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# Artificial Placenta Technology in a Preterm Lamb Model

George B. Mychaliska, MD

Robert Bartlett, M.D. Professor of Pediatric Surgery

# Artificial Placenta

- Clinical rationale
- Principles of extracorporeal support in premature infants
- Pumpless AV -ECLS configuration
- Transition to pump -driven VV -ECLS approach
- Lung management
- Long -term survival
- Organ protection and development
- Development of non -thrombogenic surfaces
- Clinical risk stratification
- Milestones to clinical application and future directions



## ELGANs

- < 28 weeks EGA
- Mortality and morbidity of ELGANs particularly high
- Among survivors, long -term medical problems are common
- The short and long -term costs are staggering
- Severe complications including CLD, neurodevelopmental problems / IVH, NEC, ROP, and sepsis are due to **organ immaturity** and the unintended **iatrogenic** consequences of conventional postnatal therapy.
- Significant organ prematurity (lung, brain)
- Growth and development should occur in a fetal environment



Leveraging the  
Intra-Uterine  
Environment

## Development of an Artificial Placenta for Support of Premature Infants





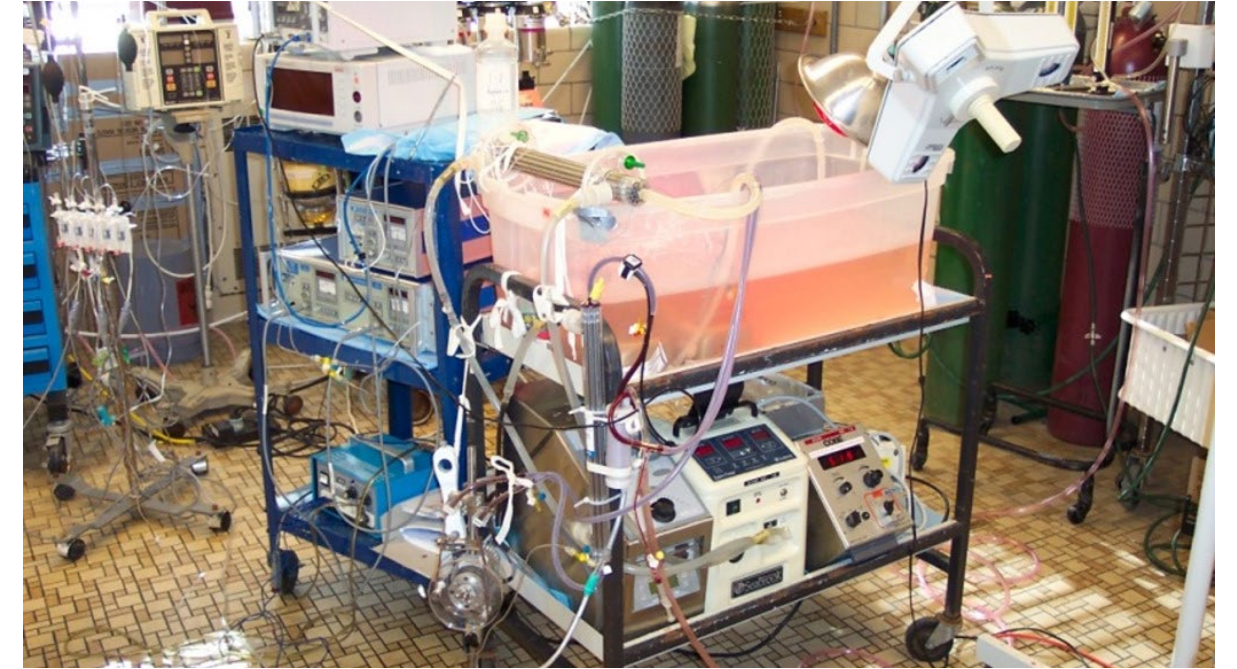
## Artificial Placenta

- **Maintaining fetal circulation**
- **Low  $pO_2$**
- **No mechanical ventilation**
- **Fluid filled lungs**
- **VV or AV - ECLS**

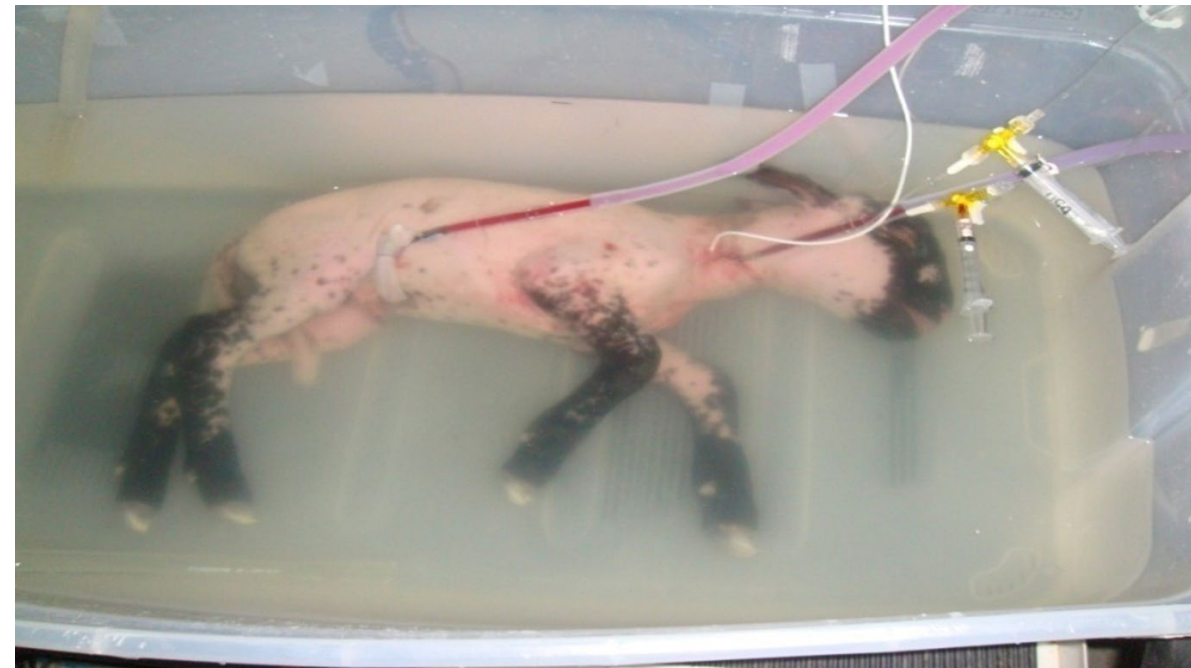
# A decade of evolution



PUMPLESS AV -ECLS



PUMP-DRIVEN AV -ECLS



VV -ECLS (submersion)



VV -ECLS (fluid -filled lungs)



- **Fetal lamb model**

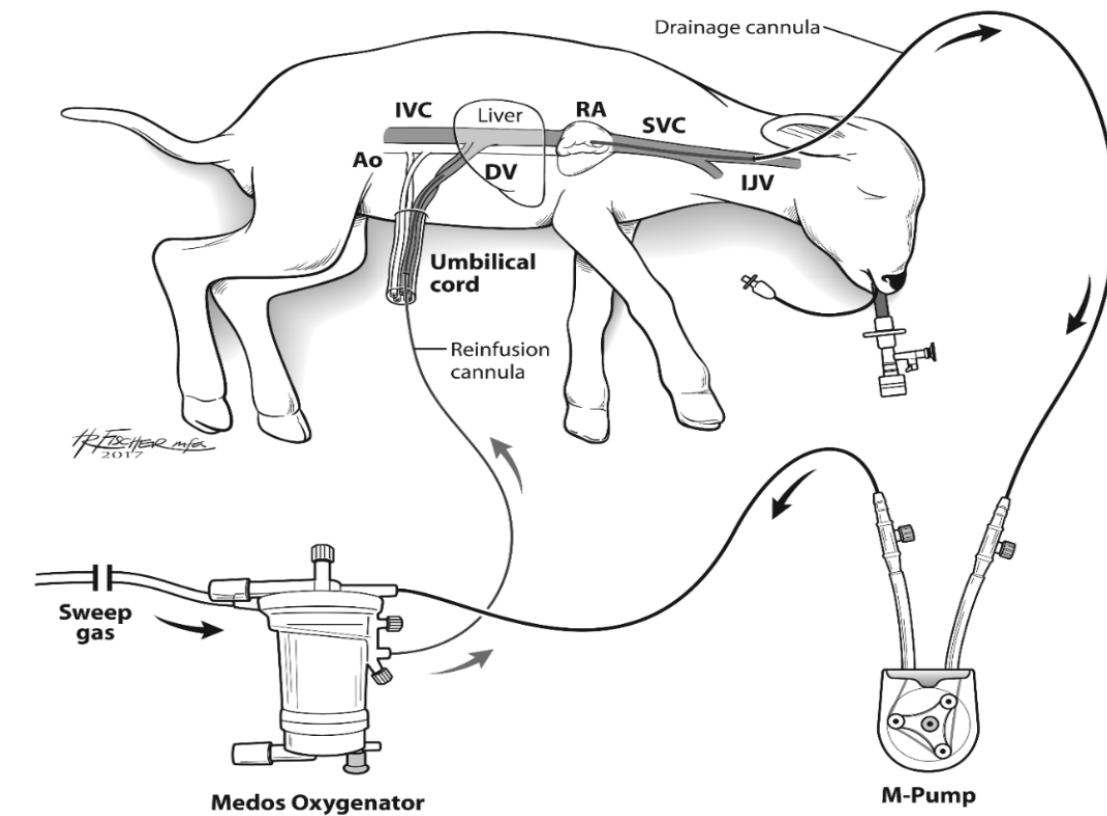
- 118-day (term=145) developmentally similar to 24 -week human in terms of lung development.

- **Artificial Placenta Support**

- Pump-driven VV -ECLS with umbilical vein reinfusion and jugular drainage.

- **Lungs filled with perfluorocarbon to a meniscus**

- **Empiric antibiotics, steroids, prostaglandins and TPN**





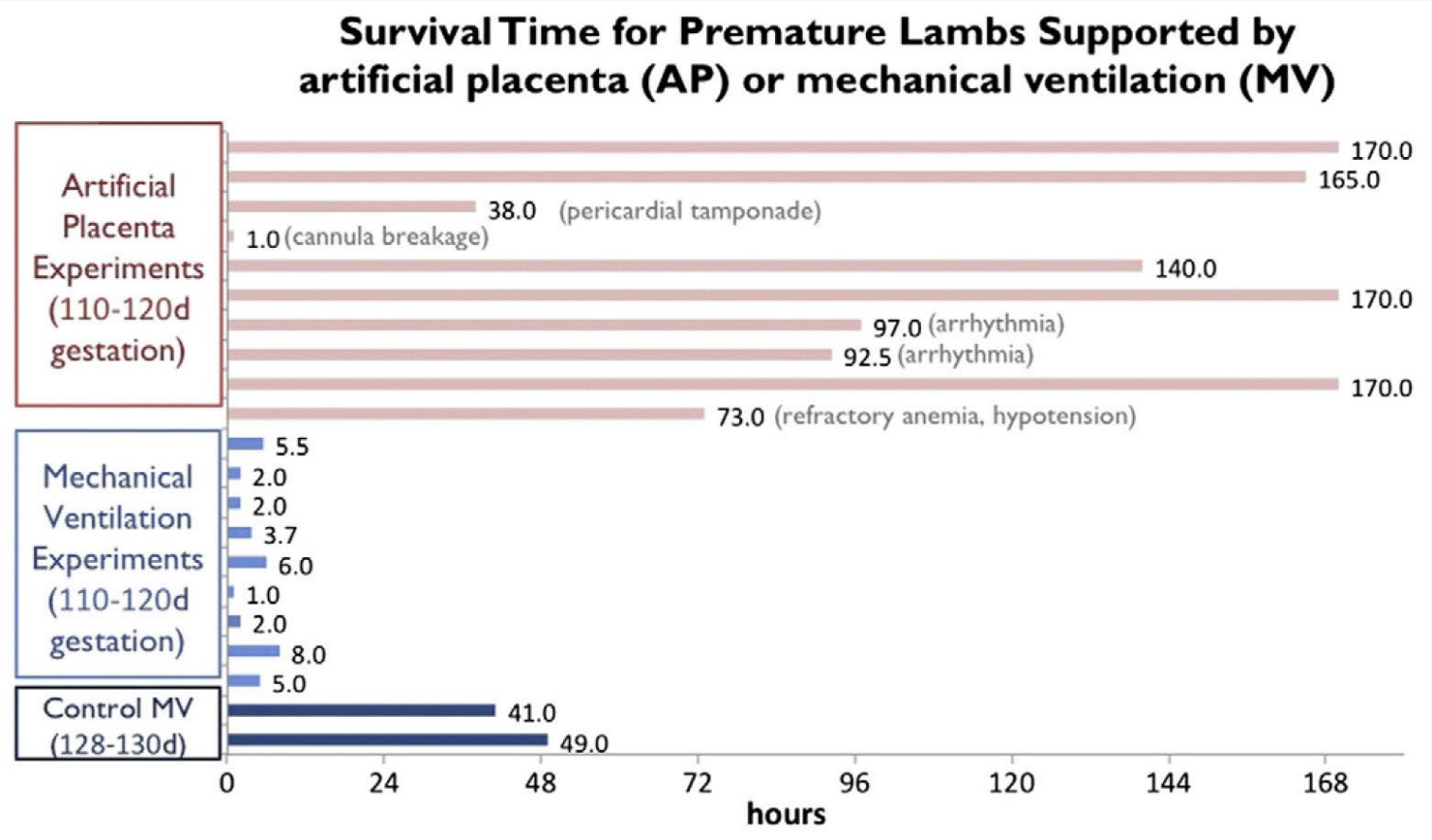
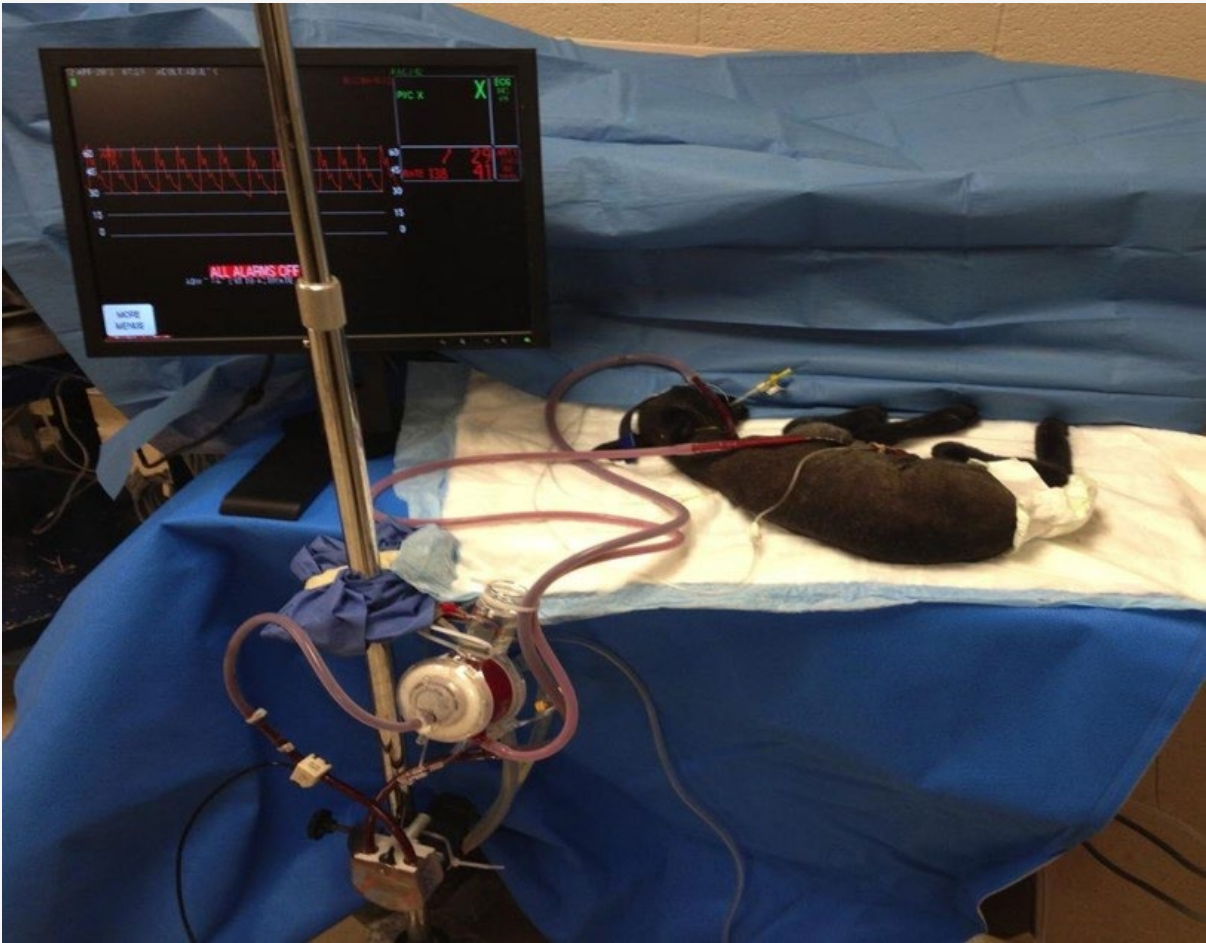
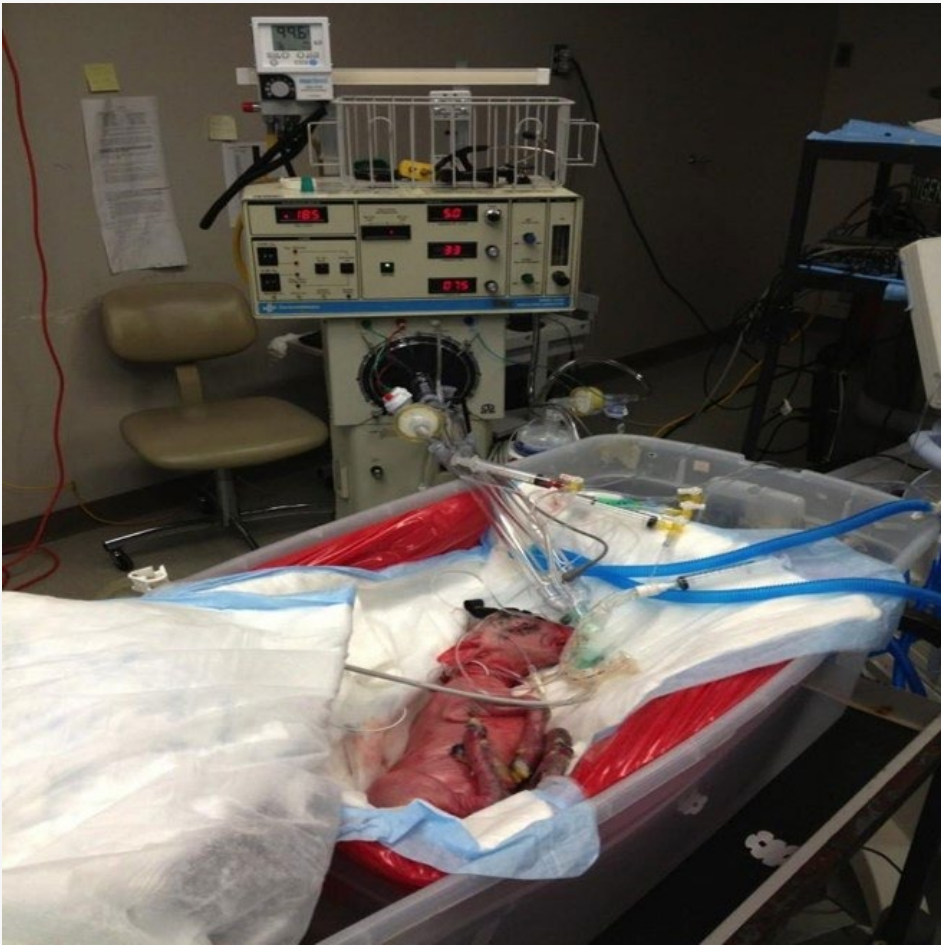






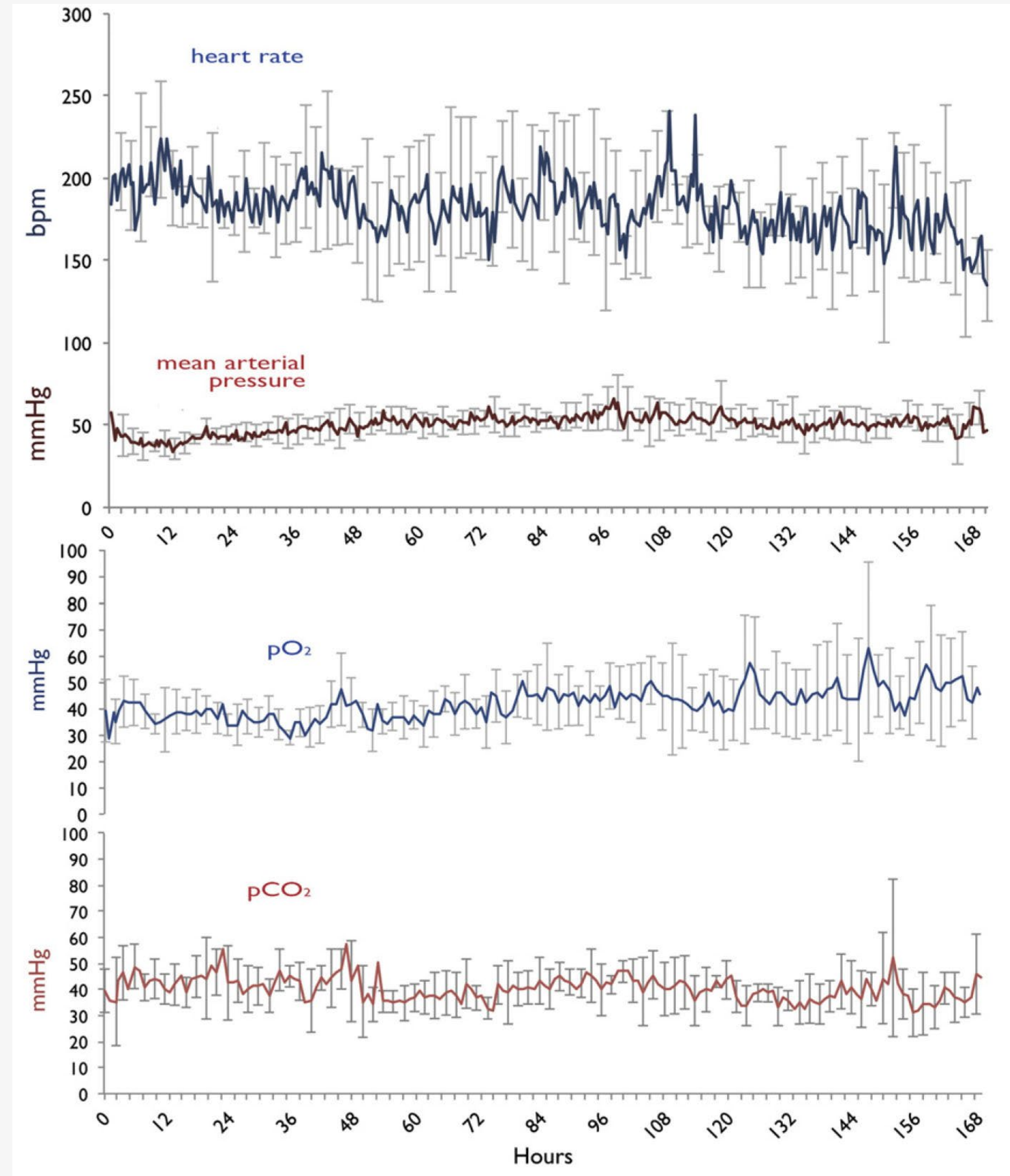
# Comparing the AP versus MV Controls

Premature lambs on the AP survived **one week** compared to **a few hours** for MV controls.



## Long-term support

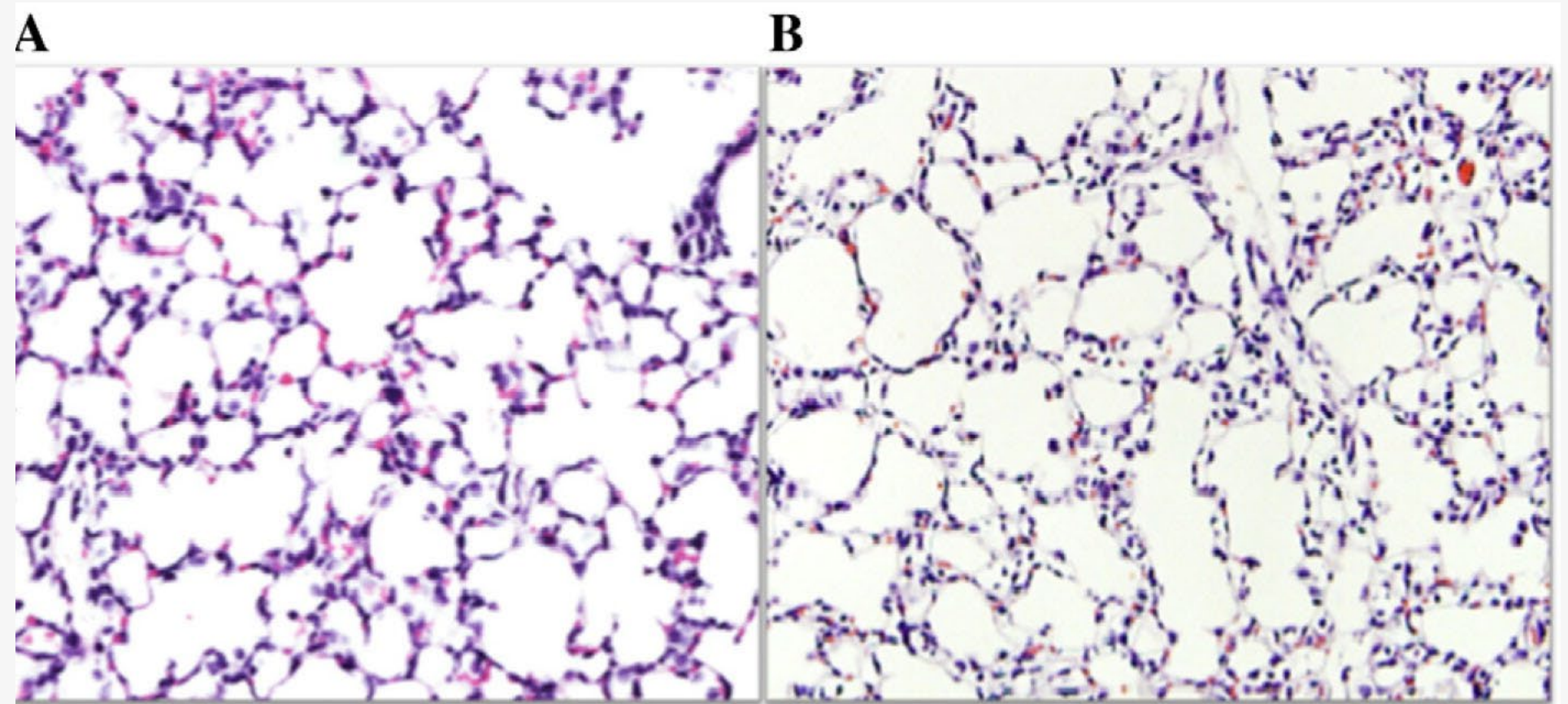
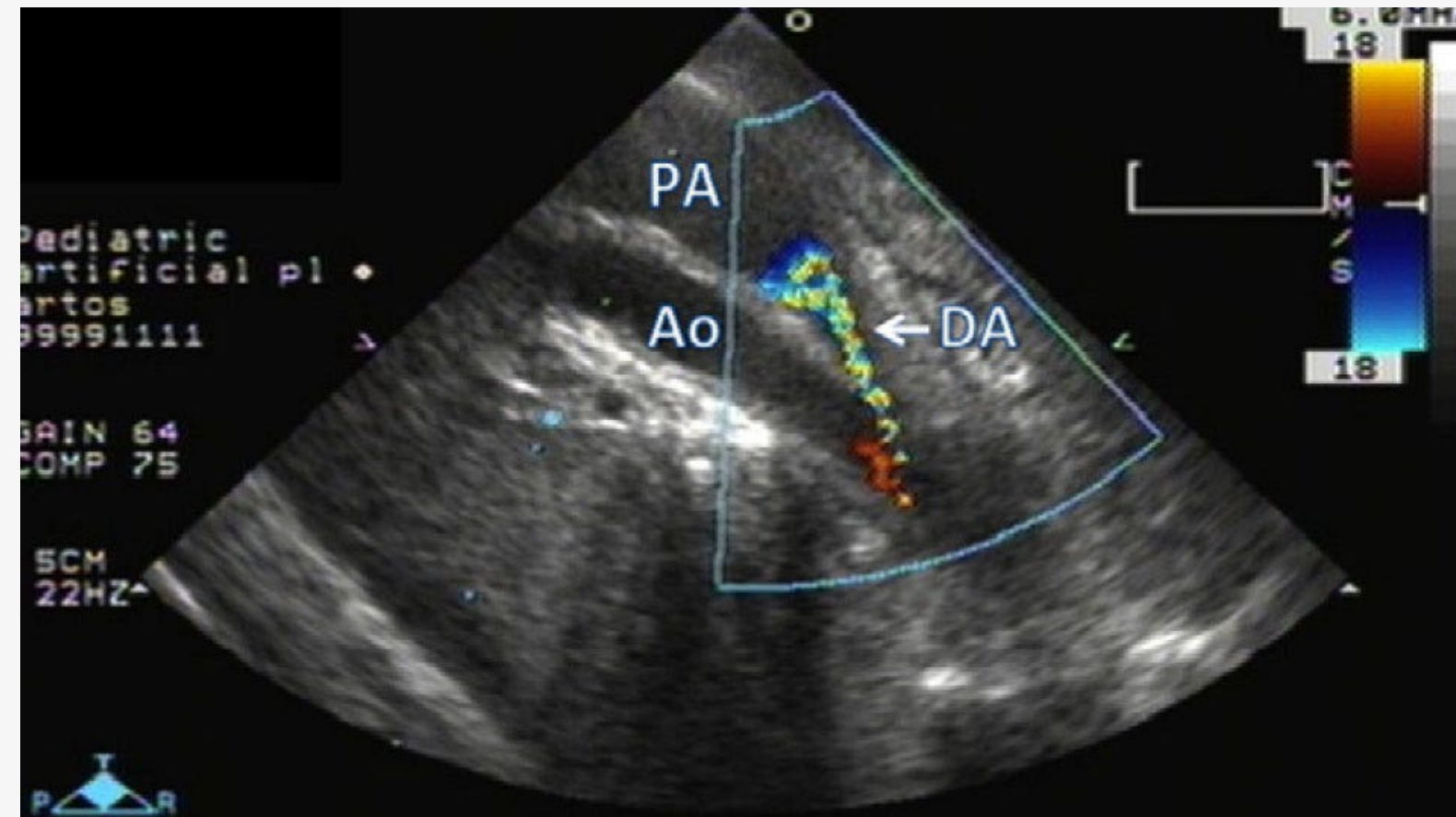
Premature lambs on the AP survived one week with stable hemodynamics, fetal circulation and gas exchange in the normal fetal range.





Application of AP  
after mechanical  
ventilation failure

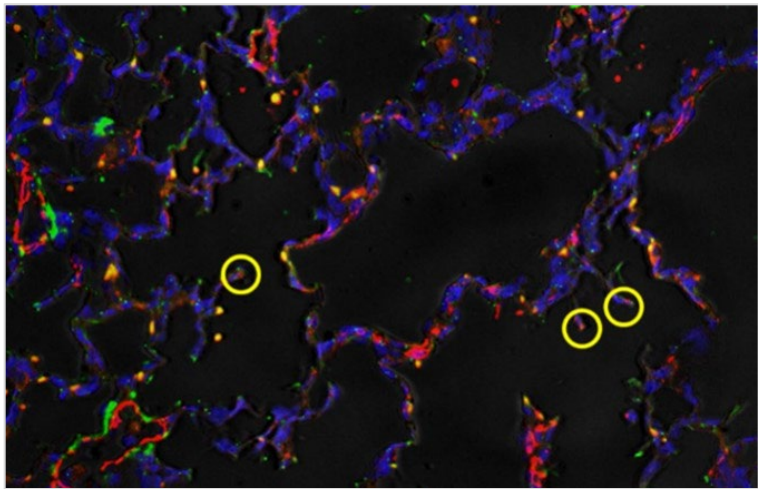
The artificial placenta  
stabilized premature  
lambs after ventilatory  
failure and fetal  
circulation was  
reinitiated with stable  
hemodynamics, gas  
exchange and minimal  
lung trauma.



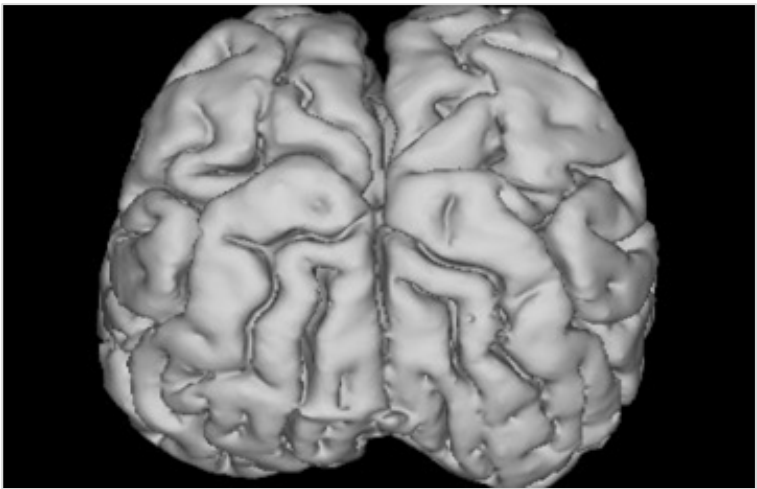


# Organ development: AP support

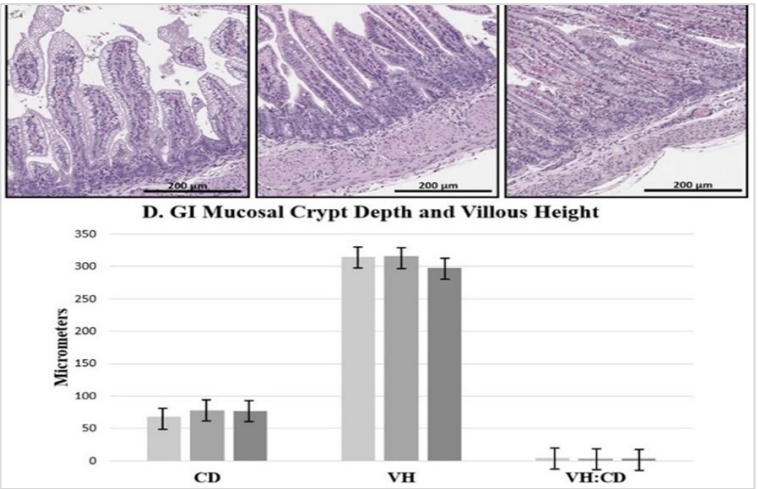
Our goal was to demonstrate ongoing organ development and **protection** during artificial placenta support.



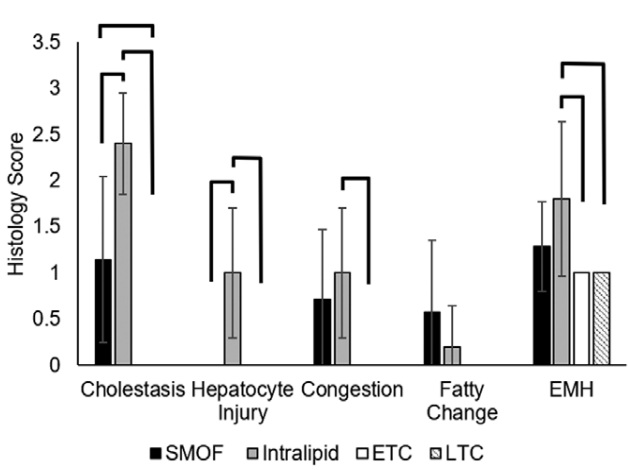
LUNG



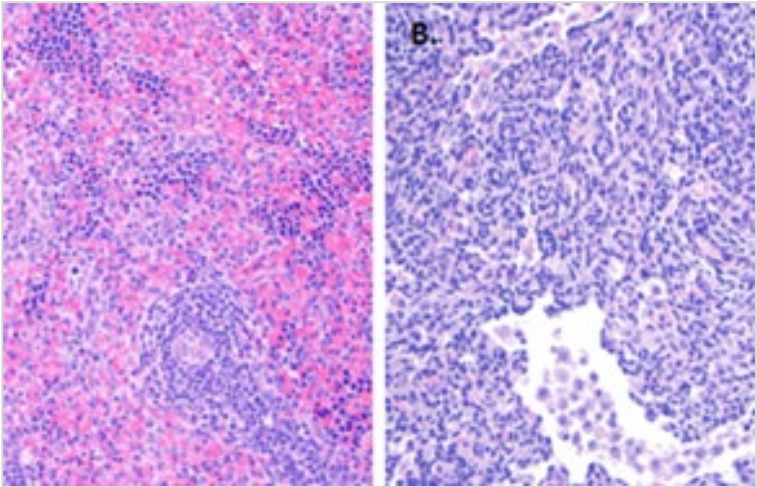
BRAIN



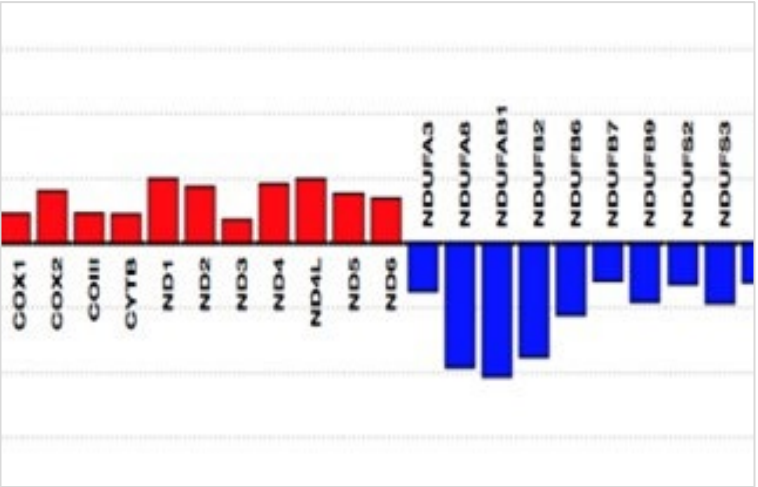
GI TRACT



LIVER



SPLEEN

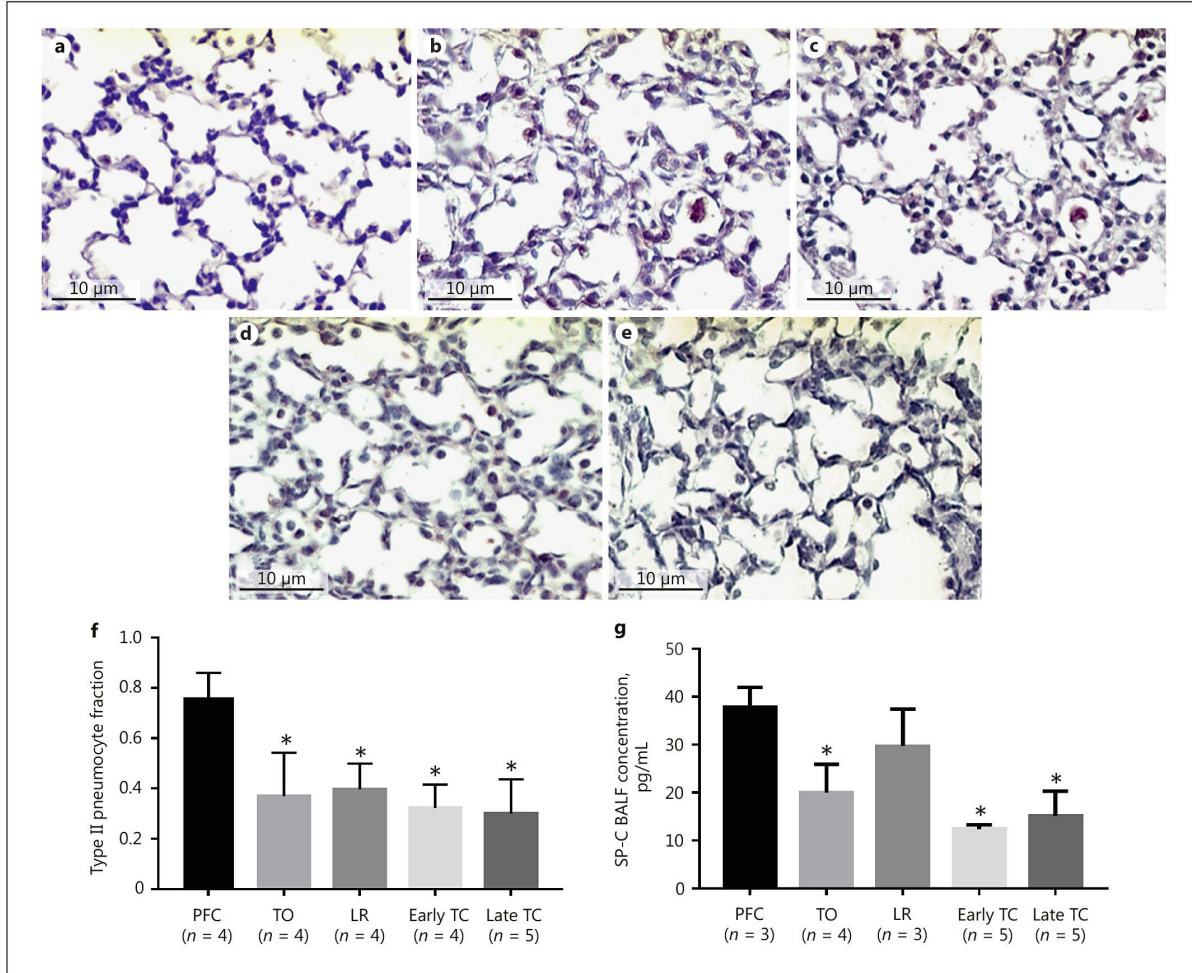
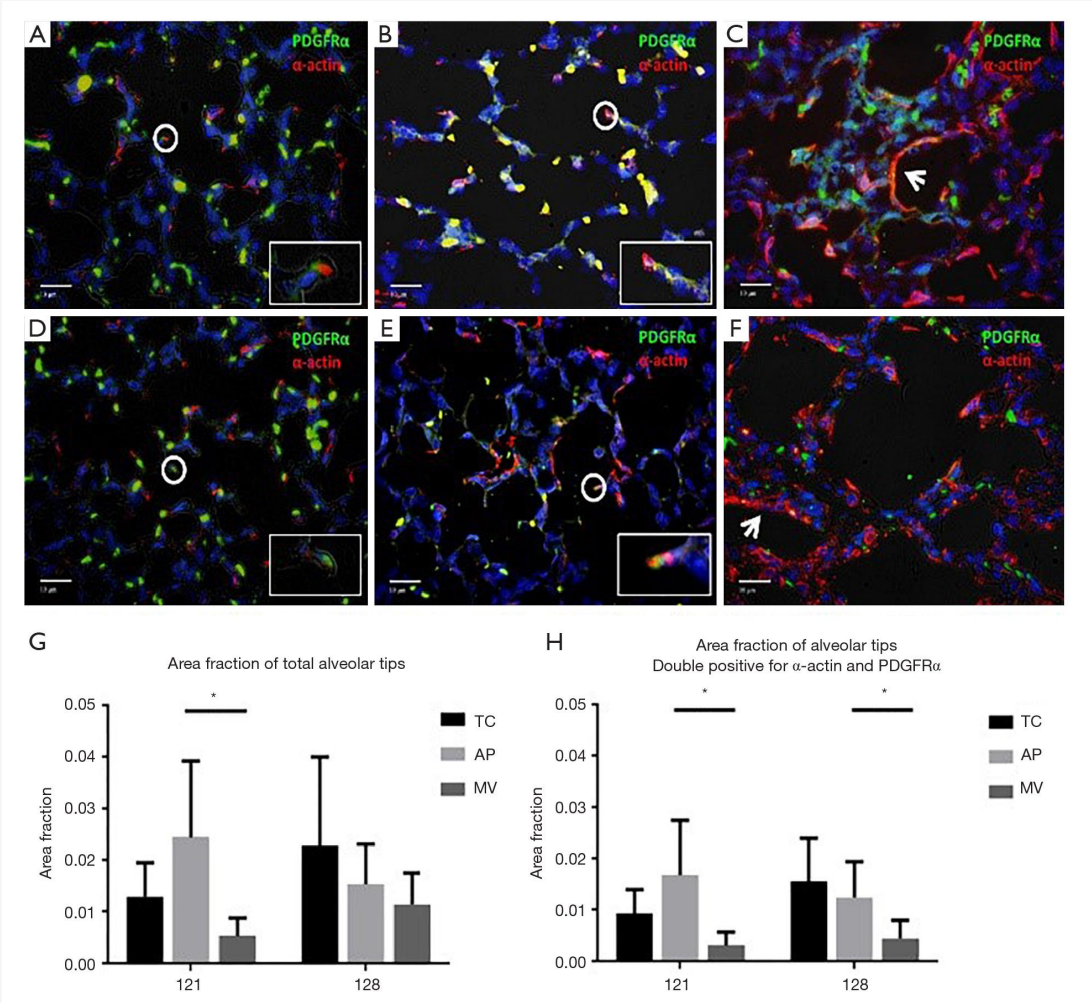


HEART (unpublished)



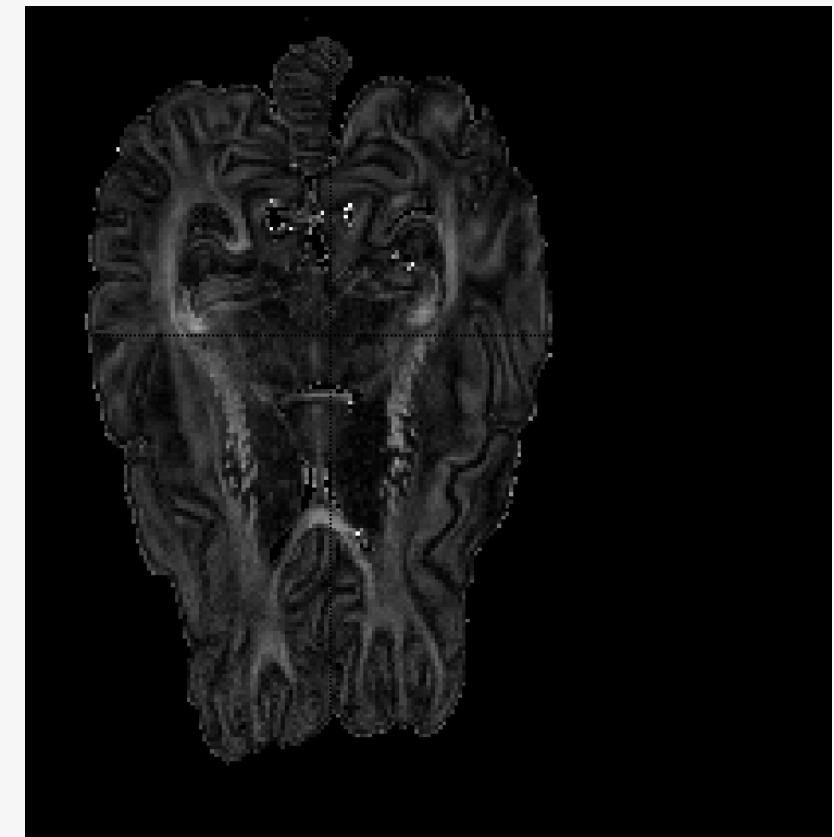
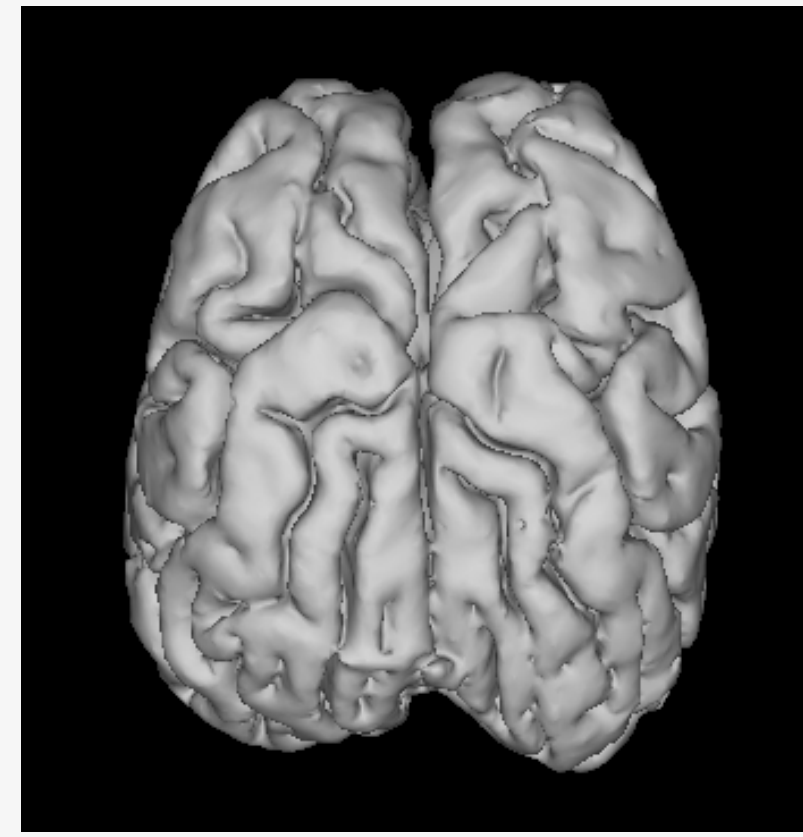
# Lung protection and development

- After 10 days of AP support, premature lambs (118 days) are able to transition to mechanical ventilation.
- Functional, morphological and molecular data indicate that development continues and lungs are protected from injury during AP support.
- Intratracheal perfluorocarbons minimize lung injury and promote normal lung development.



# Cerebral Oxygenation, Perfusion, Protection and Development

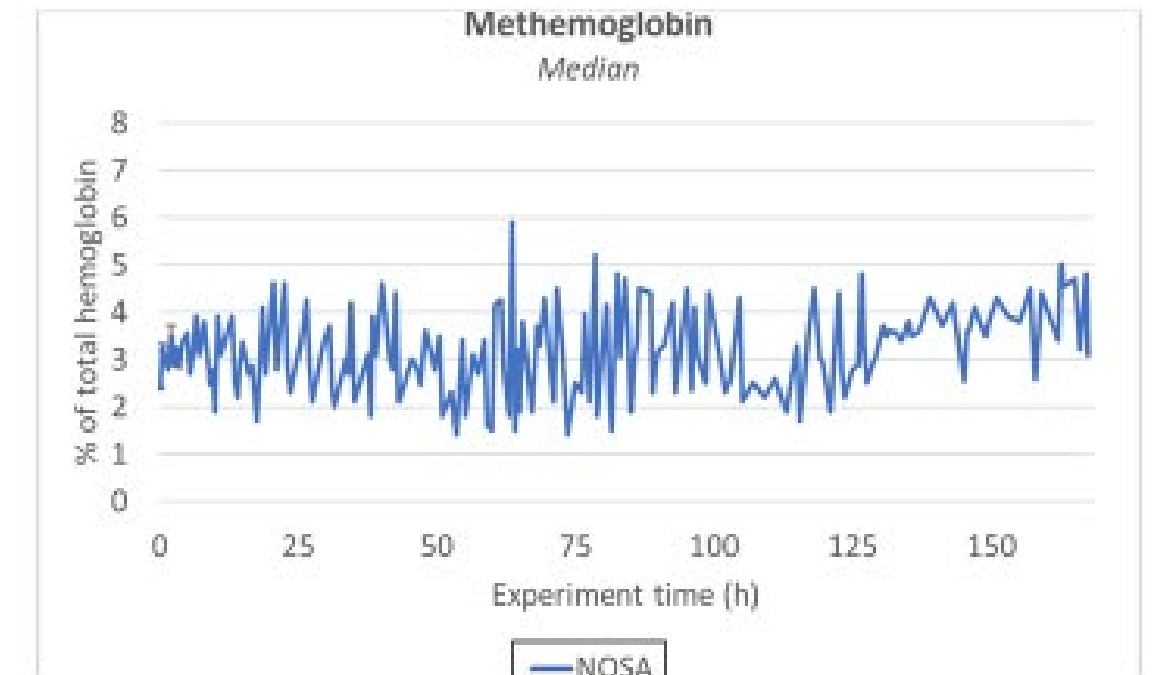
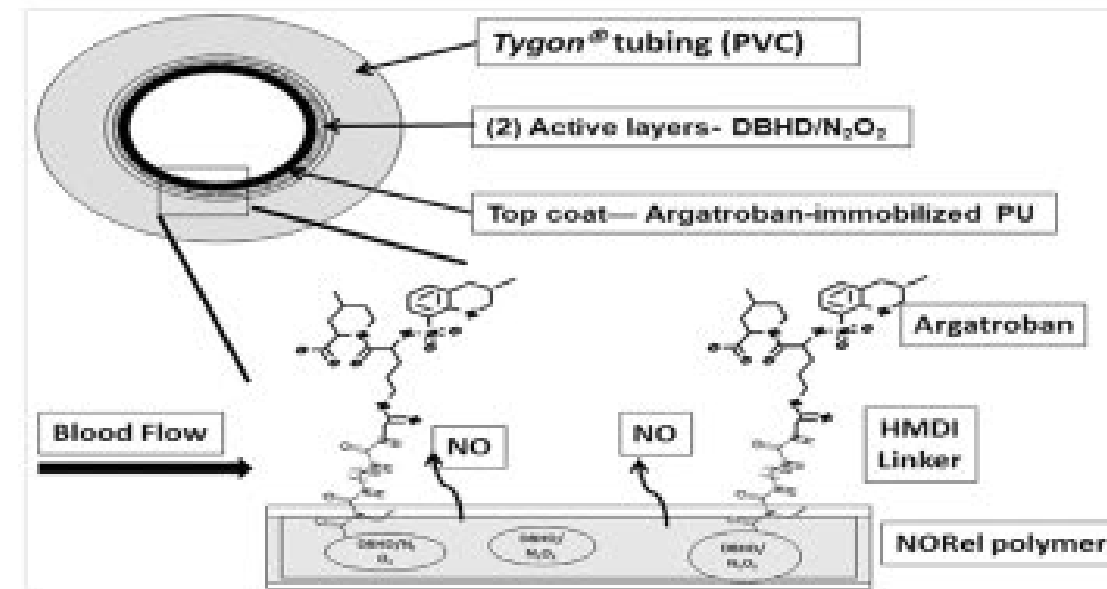
- Cerebral oxygenation and blood flow in premature lambs are maintained during AP support.
- No white matter injury and normal cortical folding with AP support.



# NOSA eliminates need for systemic anticoagulation

Five premature lambs survived for one week with no systemic anticoagulation. There was no bleeding or thrombosis.

Normal fetal gas exchange, hemodynamic stability and maintenance of fetal circulation.



## BASIC SCIENCE ARTICLE

Extracorporeal life support without systemic anticoagulation: a nitric oxide-based non-thrombogenic circuit for the artificial placenta in an ovine model

Brian P. Fallon<sup>1</sup>, Orsolya Lautner-Csorba<sup>1</sup>, Terry C. Major<sup>1</sup>, Gergely Lautner<sup>1</sup>, Stephen L. Harvey<sup>1</sup>, Mark W. Langley<sup>1</sup>, Matthew D. Johnson<sup>1</sup>, Claudia Saveski<sup>1</sup>, Niki Matusko<sup>2</sup>, Raja Rabah<sup>3</sup>, Alvaro Rojas-Pena<sup>1,4</sup>, Mark E. Meyerhoff<sup>5</sup>, Robert H. Bartlett<sup>1</sup> and George B. Mychaliska<sup>6</sup>



# Miniaturization (unpublished)

Extremely premature lambs (90 - 100 days, term=145 days) 1.5kg can maintain hemodynamic stability and gas exchange on the AP.

Developing mini -sheep model with fetal weight < 1.0kg.

Supported 1.5kg minisheep with 6F cannulas.



95 day, 1.5kg fetal lamb model



105 day, 1.0kg mini-sheep fetal lamb model

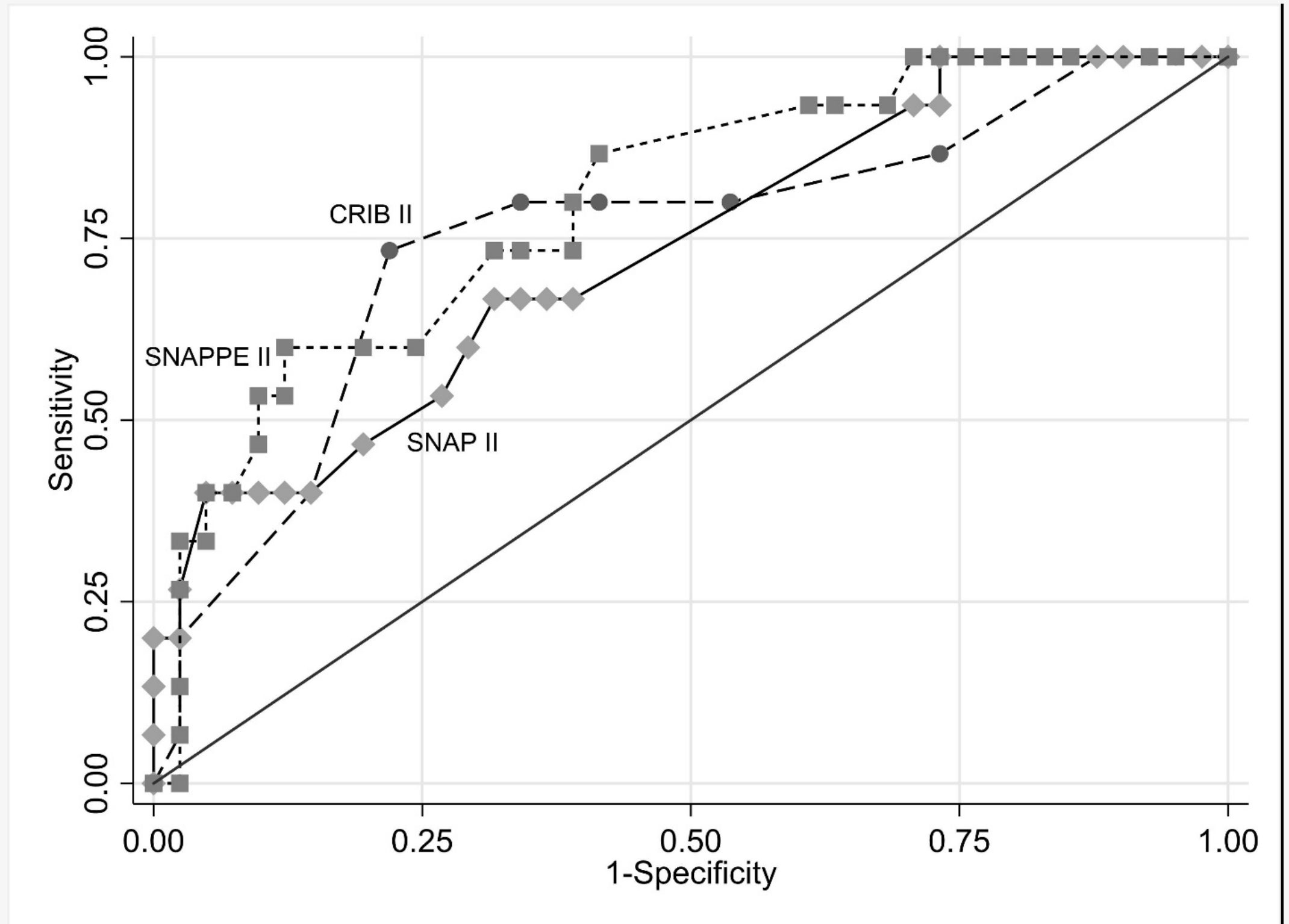


# Prediction of mortality by discharge (unpublished)

Receiver operator characteristic (ROC) curve for 4-hour SNAPPE II, SNAP II, and CRIB II associated with mortality by discharge

SNAPPE II at 4 hours of life (AUC 0.8;  $p < 0.005$ ) was the best predictor of mortality in our retrospective study

Ongoing prospective study. Additional variables included along with markers of morbidity in premature infants.



## KEY PRINCIPLES

# Clinical Translation

- Utilize the NICU and ECMO platform with modifications.
- Early AP application with postnatal risk stratification
- Late AP application with failure of medical treatment
- Ethical and regulatory considerations

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Thank you!