

Extracorporeal Support of
the Premature Infant (ESPI)
– The Artificial
Uterus/Placenta

Extreme Prematurity – The Unmet Need



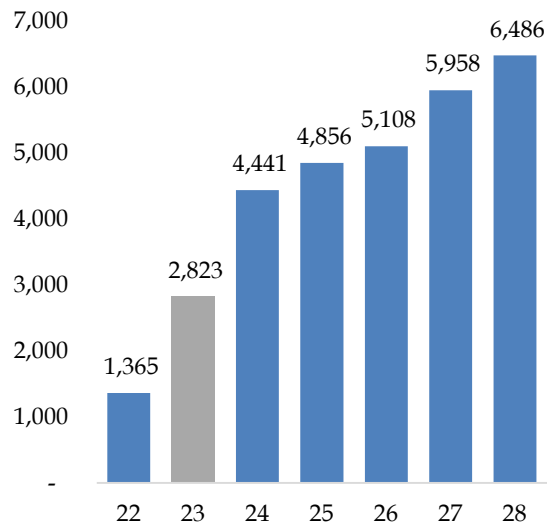
The major cause of perinatal morbidity and mortality in developed countries

- Acute Complications of prematurity:
 - Retinopathy of prematurity
 - Intraventricular hemorrhage
 - Developmental delay/Cerebral palsy
 - Respiratory insufficiency/CLD
 - Patent ductus arteriosus
 - Necrotizing enterocolitis
 - Hyperbilirubinemia
 - Neonatal sepsis

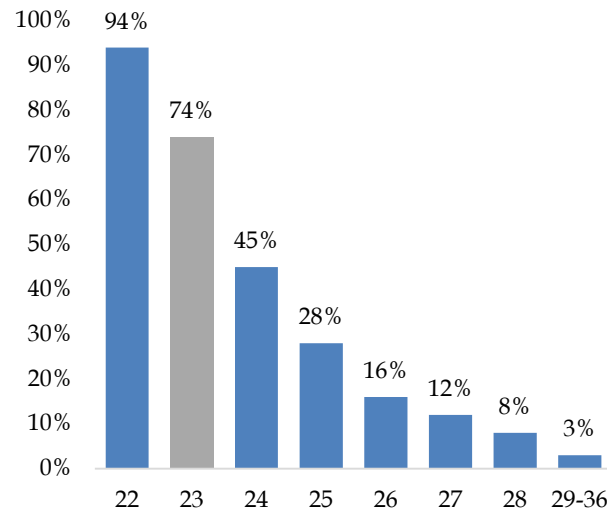
**INADEQUATE ORGAN MATURATION
IATROGENIC INJURY**

Current State of Neonatal Care

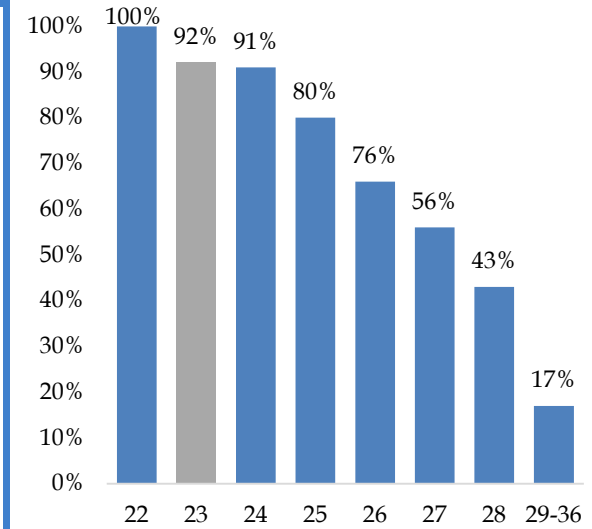
Number of Infants



Mortality by Gestation



Morbidity by Gestation



- Around 1% of all infants (~30K) born each year are born at 28 weeks or younger
- Both mortality and morbidity are significant concerns

TARGET POPULATION – 23-26 Weeks Gestation

Rationale for ESPI

Development of an extra-corporeal *physiologic* fetal support system would abrogate the deleterious effects of premature birth by allowing normal organ maturation

Initial Goal– 3 weeks of support to reach milestones with improved mortality/morbidity

OBJECTIVES

- Maintain fetal circulation and fetal PaO₂
- mimic the sterile intrauterine environment
- abrogate the need for gas-based lung ventilation
- allow normal fetal breathing and swallowing (fluid based)
- support ongoing growth and organ development

History of ESPI

1960's – UA/UV cannulation, pump assisted, Bubble oxygenators – 40 min – 2 days

1987 – 1998 – Kuwabara and Unno – UA/UV – pump assisted – hollow fiber membrane oxygenators, passive arterial filling, hemodialysis, paralysis – up to 543 hours

2000's – Mychaliska – Initially pumpless, fluid bath, UA/UV – now pumped VV – ECMO, fluid filled/clamped ET tube – 1 week

All limited by progressive cardiac failure, sepsis, inability to transition from ESPI support

Pumpless ESPI systems – 5 studies - minutes to 29 hours

All limited by cardiac failure

- Fetal heart extremely sensitive to pre-load or afterload imbalance (high resistance oxygenators, pumped circuits)

- Infection is a major limitation of fluid environments

- UA/UV – challenging due to spasm, vascular integrity

Components of ESPI

Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit

Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

“Amniotic fluid” environment

Open aquarium, Continuous fluid circulation, Micropore filters

Human (premie) TPN, fluid and Systemic antibiotics, PGE2, narcotic Sedation, heparin

Evolution of cannula placement and design

Carotid artery/Jugular vein cannulation (standard ECMO cannulas)

Prototype I

- **23 – 108 hours (5 animals 120-140 days GA)**
- **Remarkable hemodynamic Stability**
- **Limited by sepsis/cannula dislodgement**

Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit

Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

“Amniotic fluid” environment

Semi-closed plexiglass tank, Continuous fluid exchange, parallel UV light chamber

Sheep fetal TPN, fluid and systemic antibiotics, PGE2, Propofol sedation, **low or no heparin**

Evolution of cannula placement and design

Carotid artery/Jugular vein cannulation (*Modified ECMO cannulas*)

- **348 ± 93 hours (209-480 hrs, 5 animals – 120-125 days GA)**
- **Hemodynamic/metabolic stability,**
- **Improved but still limited by sepsis 3/5 animals, 1 survivor**

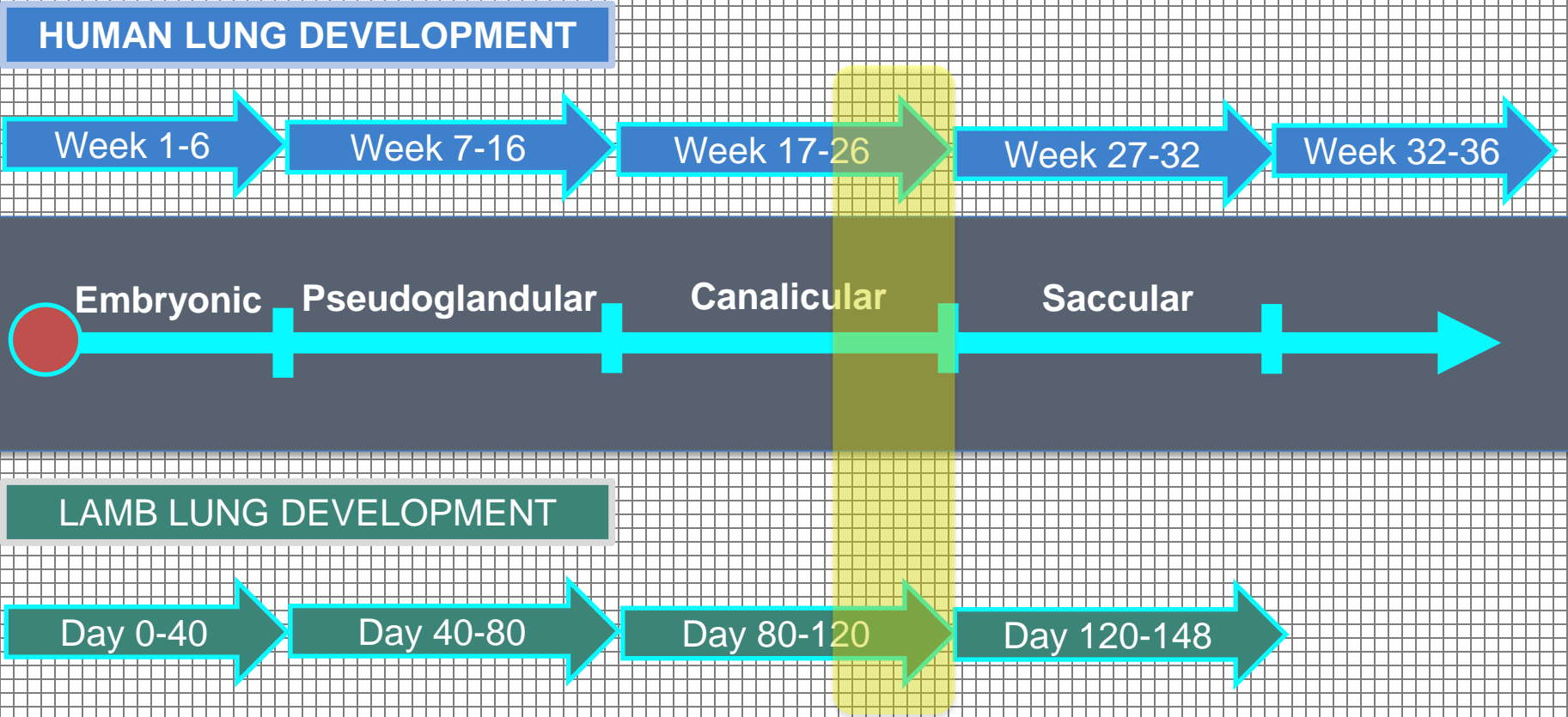
The Problem of Sepsis

Development of the “Biobag”

- Open sided design, adjustable size
- Adjustable number, size, and configuration of ports
- Metallocene polyethylene film – silver impregnated
- Once sealed, completely closed system, efficiencies of flow and volume.
- Translucent and sonolucent

Pre-Clinical Goals of ESPI

Application of ESPI to earlier gestational age fetuses - Developmental Equivalence to Human 22 – 26 week fetus



(Human) 22- 26 weeks = (Lamb) 110 – 120 days

Application of ESPI to earlier gestational age fetuses -

Problem – Development of hydrops

Oxygenator perfusion
pressure/Flow directly related to -

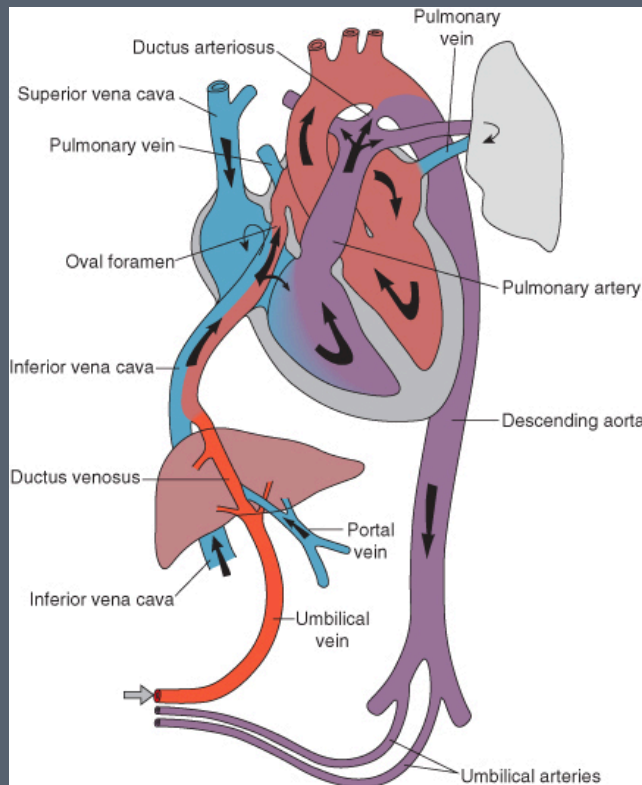
Carotid arterial pressure - SVC pressure



Decreasing GA



Jugular/SVC
venous return



Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit

Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

“Amniotic fluid” environment

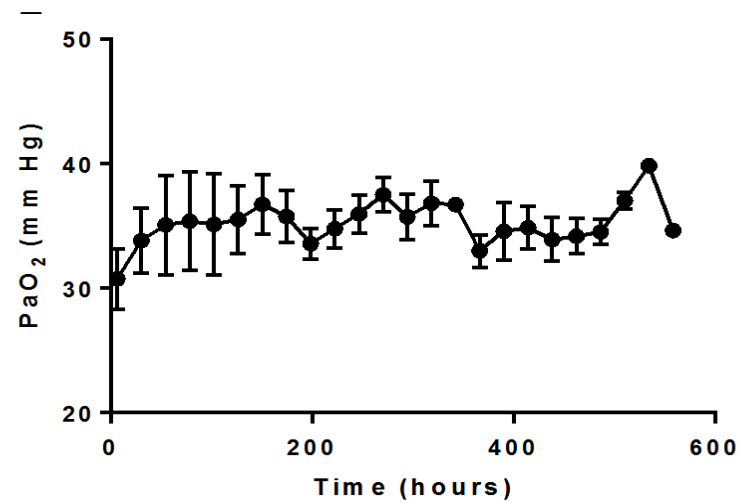
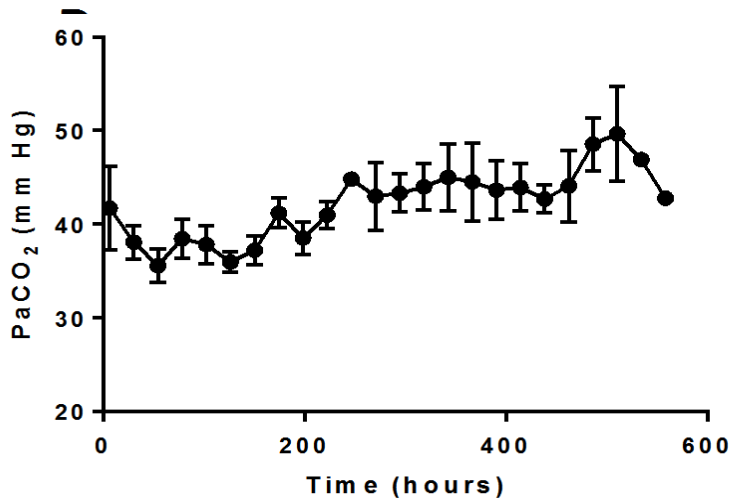
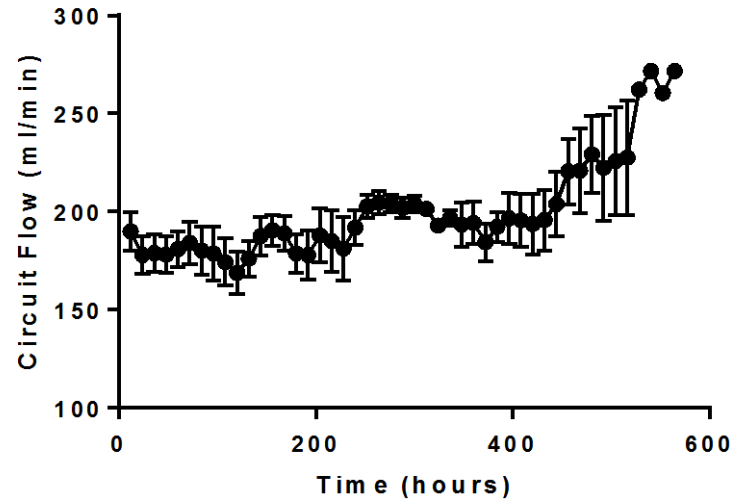
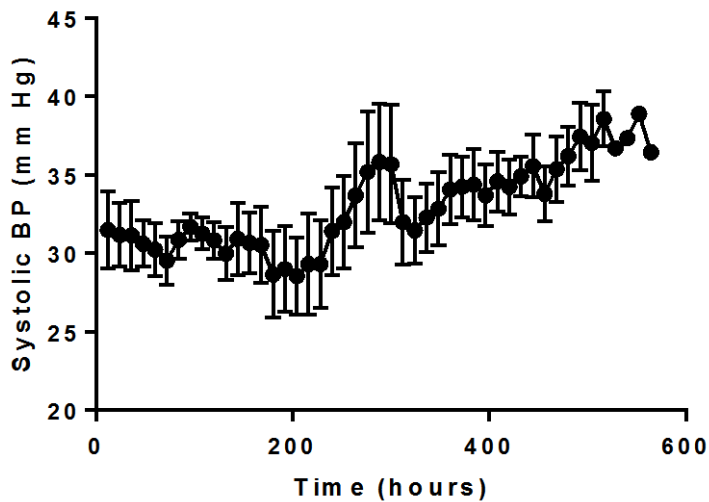
Closed Biobag system, Continuous fluid exchange

Sheep fetal TPN, systemic antibiotics, PGE2, Propofol sedation, low or no heparin

Evolution of cannula placement and design

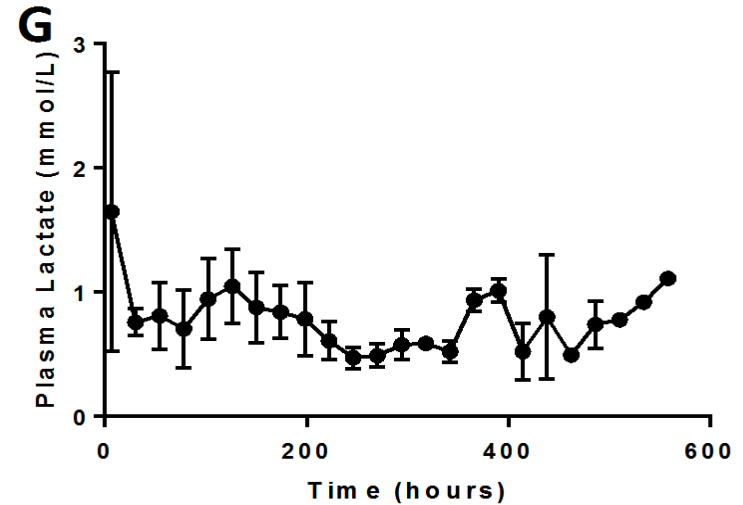
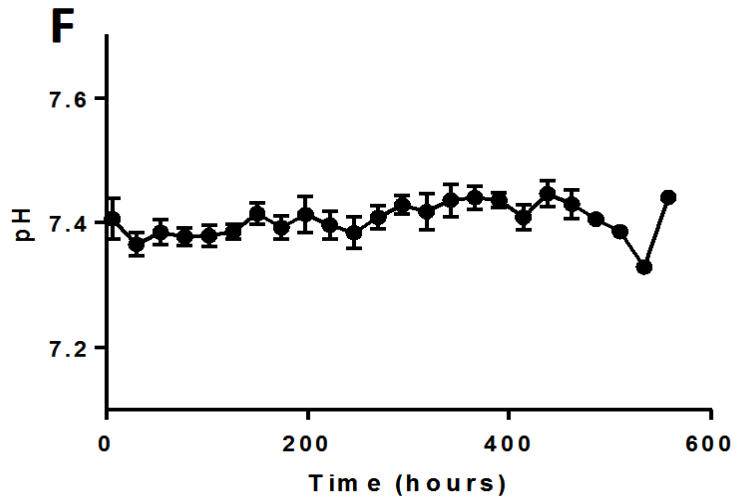
Carotid artery/*Umbilical vein* cannulation (*Modified ECMO cannulas*)

Hemodynamic/metabolic Stability on ESPI



GA – 108 – 113 Days – 5 animals/20 – 26 days on ESPI

Hemodynamic/metabolic Stability on ESPI



	In utero (GA 125 d)	Lamb 1	Lamb 2	Lamb 3	Lamb 4	Lamb 5	Mean
Hgb (g/dl)	8.9	13.2	12.1	11.6	11.7	11.5	12.0
“Circuit” flow (ml/ kg*min)	200 (umbil. flow)	76.8	83.2	83.1	94.0	117.8	91.0
Total O ₂ delivery (ml/ kg*min)	19.6	14.3	13.7	13.5	17.0	19.2	15.5
Total O ₂ consumption (ml/kg*min)	6.7	6.9	6.2	5.0	5.5	8.6	6.4
Total O ₂ extraction (%)	34.2	48.0	45.5	37.8	33.4	44.2	41.8
Carotid P _{O₂} (mm Hg)	23.1	31.2	34.5	36.9	42.6	34.1	35.9
Carotid O ₂ sat (%)	62.0	52.7	56.5	62.6	68.5	57.6	59.6
Carotid O ₂ content (ml O ₂ /dl blood)	7.5	9.5	9.3	9.8	10.9	9.0	9.7
Plasma lactate (mmol/L)	1.8	1.5	0.7	0.5	0.4	0.8	0.8

GA – 108 – 113 Days – 5 animals/20 – 26 days on ESPI

Growth and Development - Lung Histology

- 5 successful 3 weeks runs on BioBag ESPI system
- Evidence of appropriate maturation with secondary septations, well-formed alveolae, wide airspaces
- No evidence of infection or inflammation
- Normal radial alveolar count (RAC), morphometrics, Surfactant staining

Control 110 Day

Control 139 Day

21 Days on ESPI – 139 Day

Pumpless, low resistance, low surface area, heparin coated, oxygenator circuit

Maquet Quadrox-ID Pediatric Oxygenator, Bioline Coated

“Amniotic fluid” environment

Closed Biobag system, Continuous fluid exchange

Sheep fetal TPN, systemic antibiotics, PGE2, Propofol sedation, low or no heparin

Evolution of cannula placement and design

Umbilical Artery (2)/Umbilical vein cannulation/New cannula design

Maintenance of the Fetal Circulation

*Ductus
Arteriosus*

Maintenance of the Fetal Circulation

Ductus Venosus

Foramen Ovale

Achievement of Normal Fetal Circulation

Problem – CA Cannulation

- Concerns related to cerebral blood flow/brain development
- Subphysiologic “placental” perfusion

70 – 100 ml/kg/min vs. 150-200 ml/kg/min

Compensations to achieve normal O₂ delivery

↑ Hb ↑ Post membrane pO₂

↓ O₂ Consumption (sedation)

- Issues related to cannula dislodgment and removal

Achievement of Normal Fetal Circulation

UA/UV Cannulation

- Ongoing studies – 2 UAs, 1 UV, 3 lambs – 105-108 d GA – 28 day Runs. 1 lamb – severe TOF -28 d

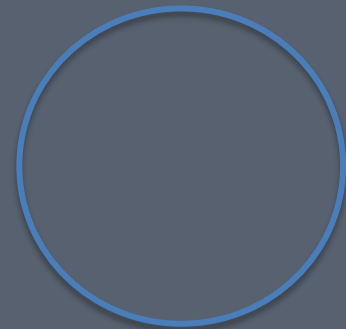
- Observations

- ↑ Circuit flows to 150-200 ml/kg/min

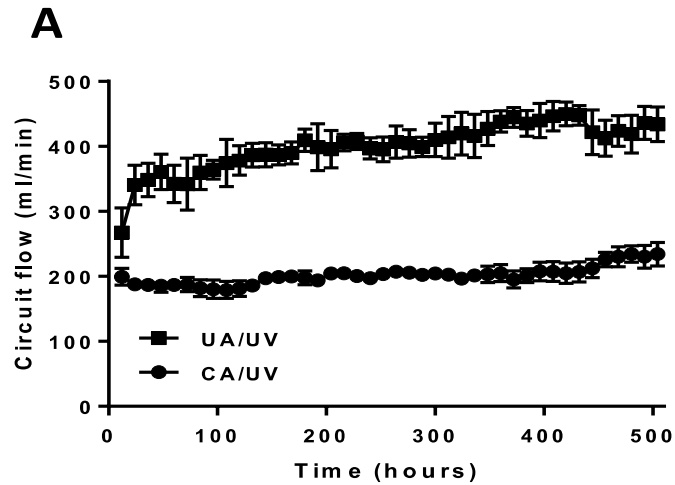
- ↑ Pre-membrane pressures
With autoregulation across the post membrane UV and DV

Normal O₂ delivery and O₂ Consumption (nutrition) without compensations

Reduced concern regarding cannula dislodgements, Reduced sedation requirements



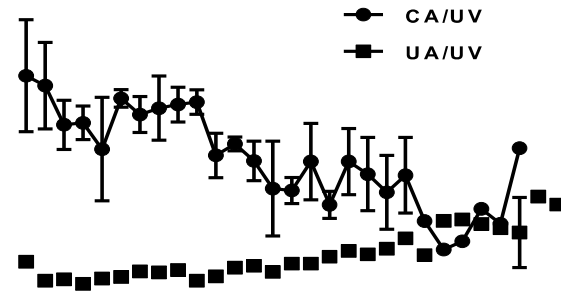
Hemodynamic/metabolic Stability on ESPI



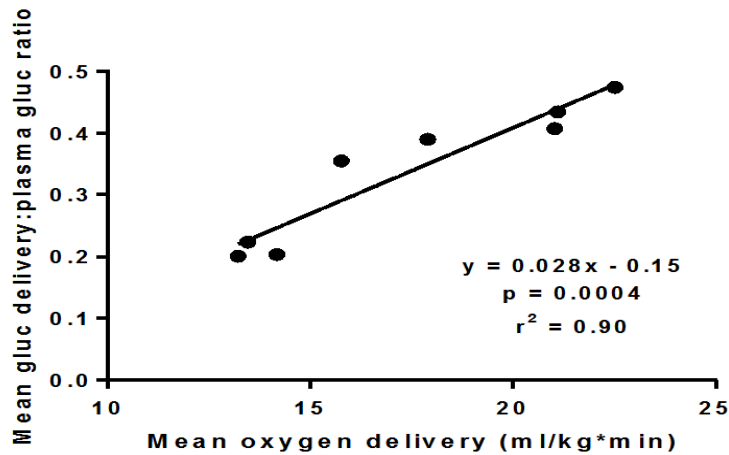
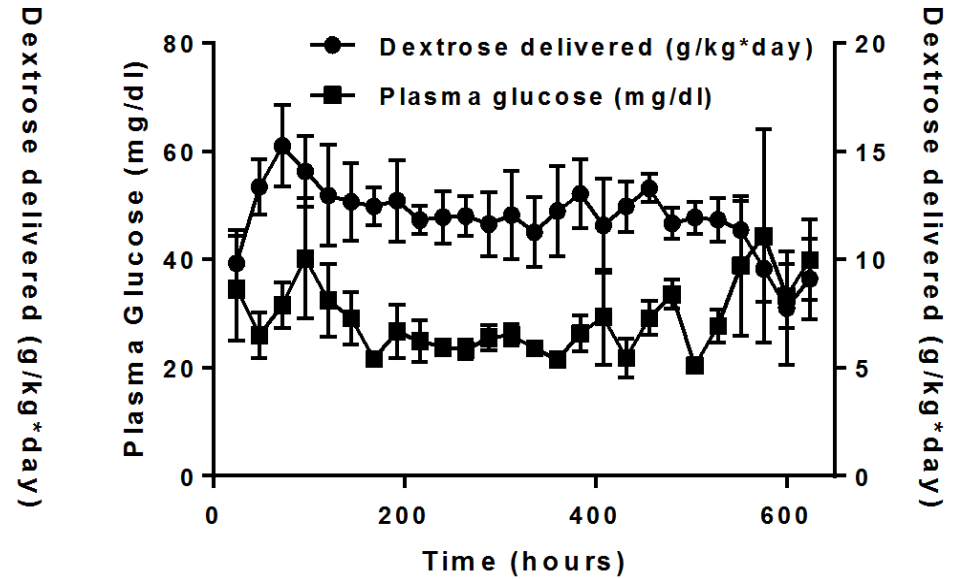
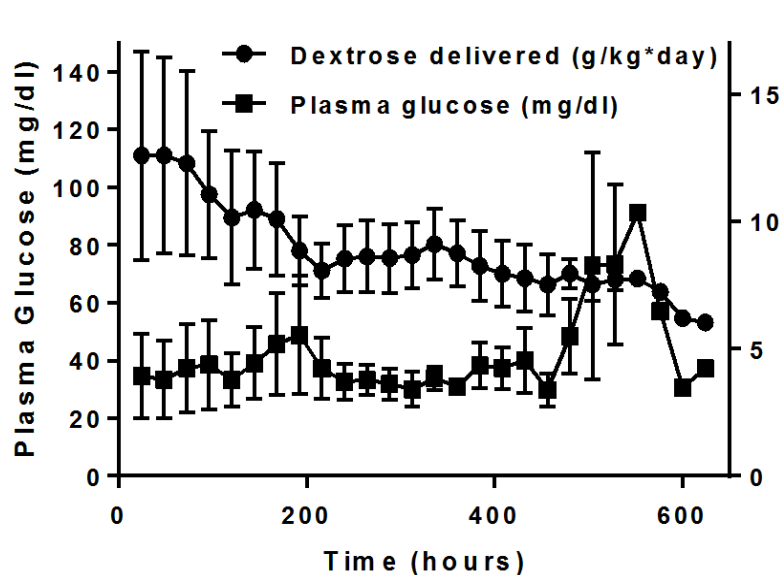
B

C

D



Hemodynamic/metabolic Stability on ESPI



ESPI Applications

Extreme Prematurity

- Initially 23 – 24 wk extreme premature infant

Transitional Applications

- CDH – EXIT to ESPI at 35 wks - 3-4 weeks of ESPI prior to gas ventilation – Pharmacologic treatment of pulmonary HTN +/- lung growth strategies, diaphragmatic hernia repair
- Fetal Growth Restriction
- Support of infants with congenital heart disease for organ/brain maturation prior to cardiac repair
- Gene therapy/cell therapy applications?

The image shows the Children's Hospital of Philadelphia building at night. The building is illuminated with a vibrant, multi-colored light display that forms a grid-like structure, resembling scaffolding, over the facade. The colors include red, yellow, green, blue, and purple. The text "The Children's Hospital of Philadelphia" is visible on the top edge of the building. The sky is dark blue, and the foreground shows a street with light trails from passing vehicles.

The Center for Fetal Diagnosis and Treatment

The Center for Fetal Research

**Children's Hospital
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