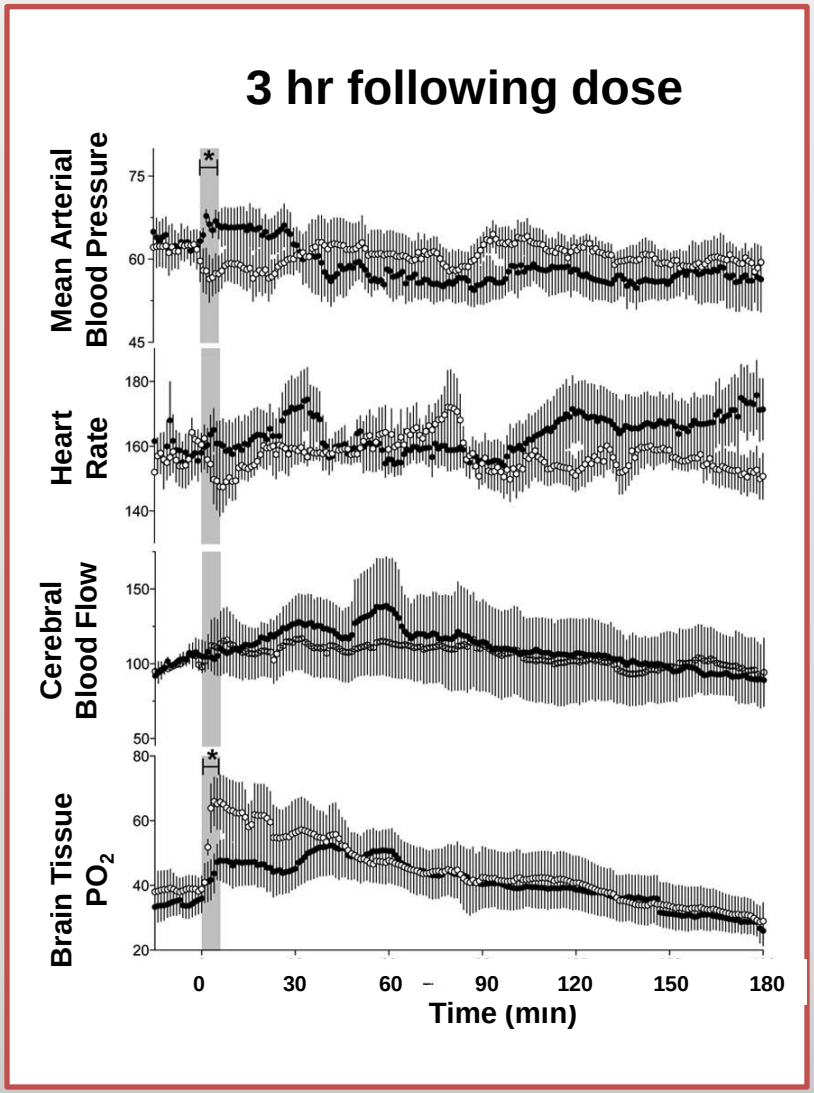

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Conclusions

- Larger volume of surfactant bolus instillation results in more uniform distribution of the surfactant in the lung.
- There is no convincing evidence that the volume used in any current clinical formulations results in detrimental disturbances in cerebral perfusion.

Future Areas for Study

- Could we give more volume?
- What are the ideal ventilation parameters?
- How will aerosolized surfactant compare?

Acknowledgements

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Gordon Power
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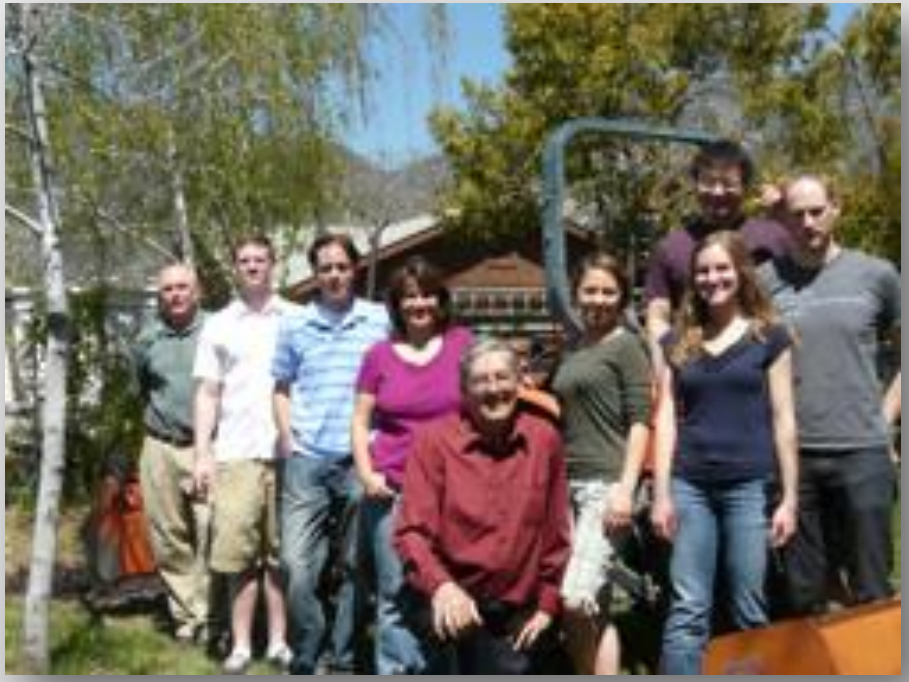
Shannon Bragg
Allen Merritt

Michael Terry
Jeanette Merrill-Henry



QUESTIONS?

New Perspectives in the Management of Neonatal Respiratory Distress Syndrome

A free CE-accredited satellite symposium

Chair: Stephen Welty, MD; Texas Children's Hospital

Supported by an educational grant from DiscoveryLabs. Inspired Innovation

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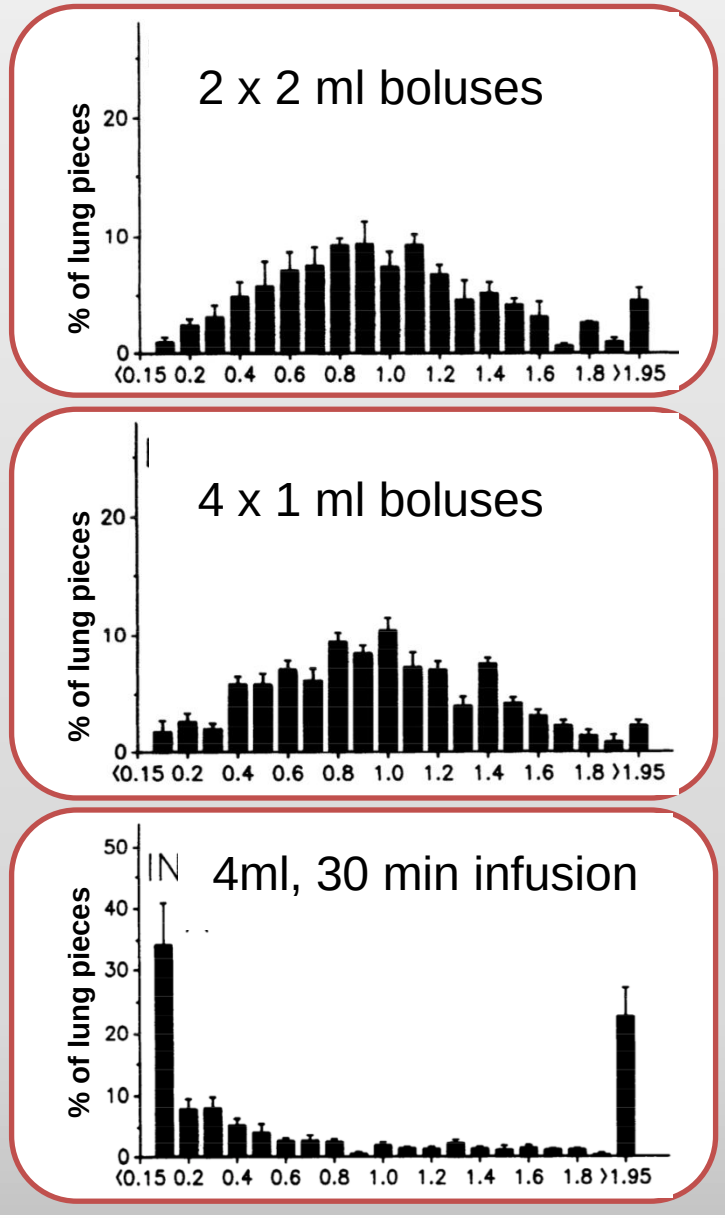

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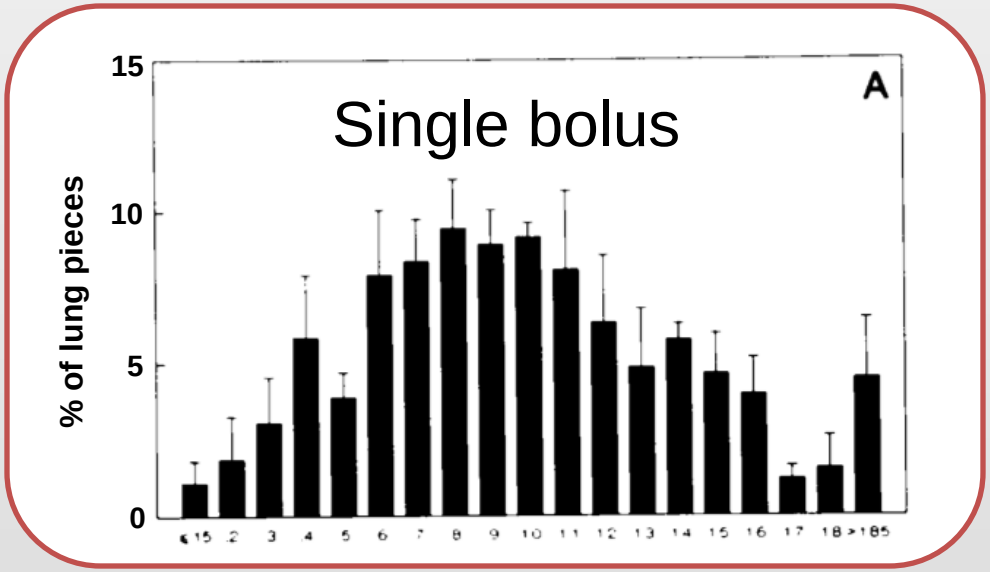

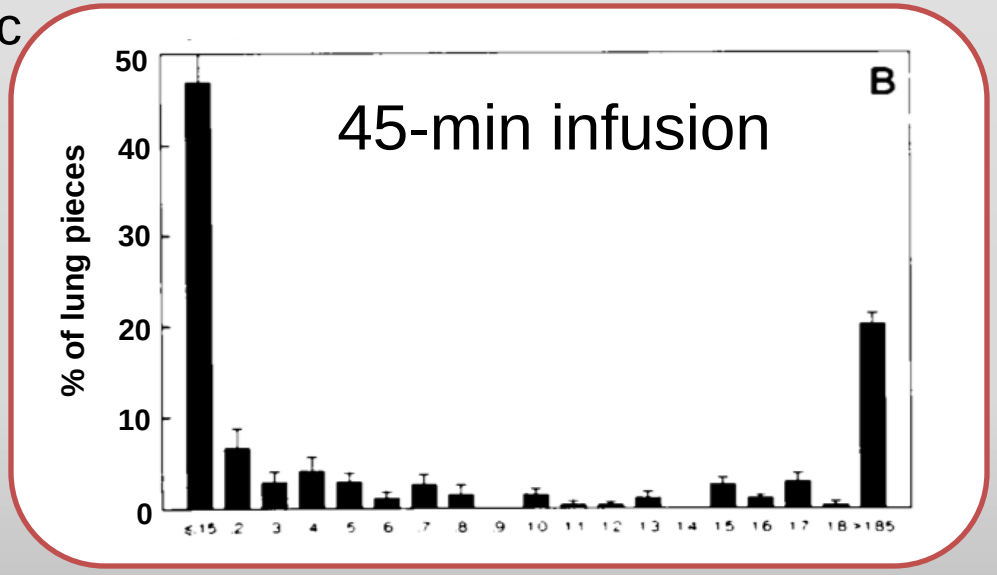

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