Perfluorochemical Liquid Ventilation in BPD

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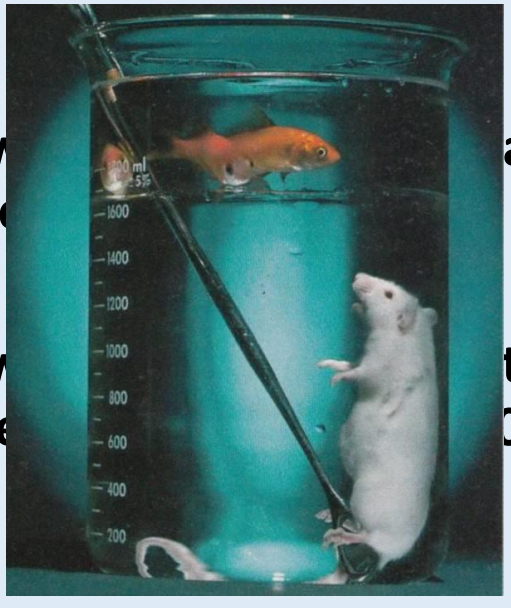
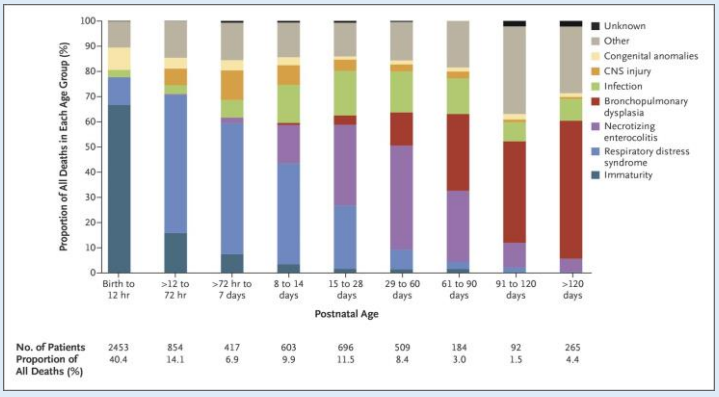
https://www.researchgate.net/figure/Mouse-liquid-breathing-in-oxygenated-PFC-solution_fig3_272168561



Do you w an be used all

Do you w t you can leave 0 days?

What is the problem we are facing?



- Red bar = Bronchopulmonary Dysplasia (BPD)
- After 90 days, BPD is responsible for the most deaths in infants born at less than 1000 grams.

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ARTICLE

Patterns of Respiratory Disease During the First 2 Postnatal Weeks in Extremely Premature Infants

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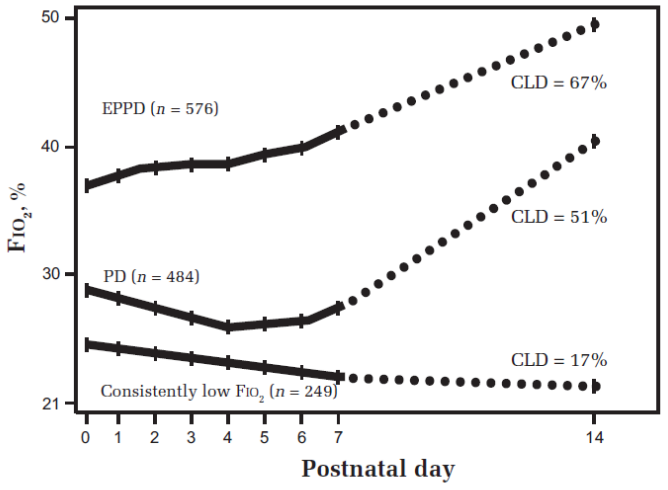
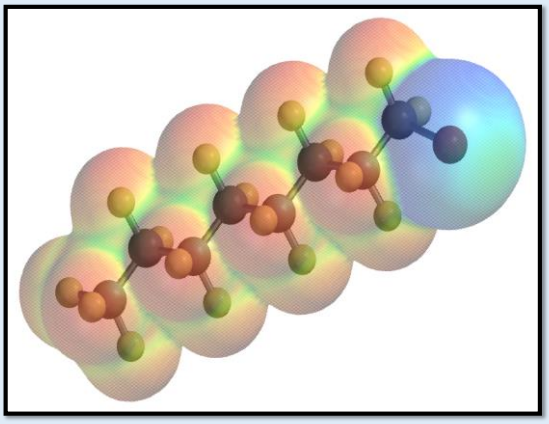


FIGURE 1
Median of the mode F_{IO_2} on postnatal days 0 to 7 and on postnatal day 14 and frequency of CLD among 1340 ELGANs with 3 patterns of respiratory disease (low F_{IO_2}, PD, and EPPD) during the first 2 postnatal weeks.

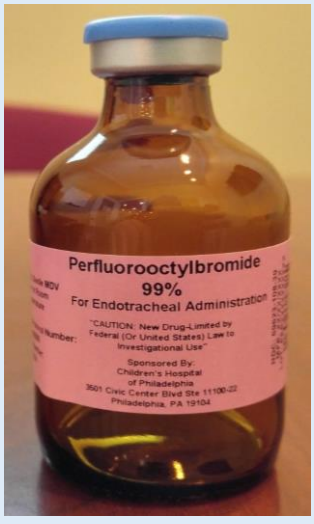
- There is an evolving and complicated understanding of patterns of respiratory disease.
- Goal: change trajectory of respiratory disease with novel and timely intervention (PFOB).

What is Perflubron (PFOB)?

- Perfluorooctyl bromide ($C_8F_{17}Br$)
- **Biochemically inert** – strong C-F bonds
- Insoluble in **water**
- Purified to a minimum of 99.4%
- Does **not** support microbial growth



https://commons.wikimedia.org/wiki/File:Molecular_ball-and-stick_model_of_Perflubron,_overlayed_with_electron-density_coded_VdW_model.png



- Clear, odorless, stable
- Anti inflammatory
- Low surface tension (surfactant)
- 2x the weight of water
- Radiopaque
- High O_2 and CO_2 diffusion rate

How does PFOB help?

Improves:

- **Compliance** - more volume is displaced per unit pressure change
- **Uniformity** – liquid can access collapsed lung regions
- **Ventilation-perfusion matching** – surfactant properties

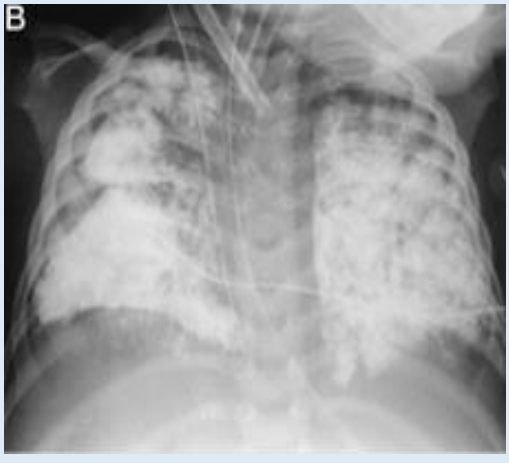
Reduces:

- **Distending Pressures**
- **Inflammation**
- **Surface forces** - replaces gas/liquid interface with liquid/liquid

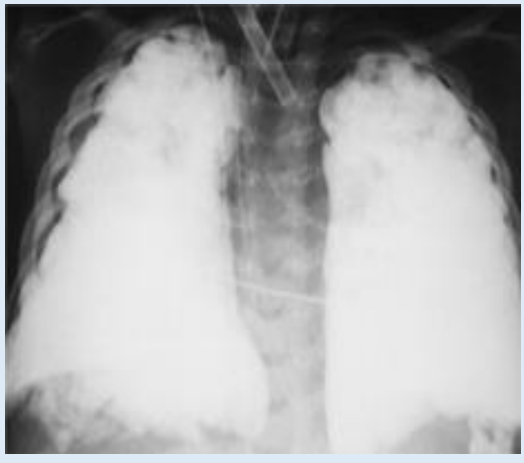
What are the limitations?

- High Density
- High Viscosity
- Increased work of breathing
- Longer inspiratory & expiratory time
- Requires a ventilator

Partially Filled with PFOB



Fully Filled with PFOB



A Brief History of PFOB

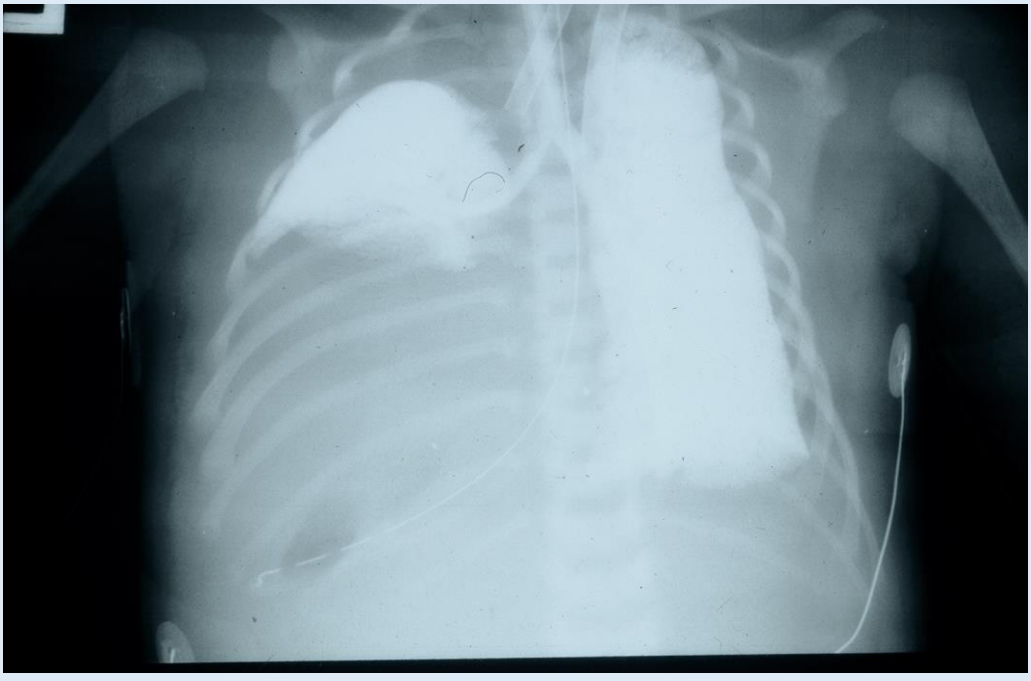
- Early days: Liquid Ventilation to understand lung physiology.
- Saline and PFOB emerged as feasible mediums.
- PFOB carries more oxygen and carbon dioxide.
- 1970-1990s: Dr. Shaffer develops Total Liquid Ventilation (TLV). Costly and difficult. Introduction of Partial Liquid Ventilation as standard.
- 1990s: Series of Clinical Trials in Adults, Peds, and Infants.

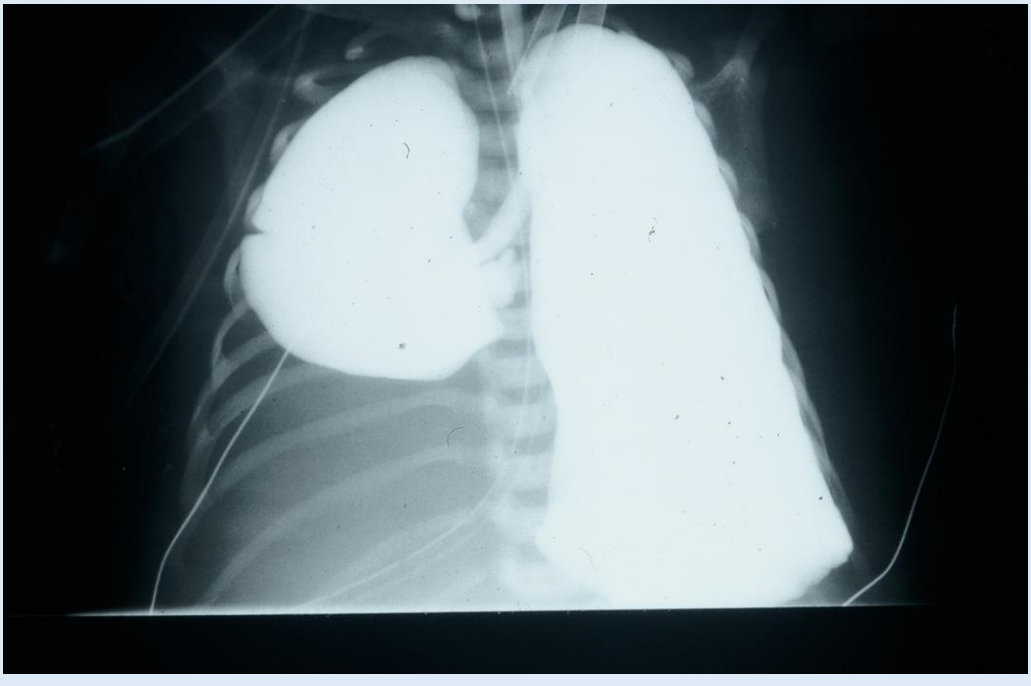
How has PFOB been used?

- Patient on standard ventilator – high frequency evaporates too quickly.
- Fill lungs slowly endotracheally
- Previous studies looked to fill to the Functional Residual Capacity (FRC). We have used lower doses – starting at 2.5 mL/kg.
- Add liquid every 2 hours if not visible in ETT, to account for evaporation.

U.S. Neonatal Studies: 1993-1996

- Severe lung disease: 80% expected mortality
  - CDH, ECMO Term, ECMO and RDS – varied populations, similar severity.
- No deaths caused by PFOB administration – several later died from lung disease.
- Few controls, mostly a rescue drug.
- Indication of improvements in lung compliance and general physiology. Some with major responses.

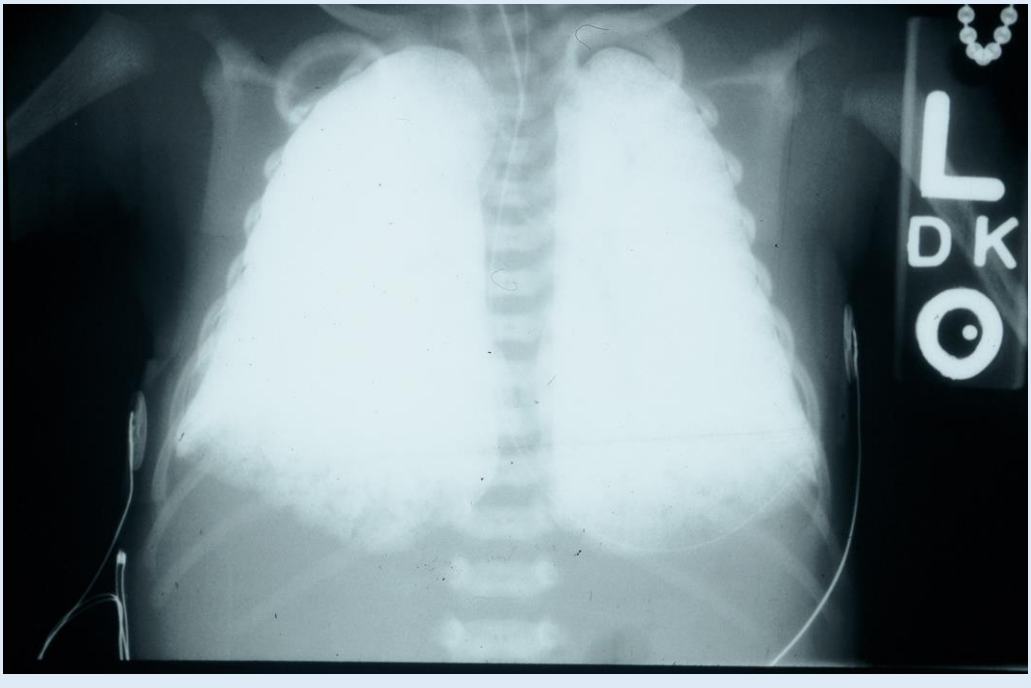


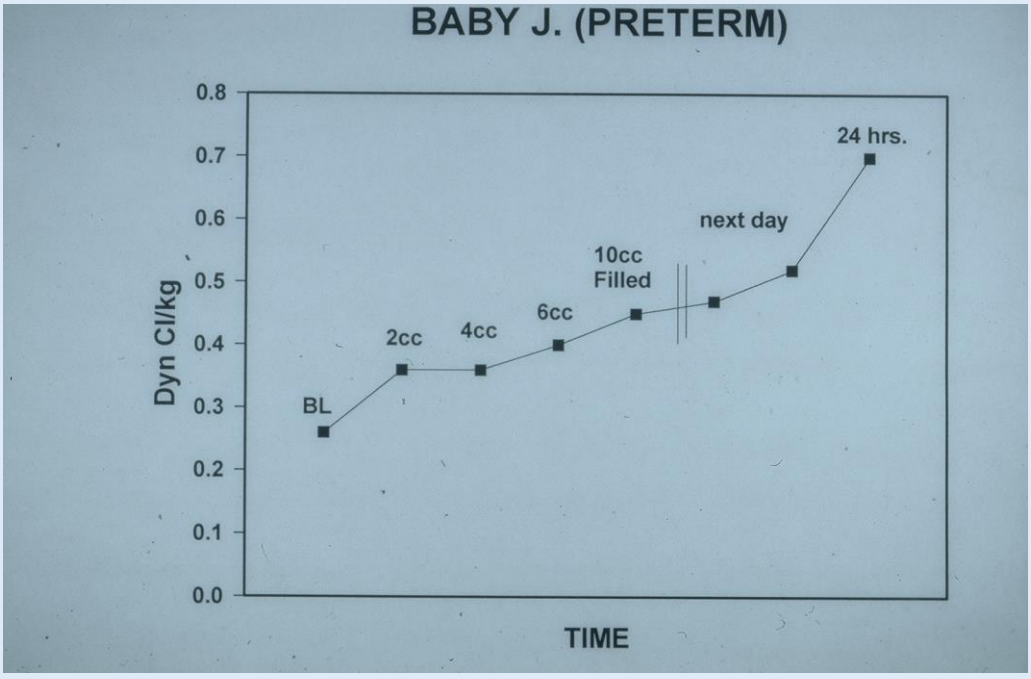


Case Study: Premature Infant, 1995

- 1200g male with severe RDS
- 80% oxygen
- 18 days old, x-ray shows early chronic changes
- PIP of 38

- **On liquid:** In 72 hours, down to 35% oxygen, PIP of 18
- Stopped Liquid at day 4 and continued to wean
- Did not require high fractions of oxygen after.





Adult Study – Kacmarek et. al. 1996

- Large, multisite trial. Lower than expected Control Group mortality. Risk of pneumothorax. Not enough improvement from liquid.

- Problems:

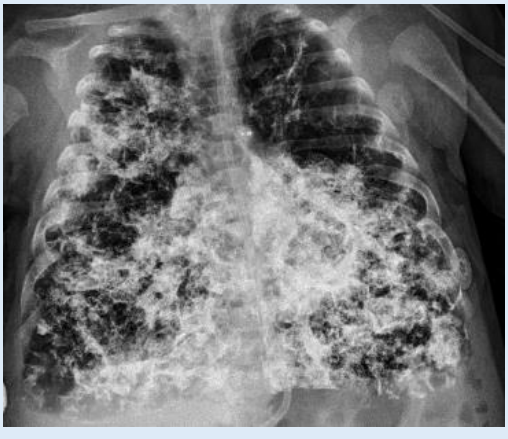
  - ARDS has many causes with complex physiology
  - No mechanism to detect amount of liquid in lungs
  - Older population – better results under 55 years of age
  - Coincided with change in ARDS treatment standard of care

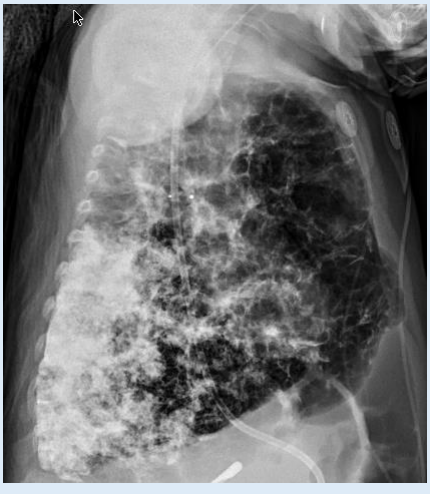
RESULT: All PFOB Studies stopped

Our Work

- Contracted with manufacturer near Austin, Texas.
- New IND, several still-evolving protocols. Restarting research on PFOB administration.
- Initially working in older, sicker infants with BPD.
- Promising Safety Signals.

Subject #2





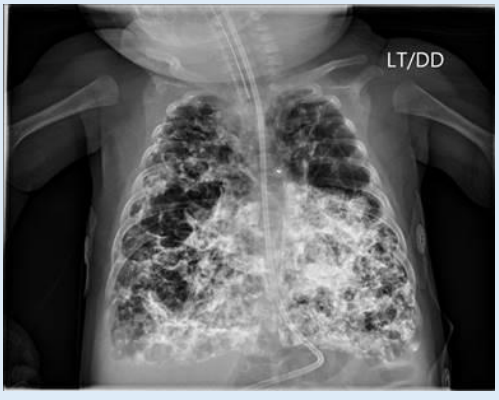
Frontier Grant – Collaborative Team Effort

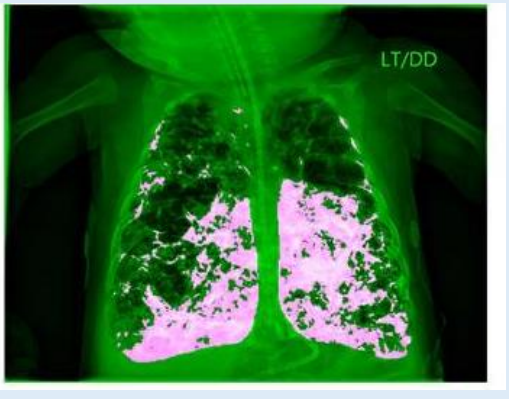
- CLD Patients – We usually have 20 babies
- 10 Neonatologists, 3 Radiologists, 1 Cardiologist & 1 Pulmonologist
- 8 Front Line Clinicians
- 2 RN data analysts
- 25 RTs
- 300 Nurses
- 1 Project Manager

What We Have Learned

Collaboration with Radiology

- PFOB stays in lungs up to **30 days** after treatment
- Creation of radiology-specific tools for detection and analysis





New Techniques and Collaborations

- Cardiology – Pulmonary Hypertension
- Immunology – Inflammation
- Pulmonology – Pulmonary Functions
- Neurology – Cerebral Oxygenation
- Nebulization – University of Colorado

What Have We Learned about Severe BPD?

- Every baby tolerates PFOB differently
- BPD is a disease of heterogeneous injury
- Filling patterns are different for each subject
- No adverse events with low dose
- PFOB stays in lungs up to 30 days

Did We Alter the Course of BPD?

- Half of our PFOB subjects extubated, 3 went home
- 89% of controls trached and/or intubated

What is next for PFOB?

- PLV earlier in development of lung disease
- PLV in other populations – Congenital Diaphragmatic Hernia, Infants on ECMO, Term Infants, Early "Evolving" BPD.
- Aerosolization of PFOB
- PFOB as a drug delivery mechanism
- Longer use in patients
- Use in areas with limited access to surfactant

Thank you!

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