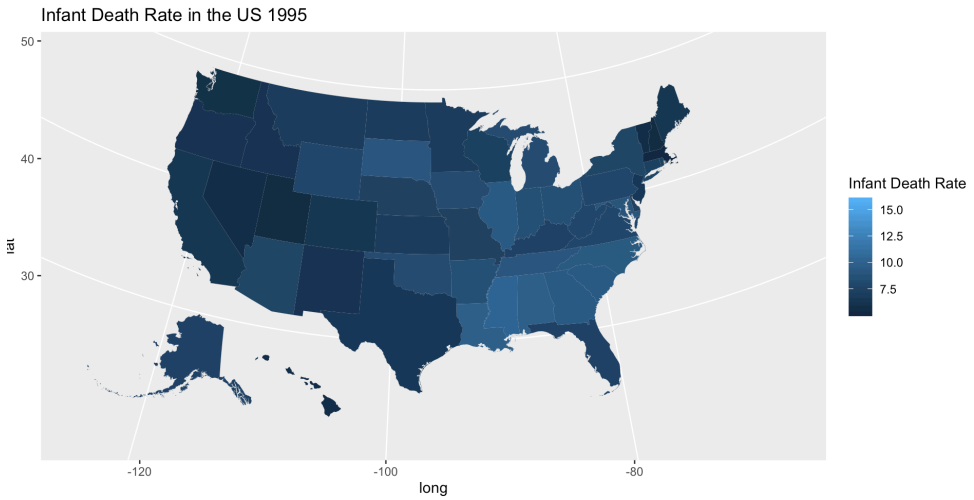
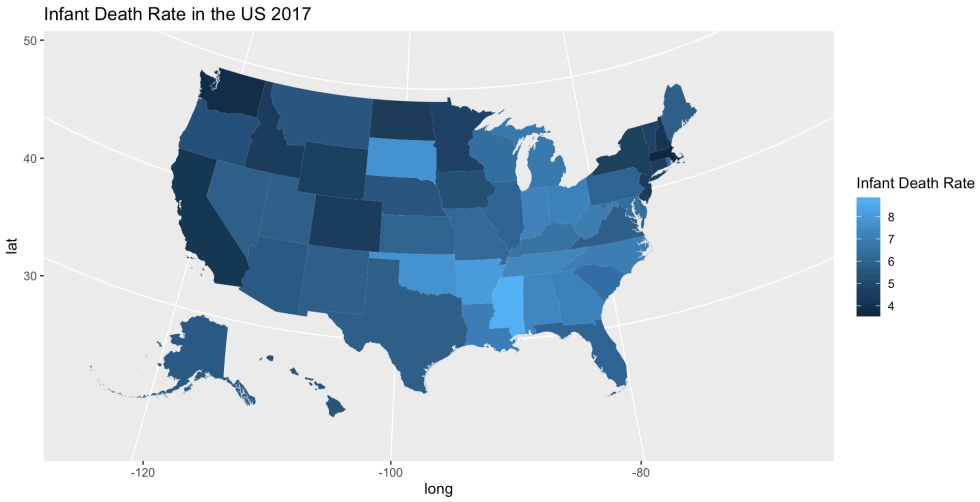
The Problems of Prematurity and BPD

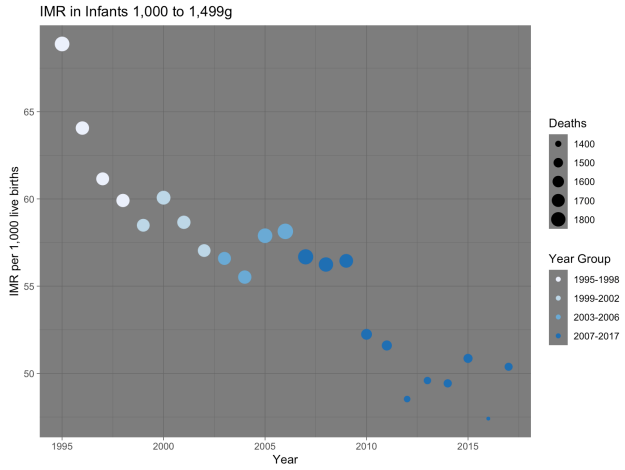
Infant Mortality In The United States



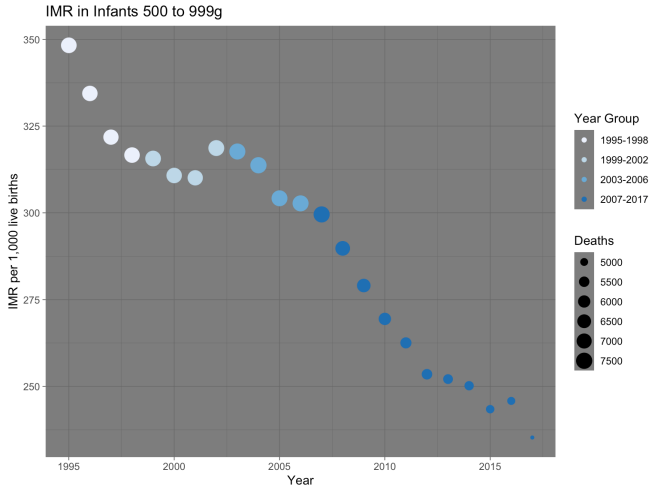


Improvements Amongst The Smallest Infants

Improvements in IMR in Infants 1,000 to 1,499g.



Improvements in IMR in Infants 500-999g.



The Smallest Infants Impact Infant Mortality The Most….

- Overall we are doing better over the last 30 years for infants born under 32 weeks and under 1,500 grams.
  - More babies are surviving now then ever before at these fragile ages.
- But in the US in 1995:
  - 48.4% of infant mortality was in infants less than 1,500 grams.
  - 42.1% of infant mortality was in infants less than 1,000 grams.
- Now in the US in 2017:
  - 53% of infant mortality was in infants less than 1500 grams.
  - 46.9% of infant mortality was in infants less than 1,000 grams.
- Maybe most important 16.9% of infant mortality was in infants born 22 weeks or less in 1995 but that has risen to 23.1%.

Changing Morbidities Over Time

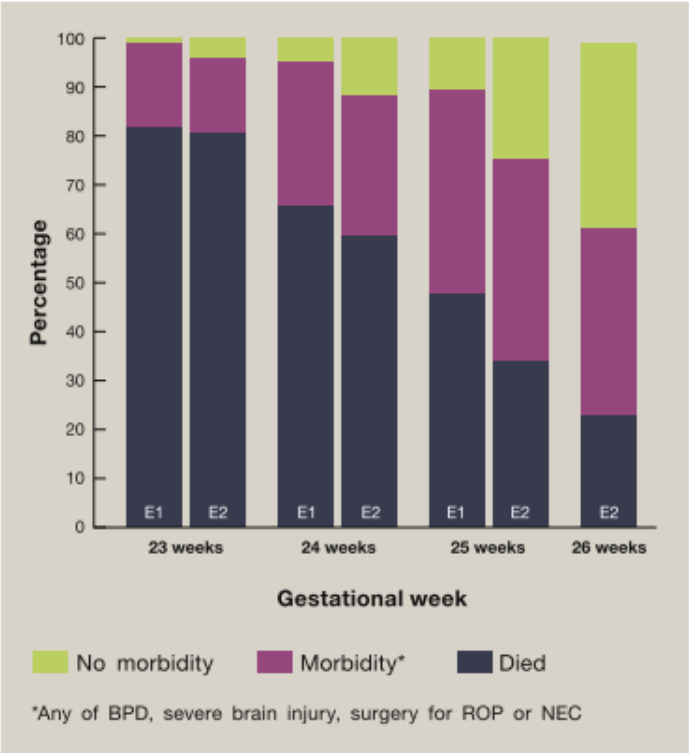
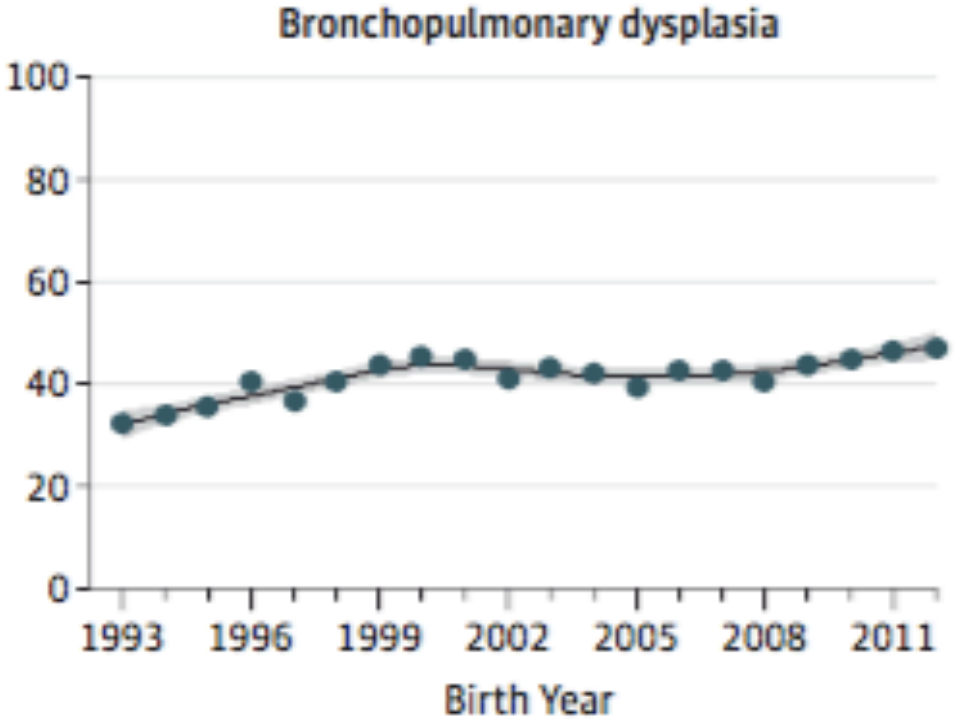
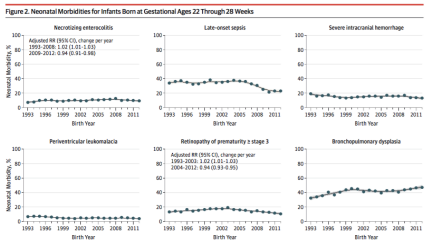


Figure 1 Survival with and without neonatal morbidity in EPICure (E1) and EPICure-2 (E2) by gestational week. Neonatal morbidity is any of bronchopulmonary dysplasia (BPD), severe brain injury, surgery for retinopathy of prematurity (ROP) or necrotising enterocolitis (NEC).

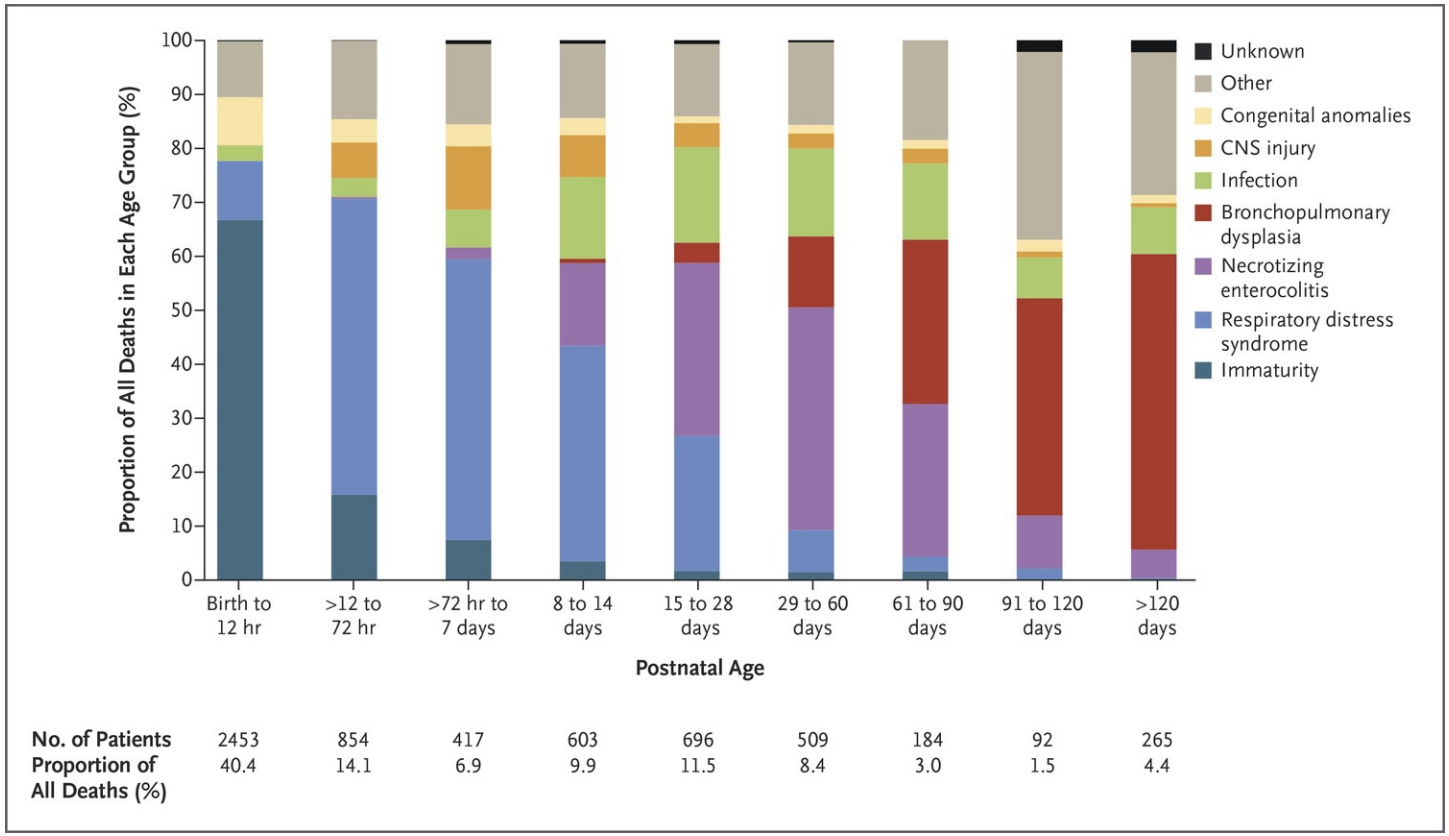
Common Morbidities





What this represents is that while some complications are getting less frequent the most important one involving the lungs is getting worse.

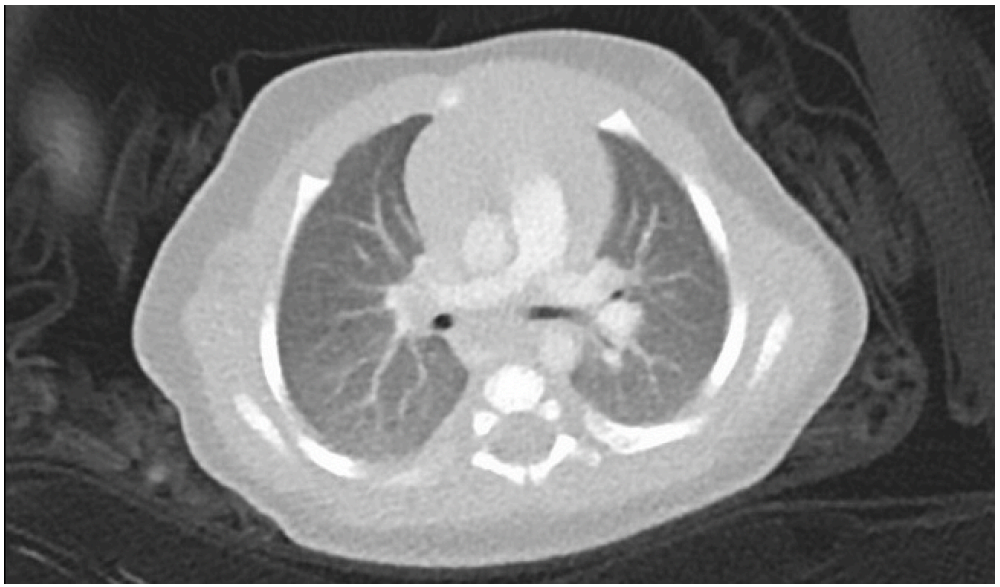
Causes of Death in Neonates Now



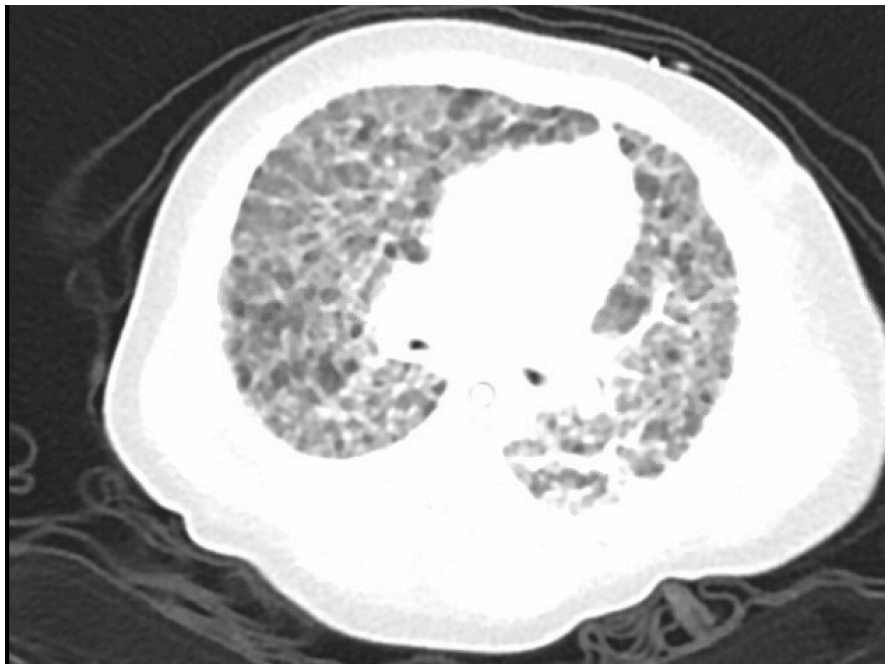
Breathing For Infants Often Helps And Hurts

- The youngest need the most respiratory support.
- The consequence of needing support for the longest and at the highest levels is often that the:
  - Support that saves your life threatens your life and your future health.
  - The lungs of preterm infants are far from developed and while they can support breathing they are fragile.
  - Think of them like young fragile trees with few leaves exposed to high wind.
- It is not just the lungs but the eyes, brains and intestines that are all too fragile too often for the exposures.

Normal Lungs



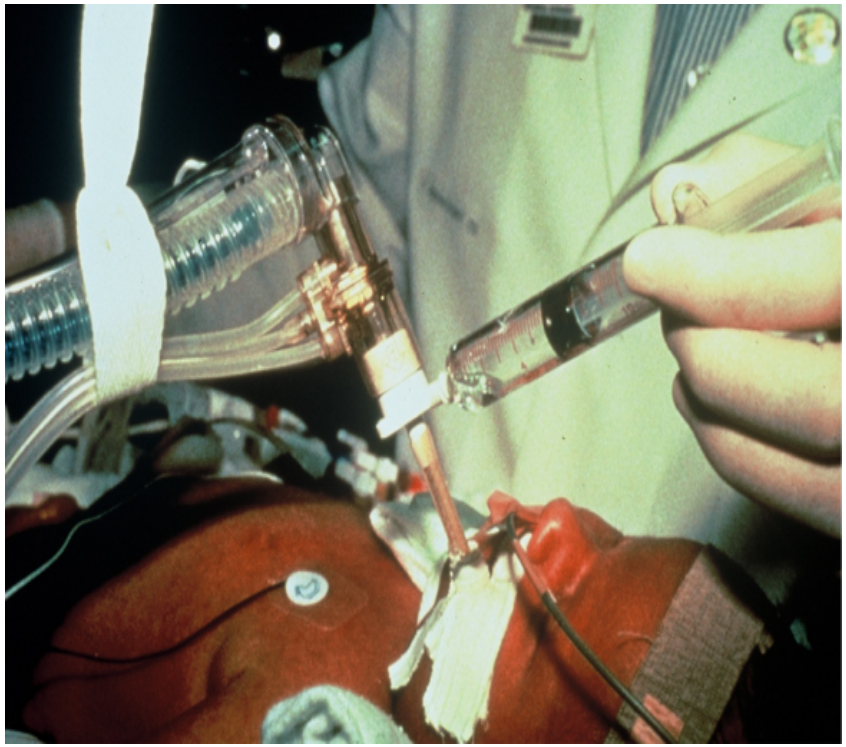
Damage Caused By The Care We Provide

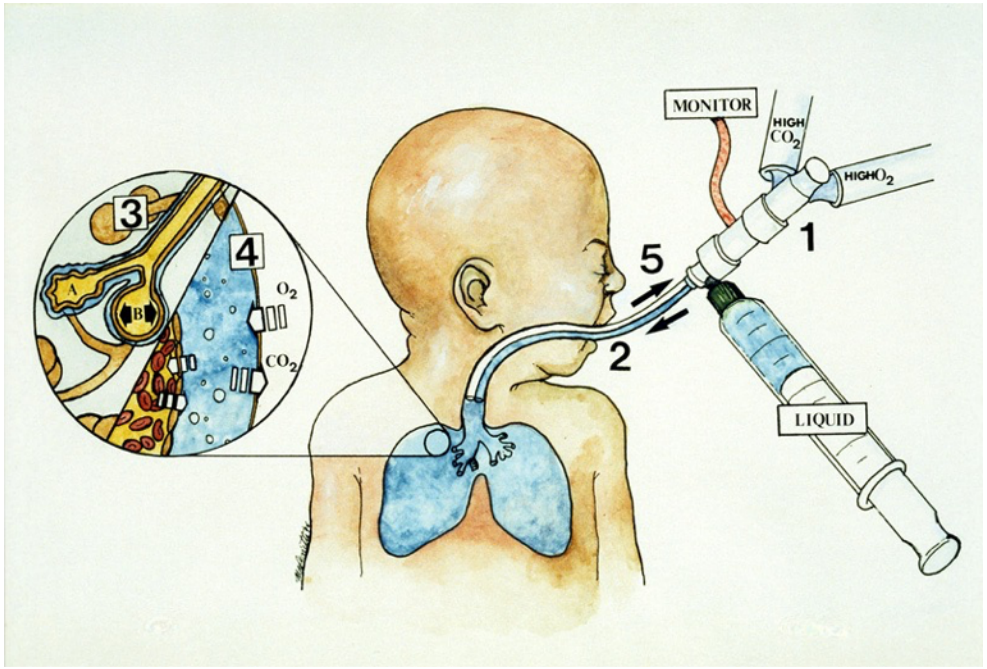


Breathing a liquid instead?

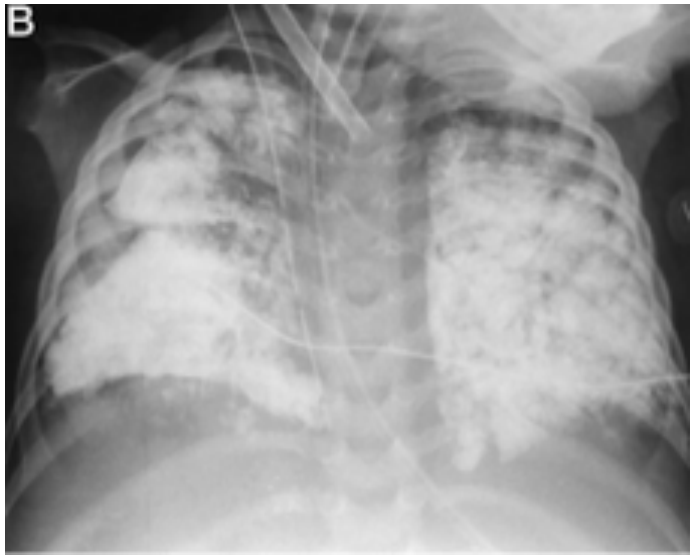
- The concept of liquid breathing is not new.
- Attempts have been made for decades with a variety of liquids including saline.
- While some liquid have been successful it wasn't until efforts with a special group of liquids, perfluorochemicals, were successful in infants that the possibility was seriously considered.
- Offers the option to establish once again a liquid-liquid interface for the immature lung and exchange gases while diminishing lung injury.

How is it given??





Chest Xray



What If We Didn’t Breathe Air?

Preclinical Work

Wolfson and Shaffer

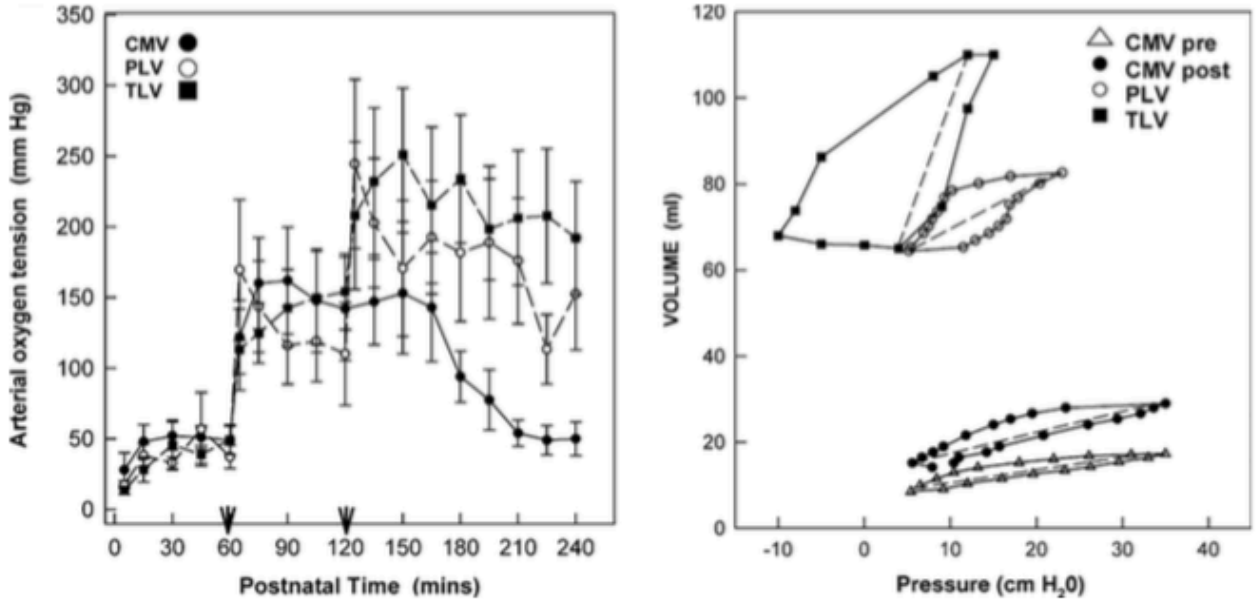


Figure 3 Preterm lambs (124 ± 4 days gestation) were delivered by caesarean section, supported using conventional mechanical ventilation (CMV) for 1 h then treated with surfactant and randomised to CMV, partial liquid ventilation (PLV) or tidal liquid ventilation at 2 h. The improvement in arterial oxgenation (left) following surfactant treatment dissipated during CMV but was further improved during either PLV or TLV. Perfluorochemical (PFC) ventilation markedly decreased the ventilatory pressures (right) required to support gas exchange and tidal volume with the greatest improvement in both oxygenation and compliance (slope of the pressure–volume loop) being noted with TLV.

Wolfson and Shaffer

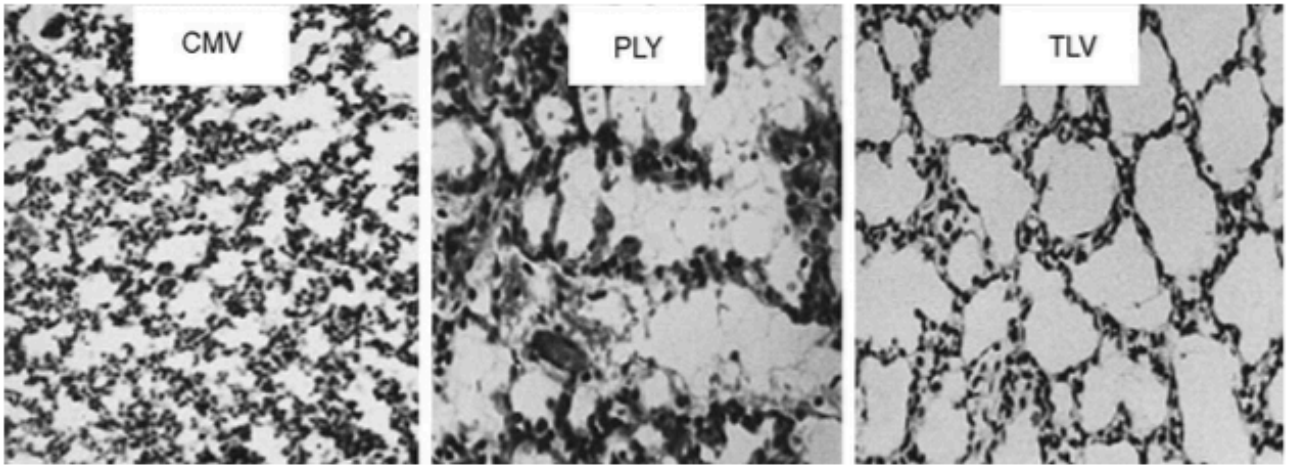


Figure 4 Lung histomicrographs of matched regional sections obtained from the surfactant-treated preterm lambs described in Figure 3, following 4 h of conventional mechanical ventilation (CMV), partial liquid ventilation (PLV), or tidal liquid ventilation (TLV). Ventilation with perfluorochemical (PFC) liquid improved overall expansion; however, marked heterogeneity and alveolar debris were noted following PLV. In comparison, following TLV, lungs were homogenously expanded, free of debris and with less evidence of inflammatory cells.

Pulmonary applications of perfluorochemical liquids: ventilation and beyond. 2005;6(2):117-127. doi:10.1016/j.prrv.2005.03.010. Pediatric Respiratory Reviews.

Past Clinical History

Early Clinical Experience

- Efforts at liquid breathing are quite old.
- Reports of mammals breathing liquids, saline, date back many years.
- Other liquids as well have been investigated:
  - Oils
  - Silicone
- Non-suitable:
  - Direct lung injury.
  - Surfactant inactivation.

ORIGINAL ARTICLE

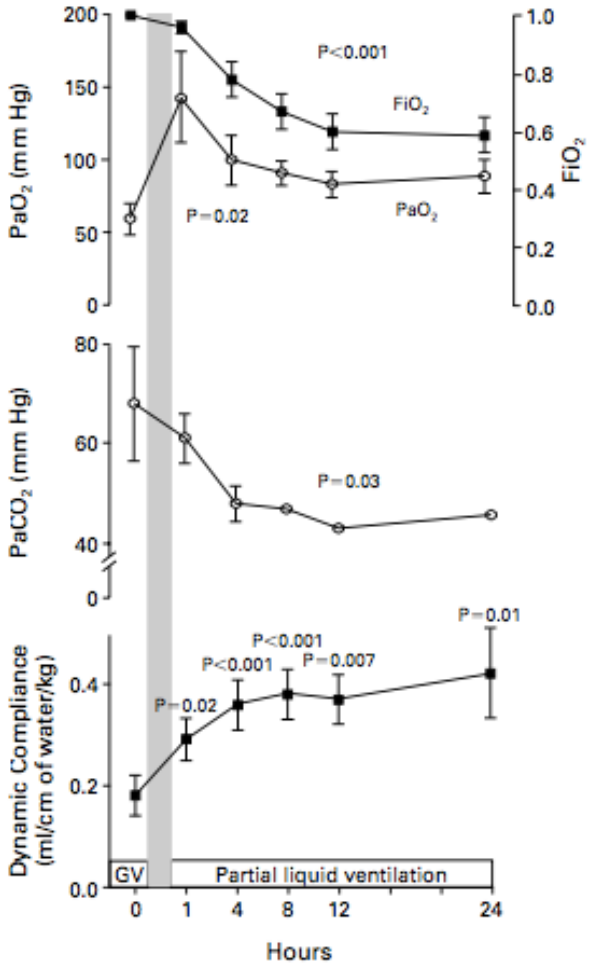
A Correction Has Been Published

Partial Liquid Ventilation with Perflubron in Premature Infants with Severe Respiratory Distress Syndrome

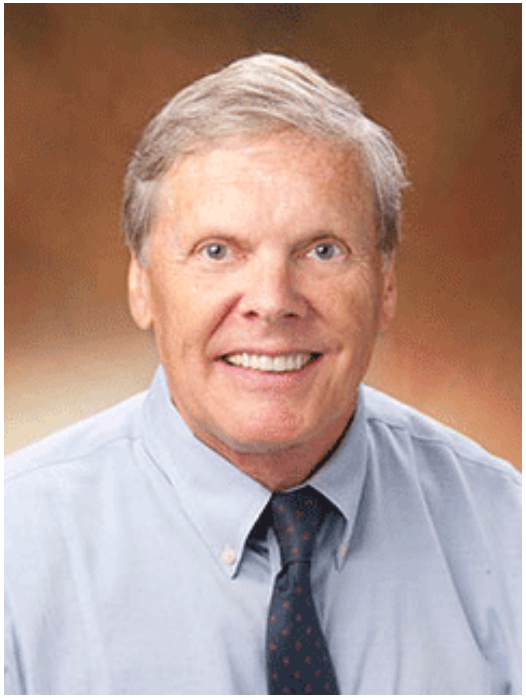
Corinne Lowe Leach, M.D., Ph.D., Jay S. Greenspan, M.D., S. David Rubenstein, M.D., Thomas H. Shaffer, Ph.D., Marla R. Wolfson, Ph.D., J. Craig Jackson, M.D., Robert DeLemos, M.D., and Bradley P. Fuhrman, M.D., for the LiquiVent Study Group*

N Engl J Med 1996; 335:761-767 | September 12, 1996 | DOI: 10.1056/NEJM199609123351101

- Reported on the use of Perfluorooctyl Bromide in preterm infants.
- 13 infants.
- Mean BW – 1057g.
- Mean GA – 28 weeks.
- Mean hour at treatment – 44h
- Mean duration of treatment – 42h.
- 8 of the 13 survived to 36 weeks PCA.


200
150
100
50
0
PaO2 (mm Hg)
1.0
0.8
0.6
0.4
0.2
0.0
FiO2
P<0.001
FiO2
P=0.02
PaO2
80
60
40
0
PaCO2 (mm Hg)
P=0.03
P=0.01
P<0.001
P<0.001
P=0.007
P=0.02
0.4
0.2
0.0
Dynamic Compliance (ml/cm of water/kg)
GV
Partial liquid ventilation
0
1
4
8
12
24
Hours

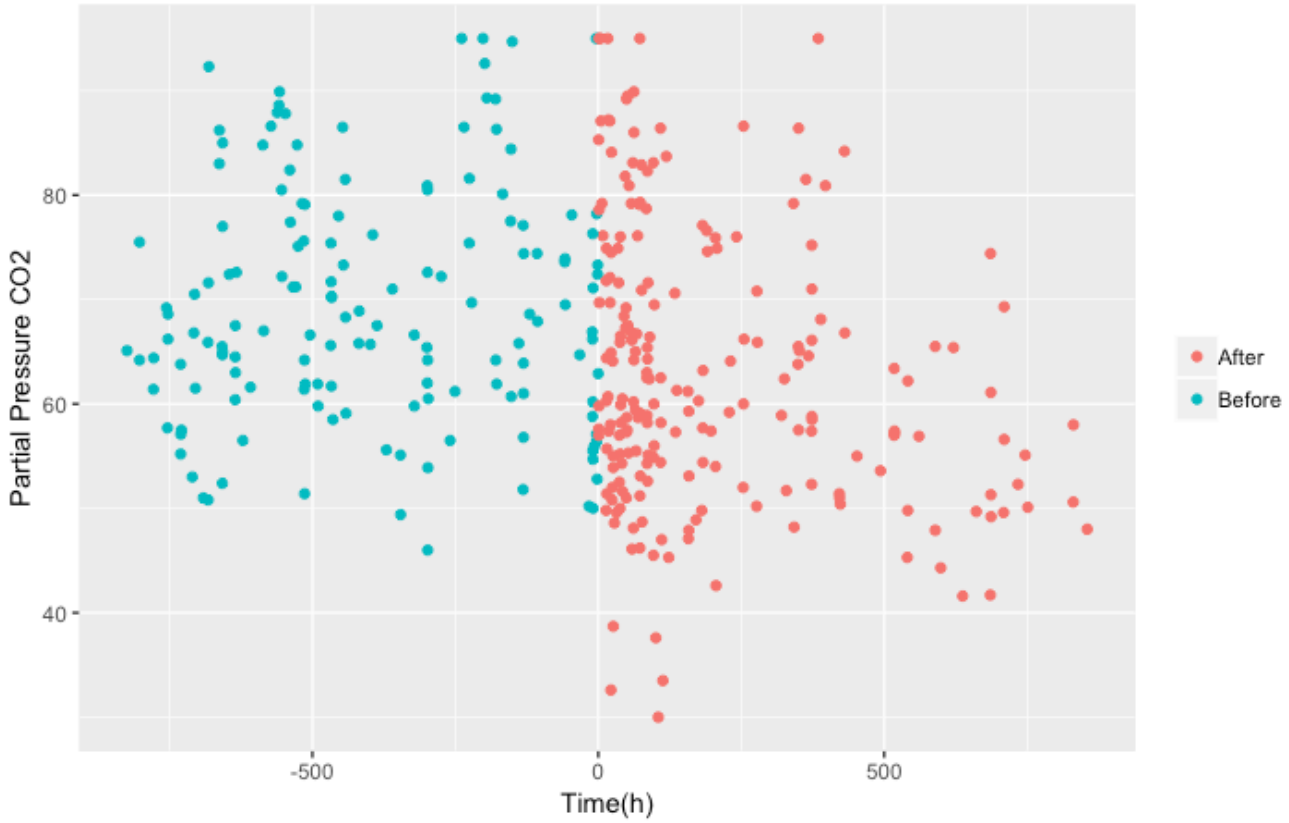
BILL FOX!!!!



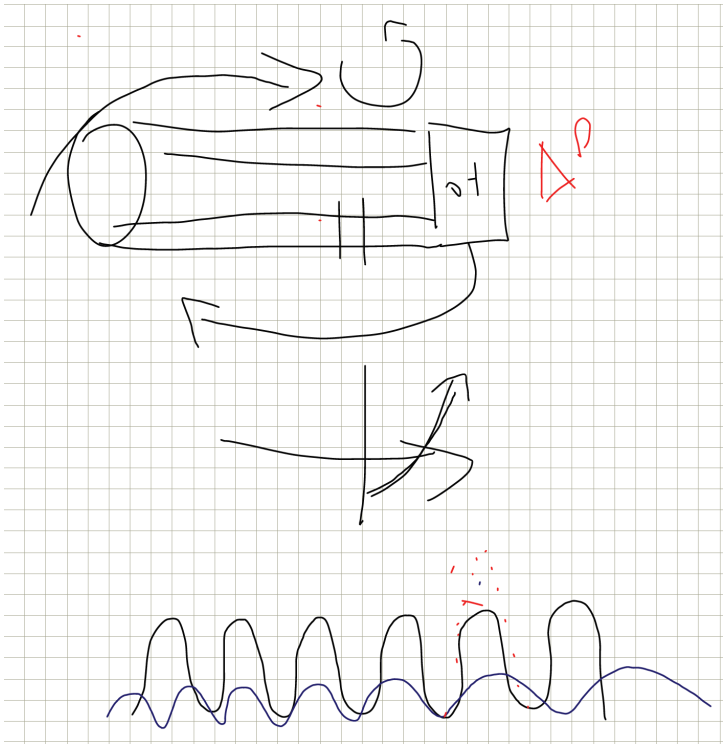
Recent Experience at CHOP

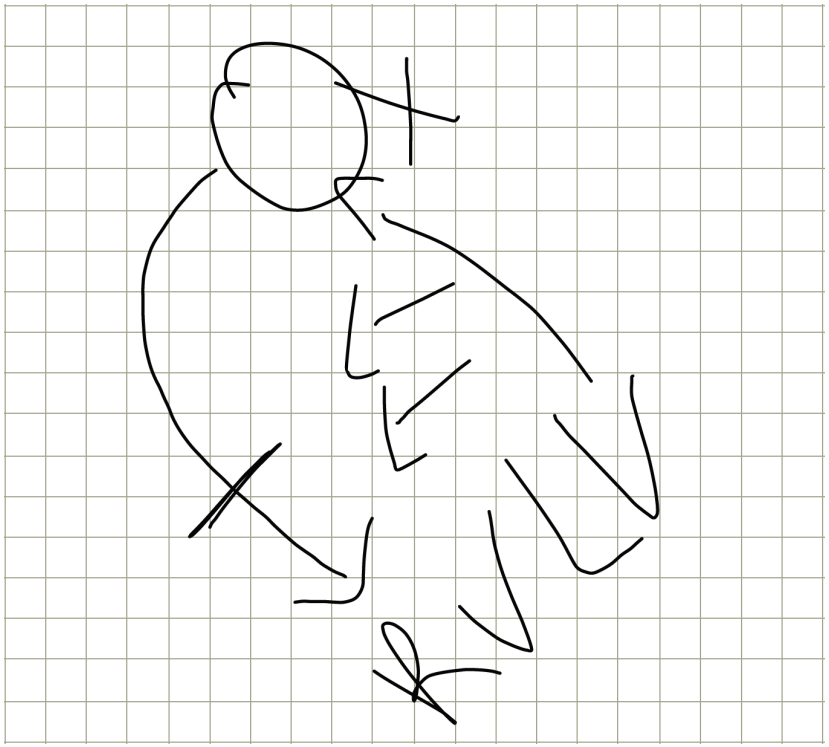
- Renewed interest coupled with stalling improvements in the outcomes of infants have lead to beginning studies once again.
- Initial study pursued those infants with the most severe lung complications.
  - Eventually came to safe dosing strategy.
  - May have limited opportunity to reverse or alter course for these infants.
- Plan to study this therapy in multiple phases.
  - Those infants with severe injury who are older.
  - Those infants who are likely an a path to have severe injury earlier in the course.
  - Those infants much younger with a novel technique to deliver the liquid developed in the last 10-20 years.
  - And of course even more novel ways in the future.

Partial Pressure of Carbon Dioxide



And Next….





What can RT contribute with BPD care

Be an active member for the interdisciplinary team

- Ventilator/ETT (prevent unplanned extubations)
- Non Invasive management
- Management of High Frequency Ventilators
- Assist with intubation/extubation
- Inhaled Nitric Oxide management
- Blood gas interpretation
- Coordinate with RN for position changes
- Assist with Kangaroo Care/therapy

Chronic Lung Disease patients need

Treatment

- **Respiratory Support**
- Medications
  - **Bronchodilators**
  - **Steroids**
  - Diuretics
  - Vasodilators
  - Antibiotics
- Management of related conditions
  - Reflux, pulmonary hypertension, ROP
- Nutrition
- Immunizations against RSV, influenza, etc

Research

- Partial Liquid Ventilation
  - Involves filling lungs with Perflubron which has anti-inflammatory and gas exchange properties

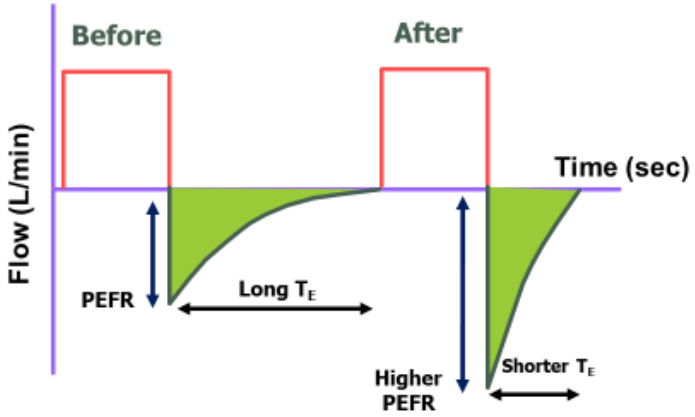
Inhaled medications

Breathing Treatment Strategies

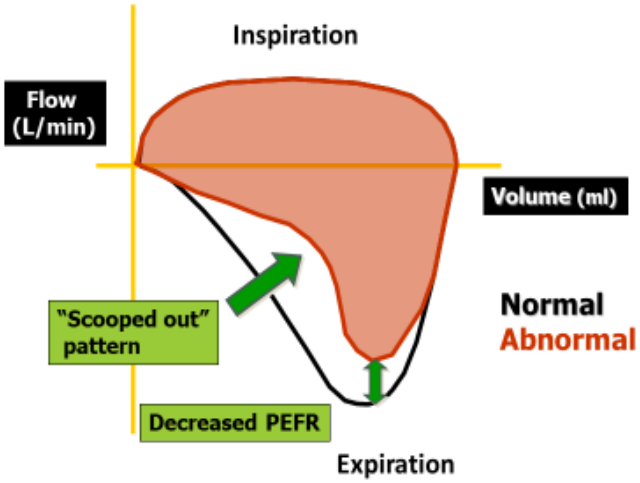
- How you maintain accurate effective ventilation with breathing treatments
- Filtering
- Changing proximal airway sensor (neoflow)
- Not disconnecting
- Spacing out treatments (comparing pre and post)

Waveforms Assessment of Therapy

RESPONSE TO BRONCHODILATOR



INCREASED AIRWAY RESISTANCE

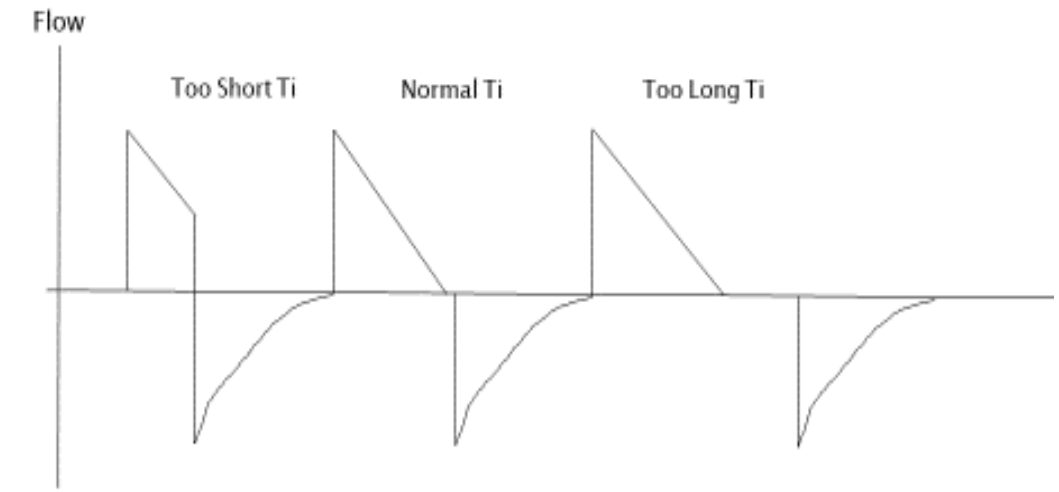


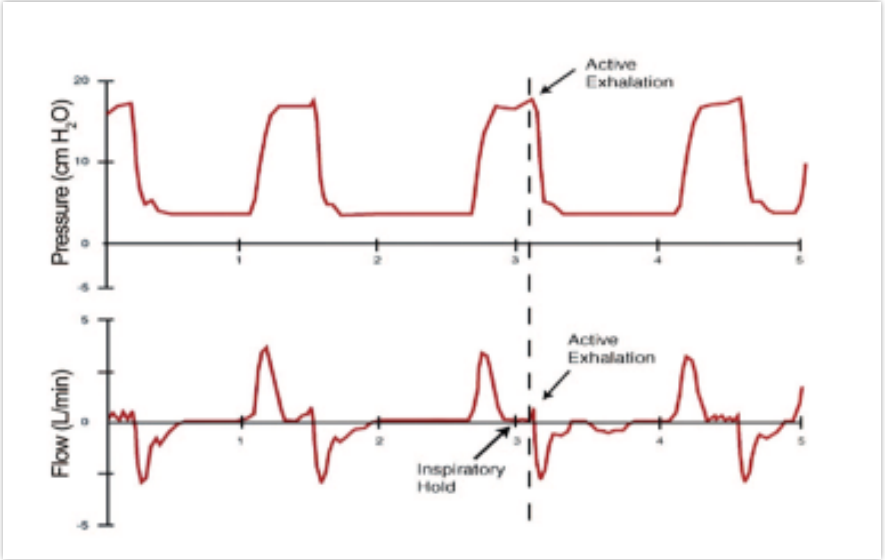
Optimization of Invasive Ventilation

There are no set and forget settings with BPD

- Trigger
- Volume vs pressure
- Inspiratory time
- Flow
- PEEP
- Assessment of waveforms

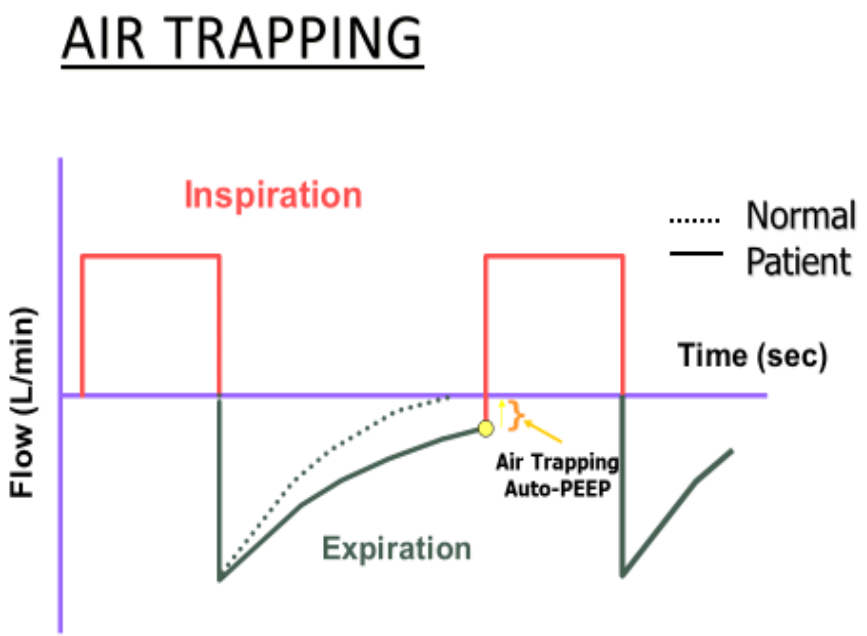
Ventilator settings



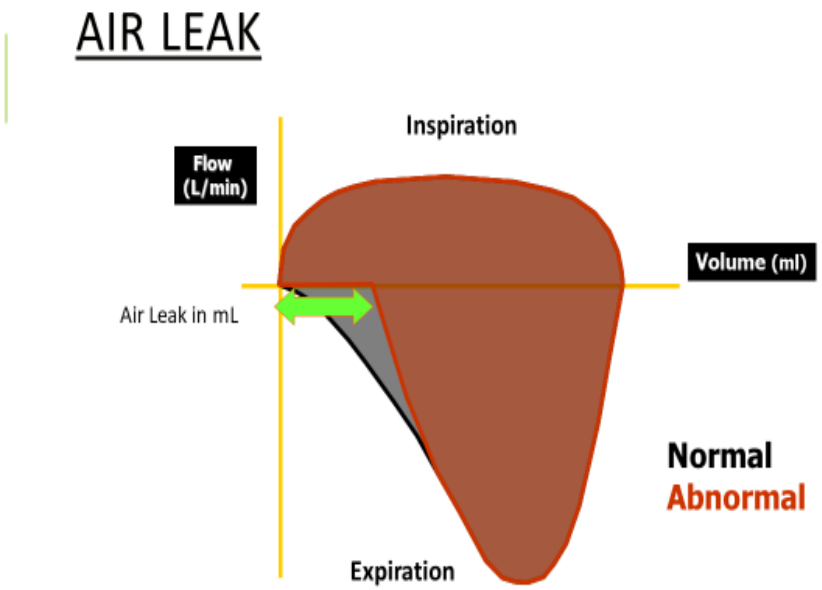


PEEP

- Look for triggering – wasted efforts, synchrony



Cuffed tubes



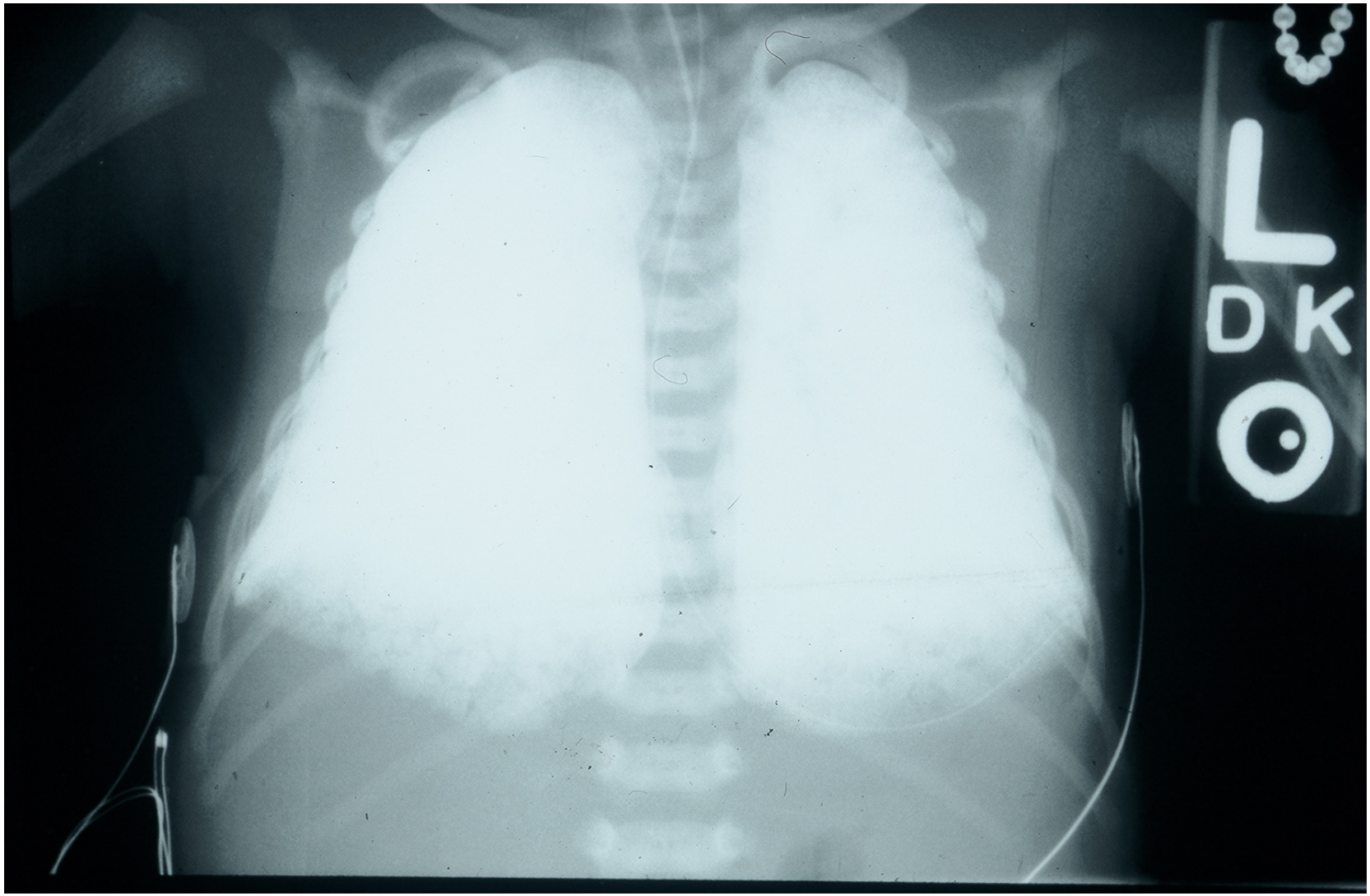
Optimization of Non-Invasive Therapy

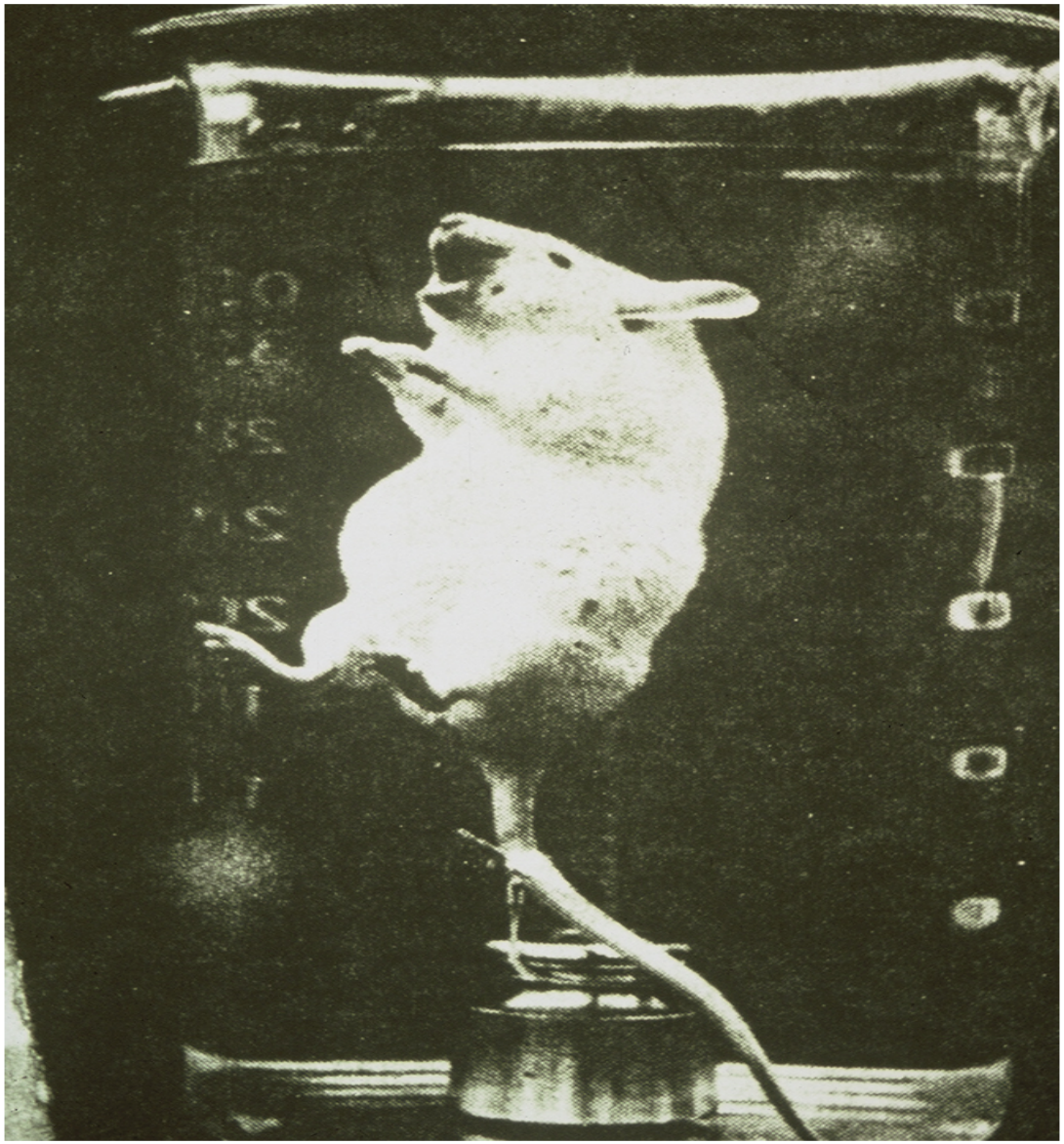
- Interface selection/fit
  mask prongs and full face head gear (Ag, Scuba)
- Device selection (able to trigger) trilogy/EVO
- HFNC therapy
- Skin checks
- Toleration

Liquid Ventilation in BPD

YOU NEED SOMETHING NEW!!!

William W. Fox M.D.


L
DK



Animal Work

- 40 yrs of study in 7 different animal species at Temple..Major studies in lambs leading to FDA acceptance that lambs are similar to Human lungs

- Drs Tom Shaffer and Marla Wolfson

Advantages of PFOB Liquid

- Low surface tension (surfactant)
- 9x O2 capacity as blood
- Inert
- Excellent distribution of ventilation
- Rapid diffusion in lungs
- Heavier than water

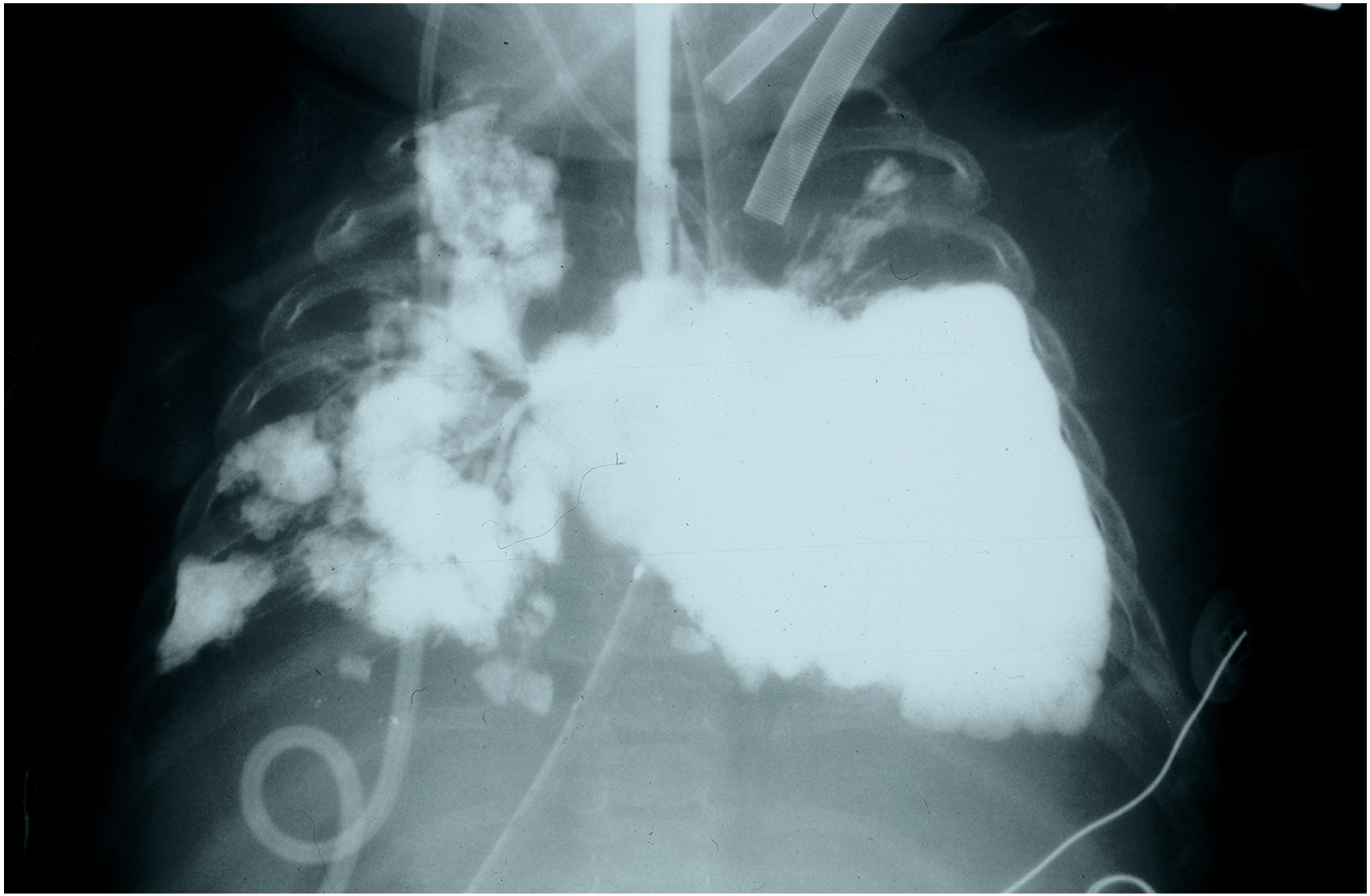
PLV- Past experience

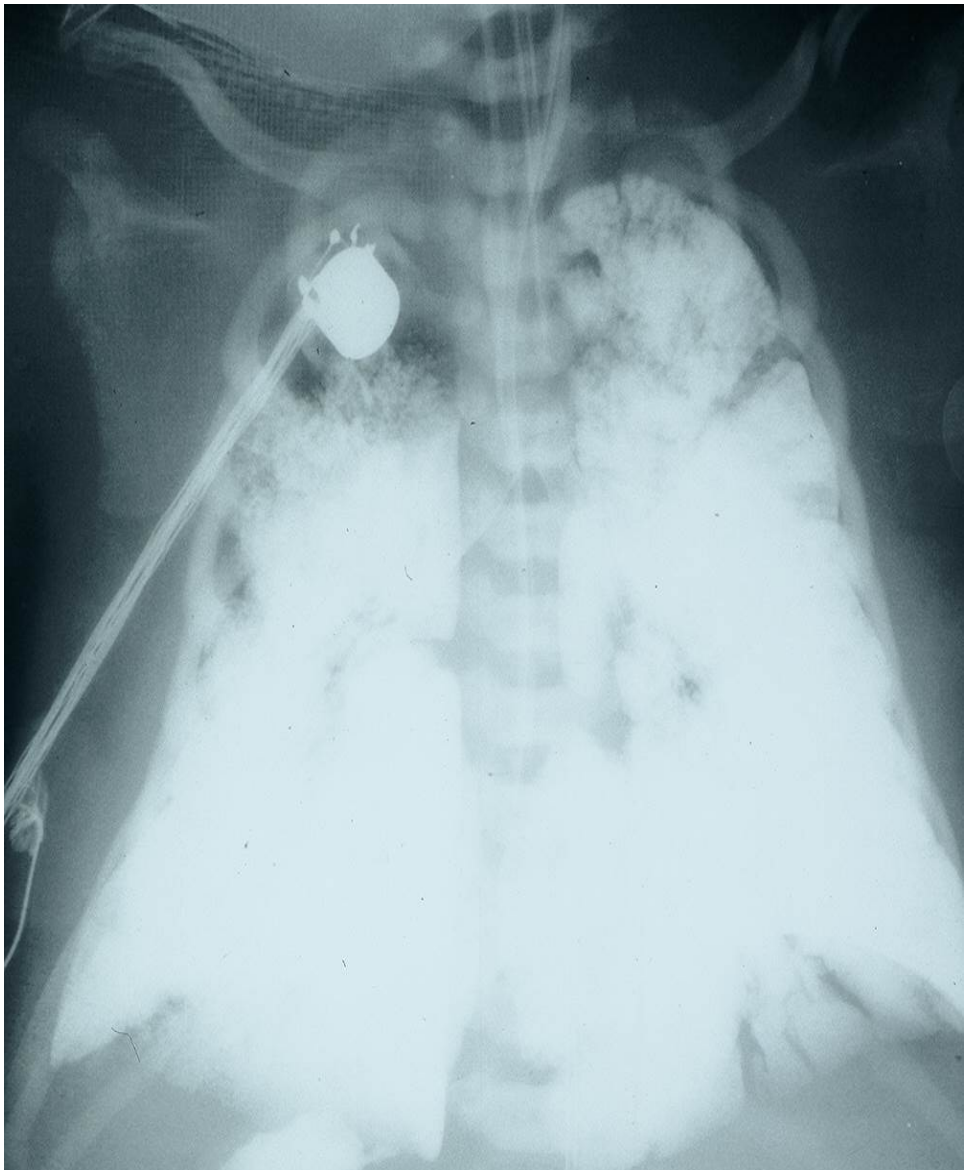
- About 100 babies treated
- Trials stopped 1996 because of ARDS adult trial –didn't show benefit, pneumothorax
- Neonates showed improved O2, Improved mechanics (Rescue)
- 10 pts treated at CHOP No adverse effects,no deaths ON PLV; some had major changes on O2 or lungs
- Several patients now in 20s doing well

PLV : FDA Approved Trials

- Total Liquid ventilation in near death infants

- PLV:
- ECMO
- Full Term
- Premies
- MAS

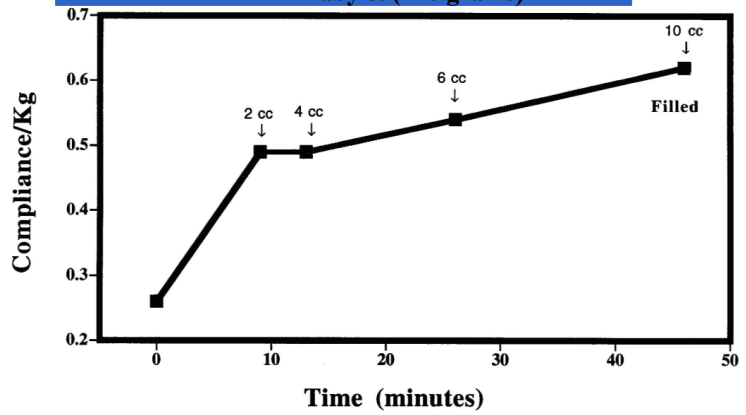




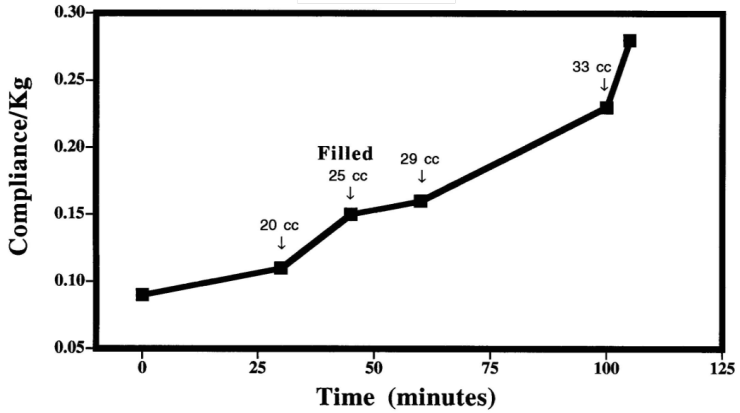
Rationale for this protocol

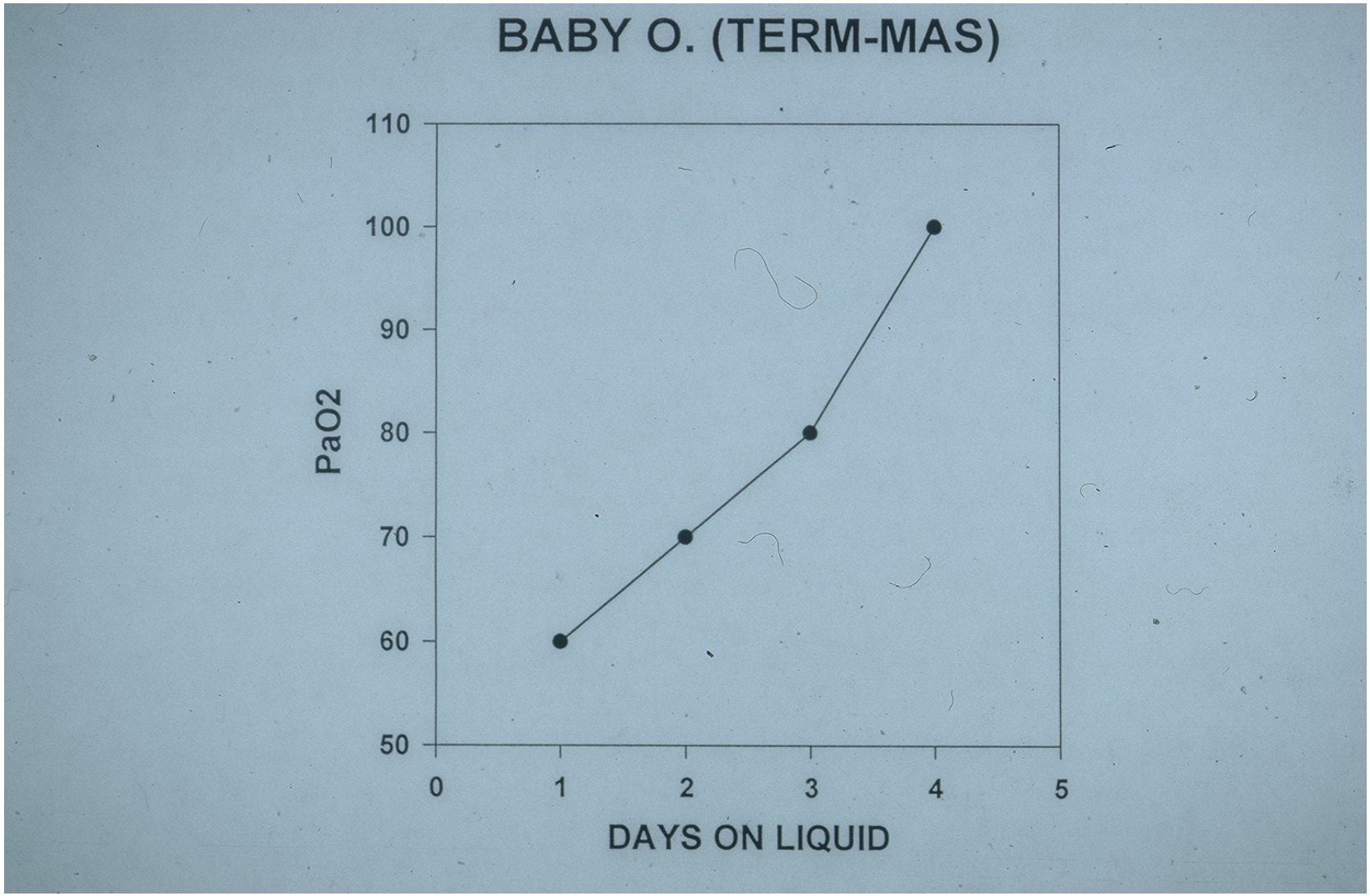
- PLV has shown some short term improvement in Vent settings and Lung Mechanics in:
- Premies
- MAS
- CDH
- Pts with chronic lung disease-not acute
- Severely ill neonates on ECMO

PLV: Change in Compliance/Kg During Filling
Baby J. (740 grams)



PLV: Change in Compliance/Kg During Filling
Baby S. (1800 grams)




BABY O. (TERM-MAS)
110
100
90
80
70
60
50
PaO2
0
1
2
3
4
5
DAYS ON LIQUID

Early PFOB in Preemies

- Rapid response
- Changes course of lung damage
- The improvement lasts!!
- ANTI INFLAMMATORY= Major Benefit !!

Can we prevent BPD ?

- Must have a better surfactant
- Drug that can’t be degraded by acidosis
- Drug that can be used for weeks
- Drug with rapid action
- Drug with no tissue damage
- Drug that can be delivered non invasively !!!,

or in bolus

AEROSOL

- Non Invasive
- No intubation or used in intubated babies
- Early or later use
- Better distribution
- Lower dose
- THERE ARE CHALLENGES!

Development of Aerosol

- Flow rate
- Particle size
- Deposition in Mouth
- Timing of Dose
- Interface: Nasal Prongs, Catheter

MAJOR TARGET

- INFLAMMATION
- INFLAMMATION
- INFLAMMATION

When Will We Have It?

1 year to characterize aerosol delivery

1 year for Premature lambs study

Protocols with ascending doses, safety etc.