From piglets to (human) babies: pediatric brain hypoxia with ICM+

Jennifer K. Lee, MD
Pediatric Anesthesiology
Johns Hopkins University
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• NIH NINDS: R01 NS107417

• American Heart Association Transformational Project Award
Objectives

1. Piglet brain hypoxia
2. Clinical pediatric brain hypoxia
3. Multi (2)-center study
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2007

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1. Piglet brain hypoxia

2010

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Objectives

2007

1. Piglet brain hypoxia

2010

2. Clinical pediatric brain hypoxia

2018

3. Multi (2)-center study
Neonatal piglet hypoxia-ischemia

\[ HVx = -0.49 \]

\[ HVx = 0.9 \]

Lee. CCM 2011
Verifying brain injury in piglet autoregulation model

SHAM

HYPOXIA-ISCHEMIA

Cortical laminar necrosis

Lose 50% of neurons

Hypoxia-ischemia protocol causes piglet learning and memory deficits: special T-maze

Singh. *Brain Behav Res* 2019
HVx in a Neonate with Hypoxic Ischemic Encephalopathy

Howlett. Pediatric Res 2013
Blood Pressure and Optimal MAP

Optimal MAP (mmHg)

~6 hours of monitoring

Calculate the area under the curve (AUC) for time and blood pressure deviation below optimal MAP.
Pediatric Cardiac Arrest (n = 29)

PCPC
1 = Normal
2 = Mild disability
3 = Moderate disability
4 = Severe disability
5 = Coma/vegetative
6 = Death
(Neurologic deficits)

Change in PCPC

Time and Deviation Below Optimal MAP

$p = 0.02$

Lee. Resuscitation 2014
Pediatric Cardiac Arrest

• More time and greater blood pressure deviation below optimal MAP

• During the 2\textsuperscript{nd} 24 hours after return of circulation
  • New tracheostomy or gastrostomy
    \( n = 28; \ p = 0.04 \)

• During the 1\textsuperscript{st} 48 hours after return of circulation
  • Declaration of brain death or withdrawal of support for neurologic futility
    \( n = 29; \ p = 0.04 \)

Lee. Resuscitation 2014
Pediatric Cardiac Arrest (n = 29)

- Optimal MAP increased with age
- Optimal MAP did not match the 50\textsuperscript{th} percentile for MAP
- Optimal MAP accounts for changing intracranial pressure

$p < 0.001$

Lee. Resuscitation 2014
Piglet Controlled Hydrocephalus: optimal MAP from ICM+

Pressure Reactivity index (PRx)

- $n = 29$
- $p < 0.001$
- $r = 0.80$ (95% CI: 0.52, 0.88)

Laser Doppler flowmetry (LDx)

- $n = 24$
- $p = 0.002$
- $r = 0.61$ (95% CI: 0.26, 0.82)
Analyses were adjusted for:

- PaCO2
- Seizures (yes/no)
- Vasopressor use (yes/no)
- Birth asphyxia severity
  - pH from umbilical cord or first hour of life blood gas
  - Base deficit
  - Sarnat stage
- 10 minute Apgar
- Emergent delivery (yes/no)
- Mechanical ventilation after delivery (yes/no)
Neonatal Hypoxic Ischemic Encephalopathy and Brain MRI at 1-2 weeks (n=64)

• Greater duration and deviation of blood pressure below MAP_{OPT} during hypothermia and rewarming:

• Greater injury in paracentral gyri and white matter

Neonatal Hypoxic Ischemic Encephalopathy and Brain MRI at 1-2 weeks (n=64)

- More time with blood pressure within $\text{MAP}_{\text{OPT}}$ during rewarming and normothermia
  - Lesser injury in the white matter, putamen and globus pallidus, and brainstem

- Blood pressure above $\text{MAP}_{\text{OPT}}$ (maximum 75 mmHg) during hypothermia
  - Lesser injury in the paracentral gyri

Neonatal HIE and Rewarming – Neurodevelopmental Outcomes at ~2 Years of Age

- Mullen Scales of Early Learning
- Gross Motor Function Measure testing
- Capute developmental & motor quotients

*\( p < 0.05 \)
Comparison of indices: 66 historic HI and sham piglets

Govindan. Develop Neurosci 2019
Moyamoya Revascularization (Pial Synangiosis) Autoregulation curves during surgery

Lee. Paediatr Anaesth 2013 & 2018
Moyamoya Revascularization (Pial Synangiosis) Bilateral Vasculopathy Ages 2 - 21 years old (n=9)

* $p = 0.048$

Intraoperative

Postoperative

Lee. Paediatr Anaesth 2018
Moyamoya Revascularization (Pial Synangiosis)  
Bilateral Vasculopathy  
Ages 2 - 21 years old (n=9)  

Poorer intraoperative autoregulation may be associated with higher risk of postoperative transient ischemic attack

$p = 0.048$
Conclusions

• Preclinical validation of autoregulation metrics is an important step for clinical investigative use

• ICM+ enabled seamless transitions between bench and bedside clinical studies for pediatric brain hypoxia