

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



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Current Financial Support (PI)

- NIH NINDS: R01 NS107417
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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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Objectives

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1. Piglet brain hypoxia

2010



2. Clinical pediatric brain hypoxia

3. Multi (2)-center study

Objectives

2007



1. Piglet brain hypoxia

2010

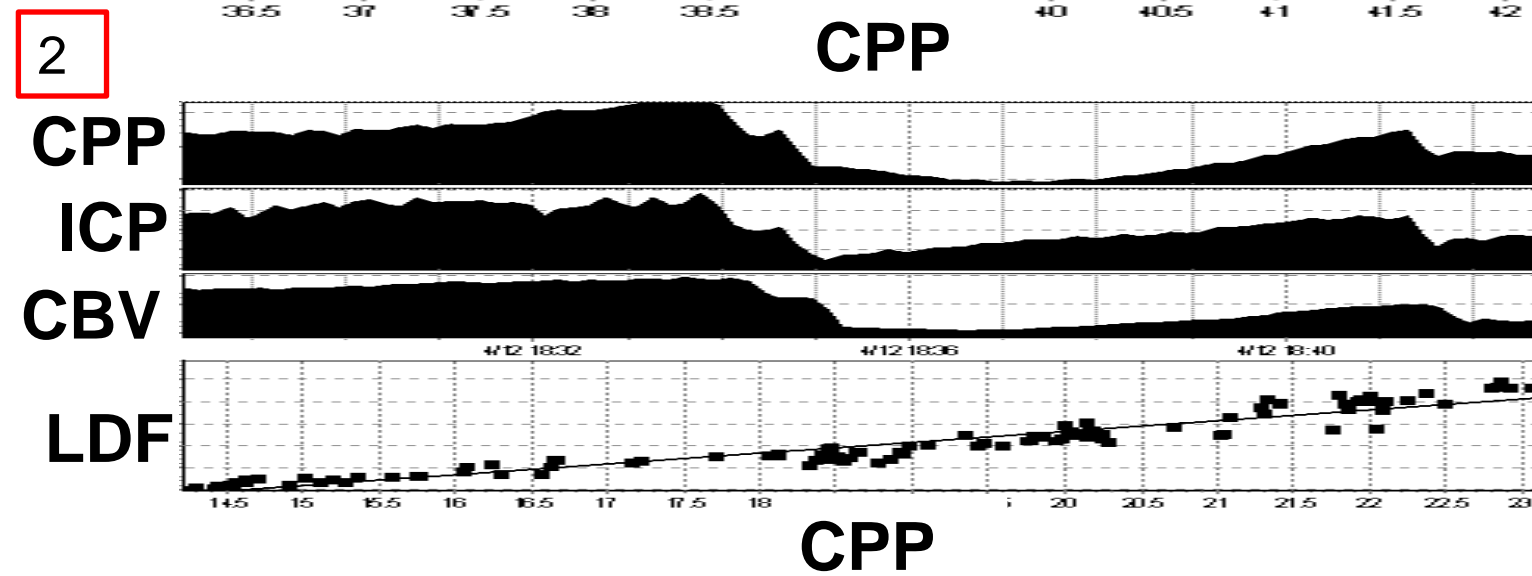
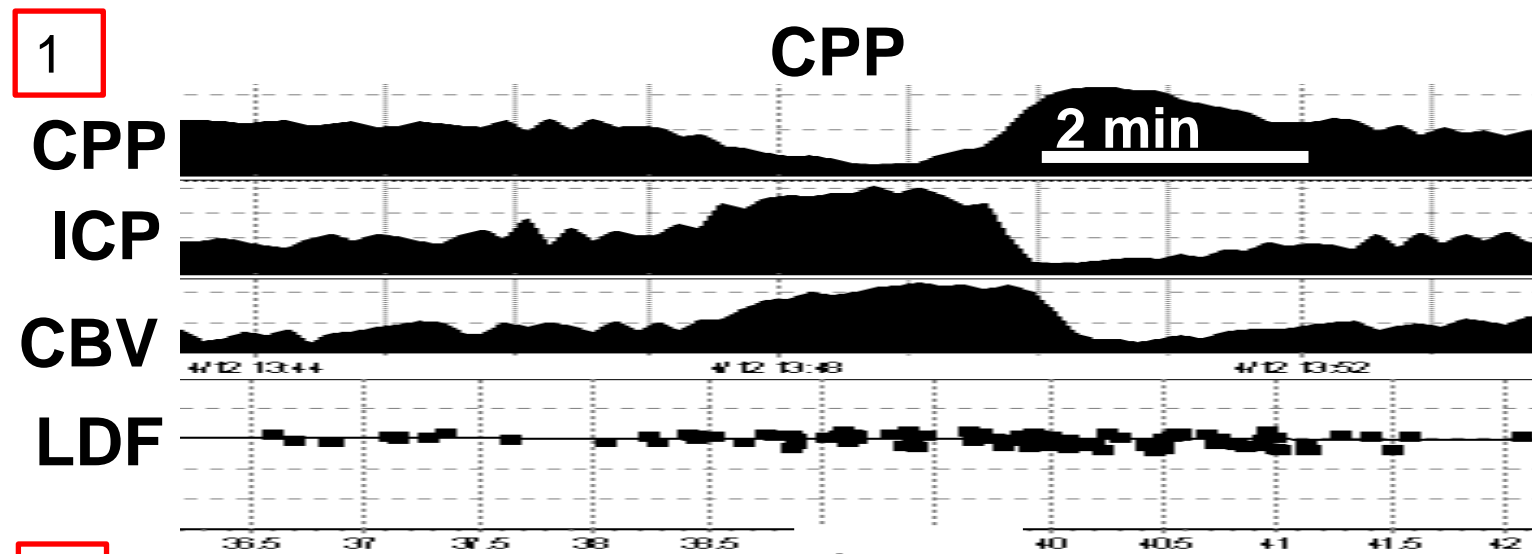
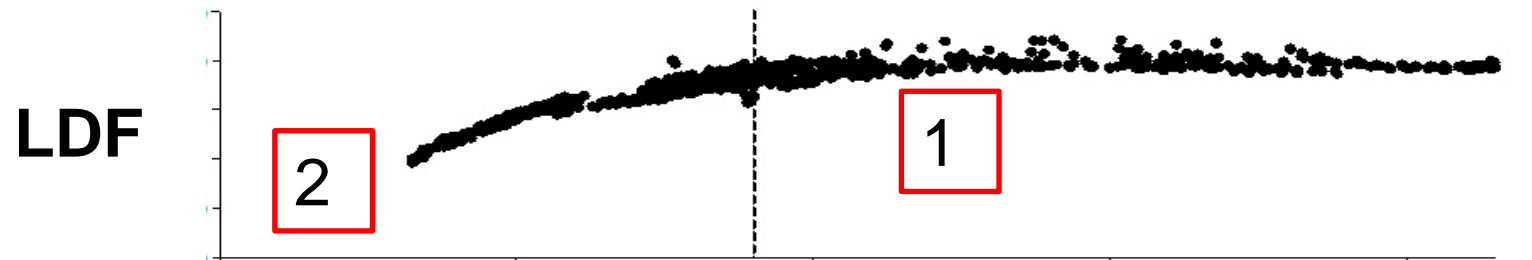


2. Clinical pediatric brain hypoxia

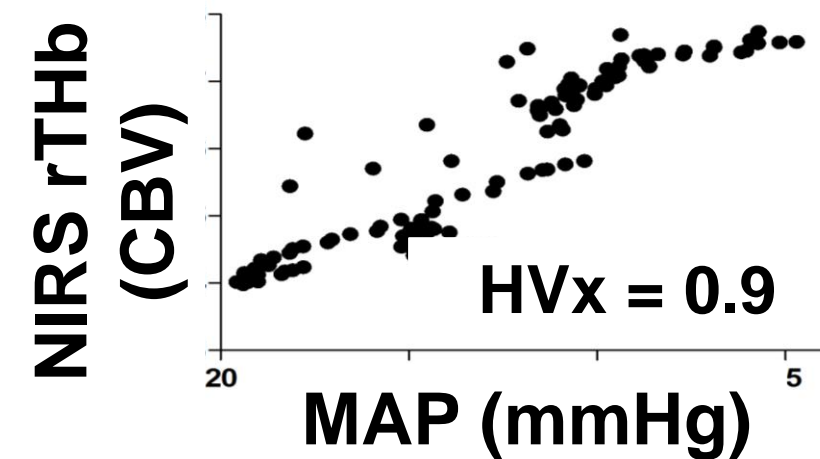
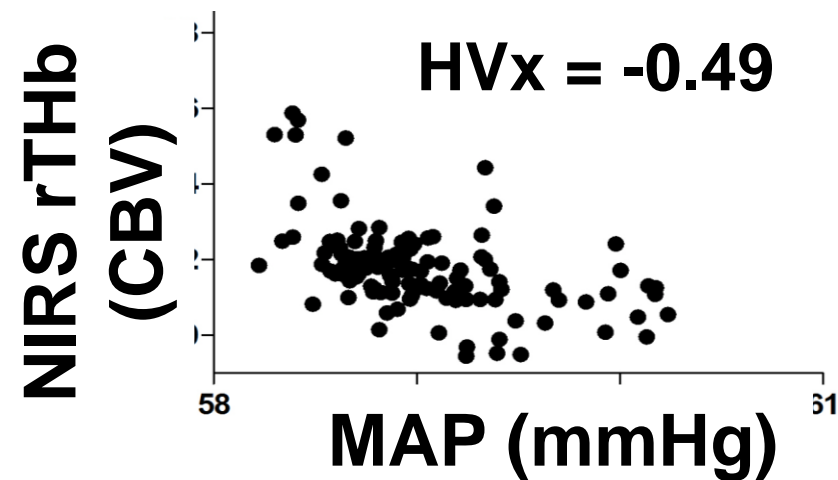
2018



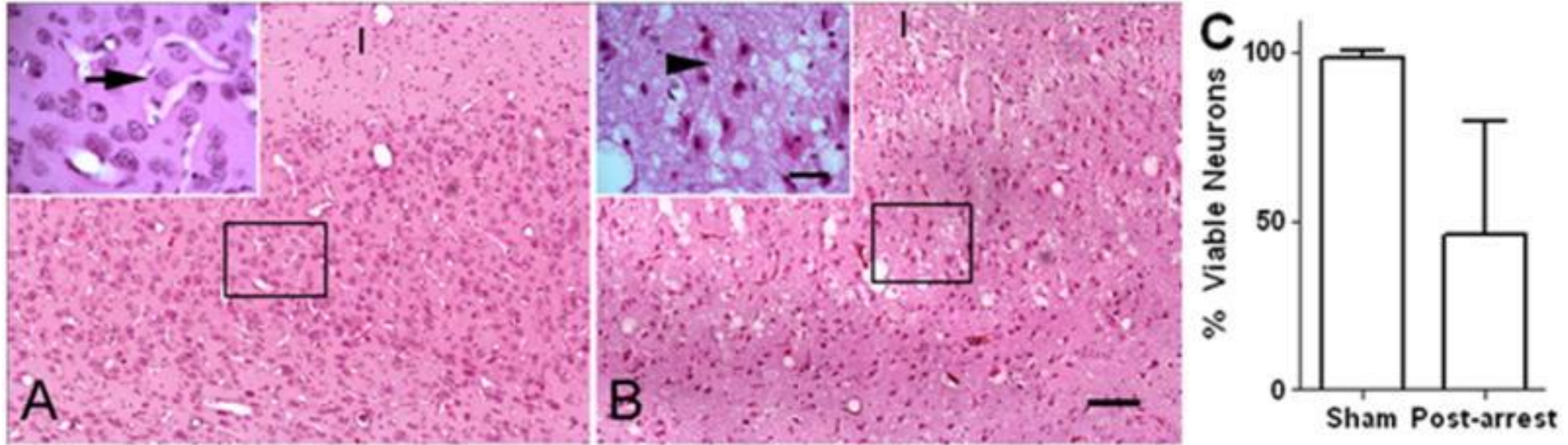
3. Multi (2)-center study



Neonatal piglet hypoxia-ischemia



Verifying brain injury in piglet autoregulation model



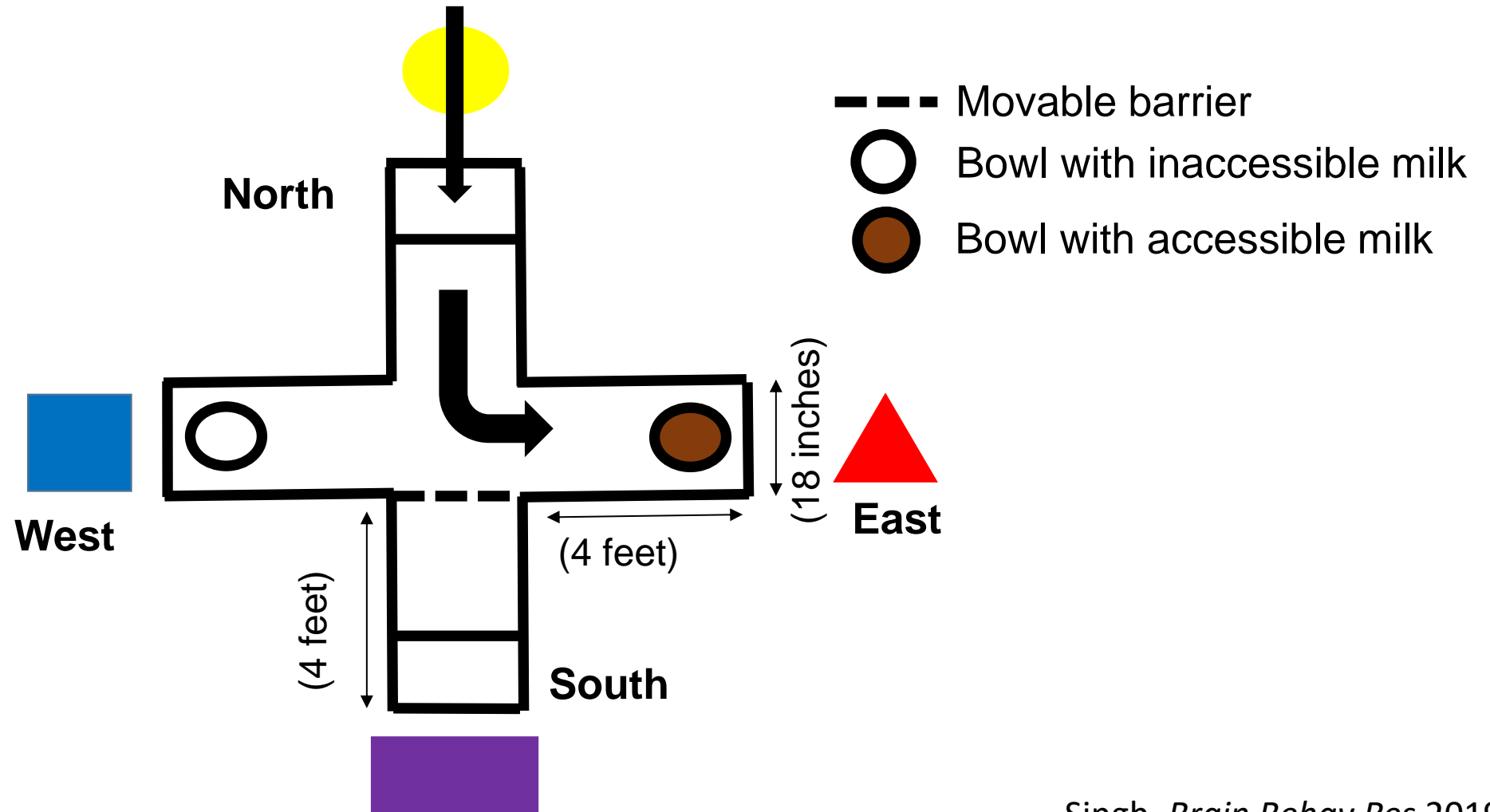
SHAM

HYPOXIA-ISCHEMIA

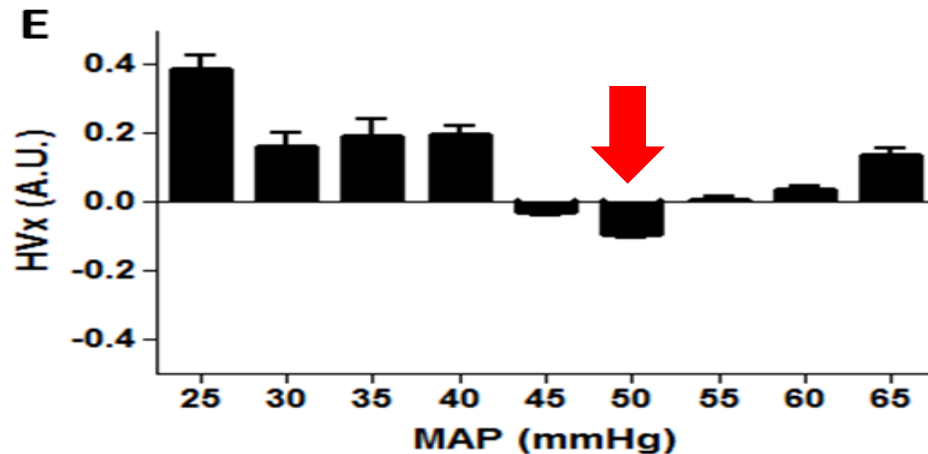
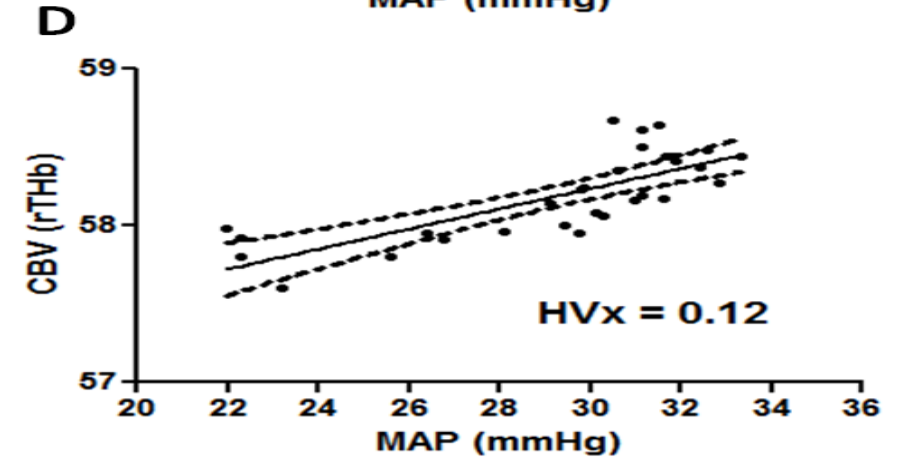
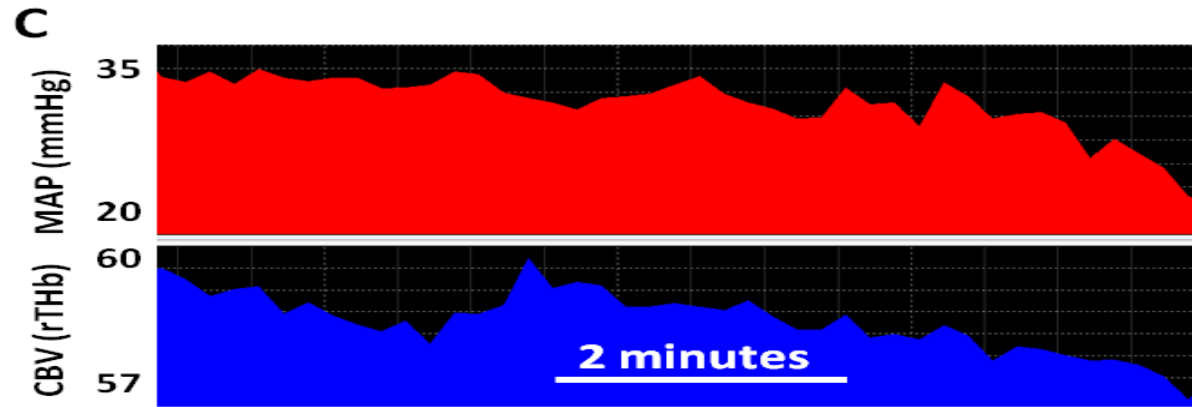
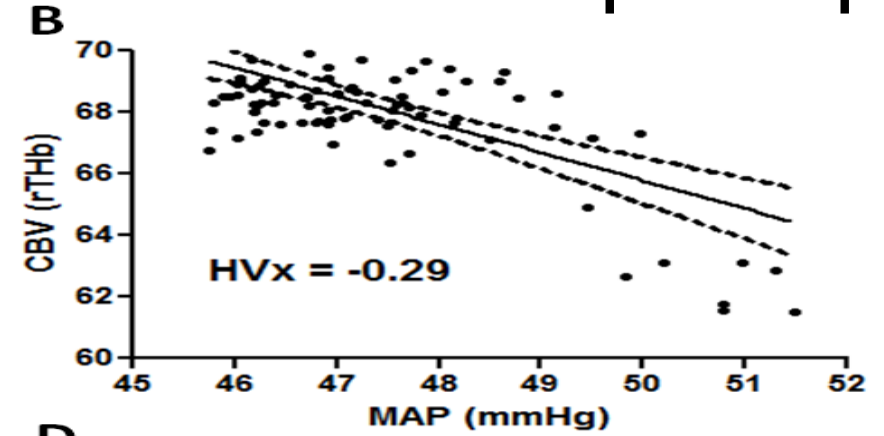
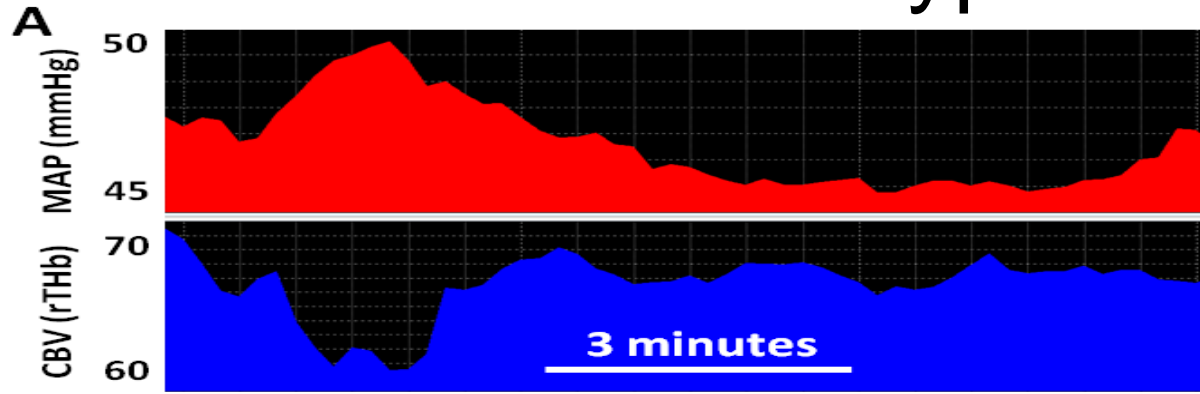
Cortical laminar necrosis

Lose 50% of neurons

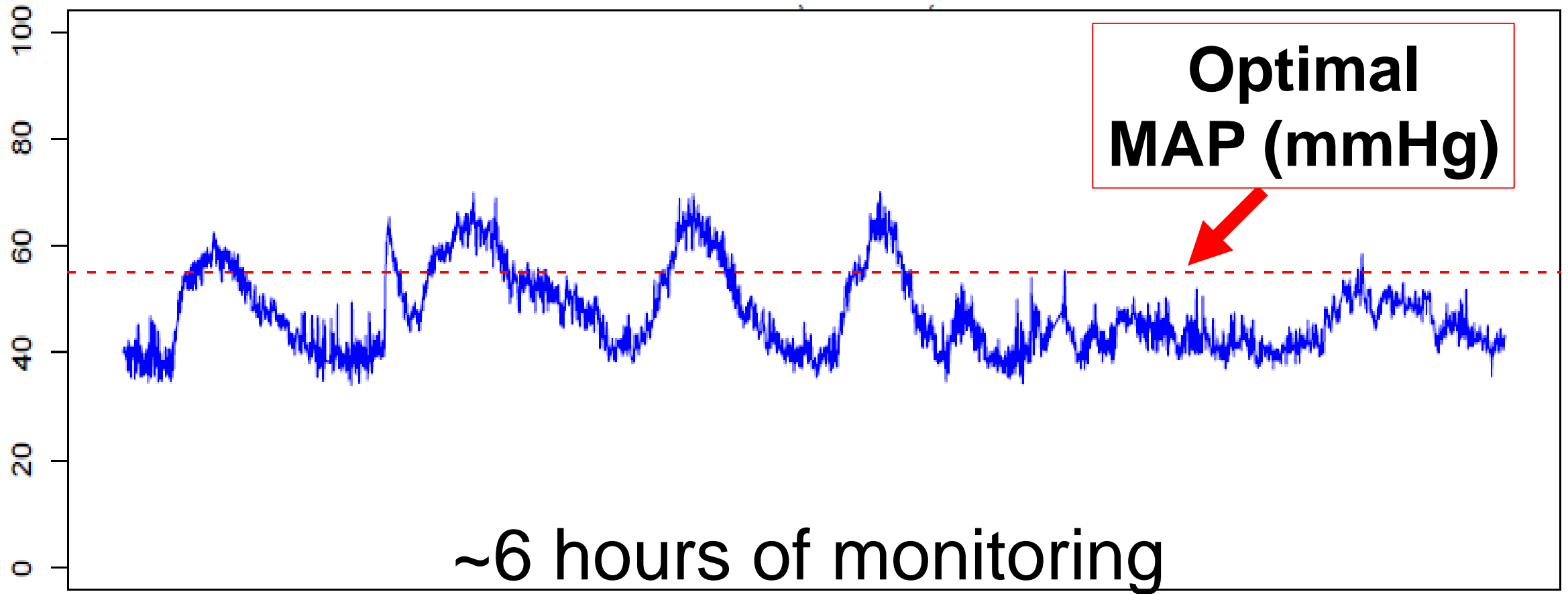
Hypoxia-ischemia protocol causes piglet learning and memory deficits: special T-maze



HVx in a Neonate with Hypoxic Ischemic Encephalopathy



Blood Pressure and Optimal MAP



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

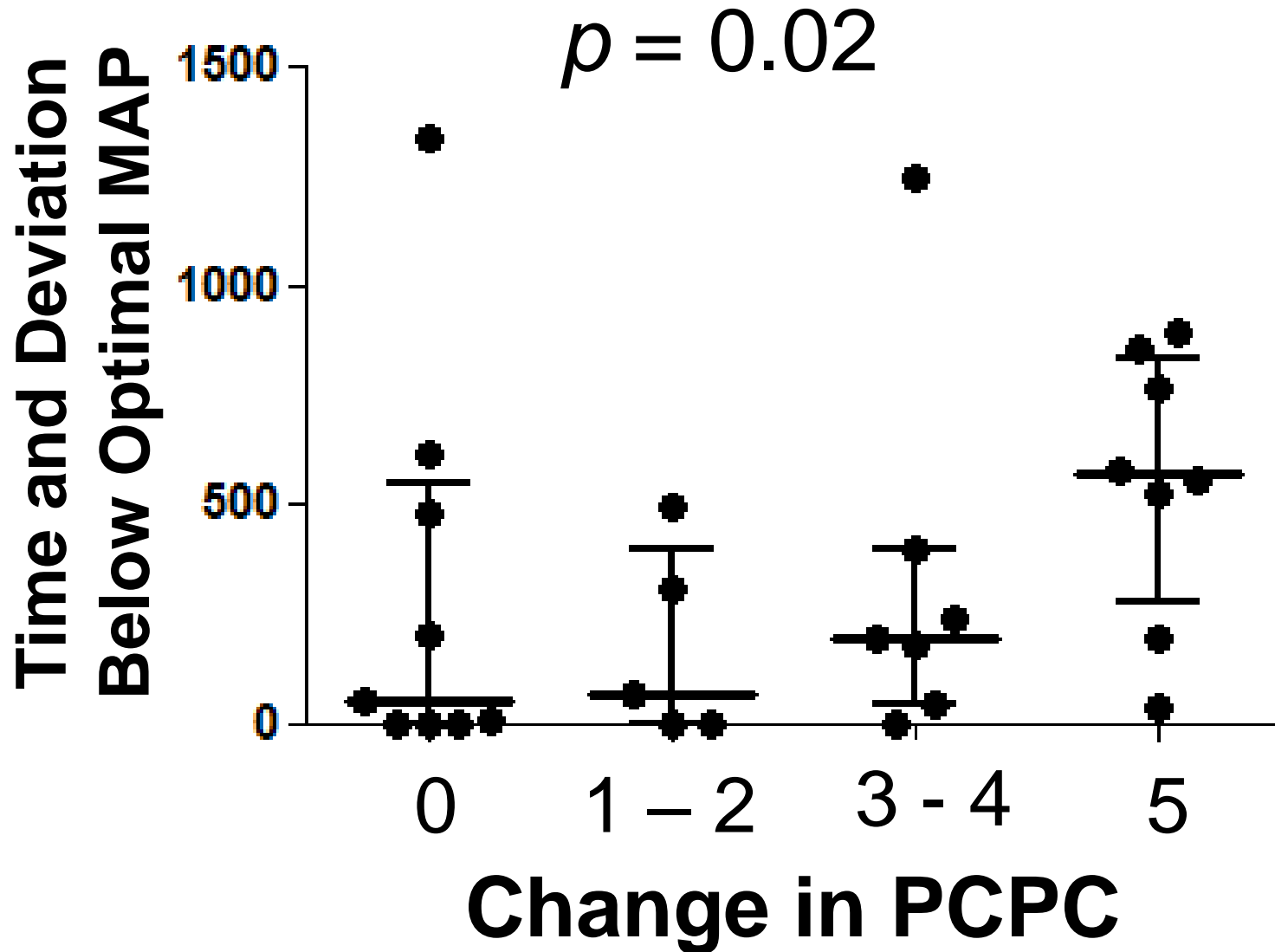
4 = Severe disability

5 = Coma/ vegetative

6 = Death

(Neurologic deficits)

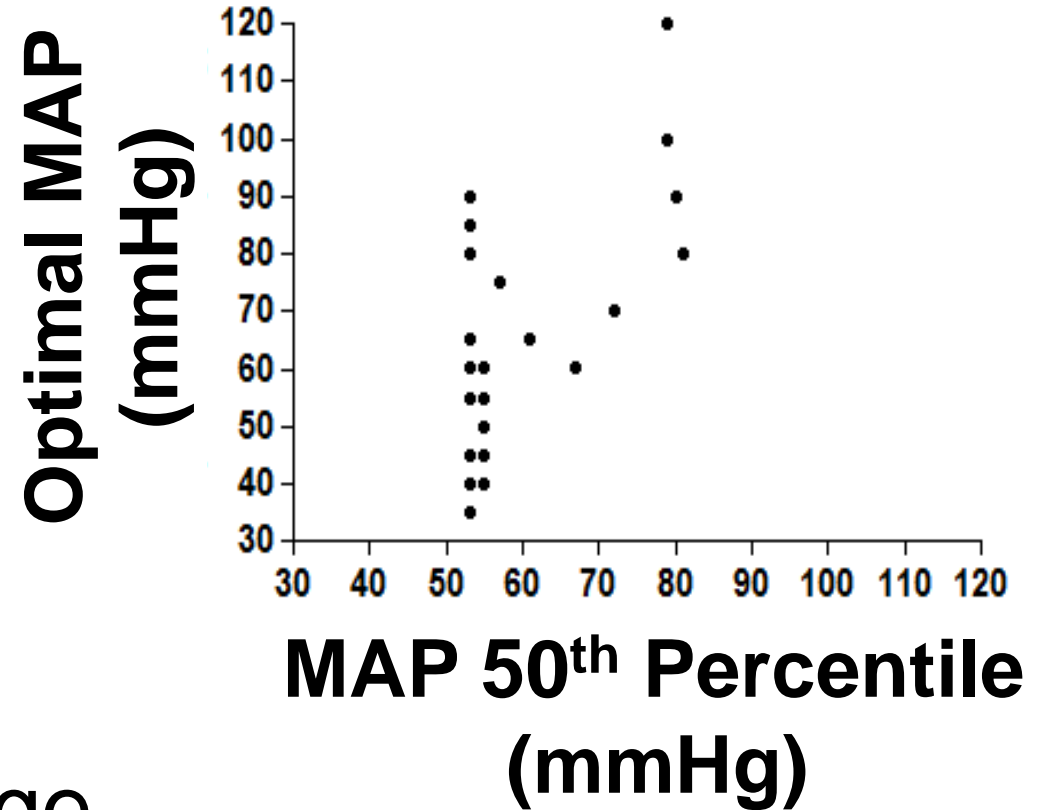
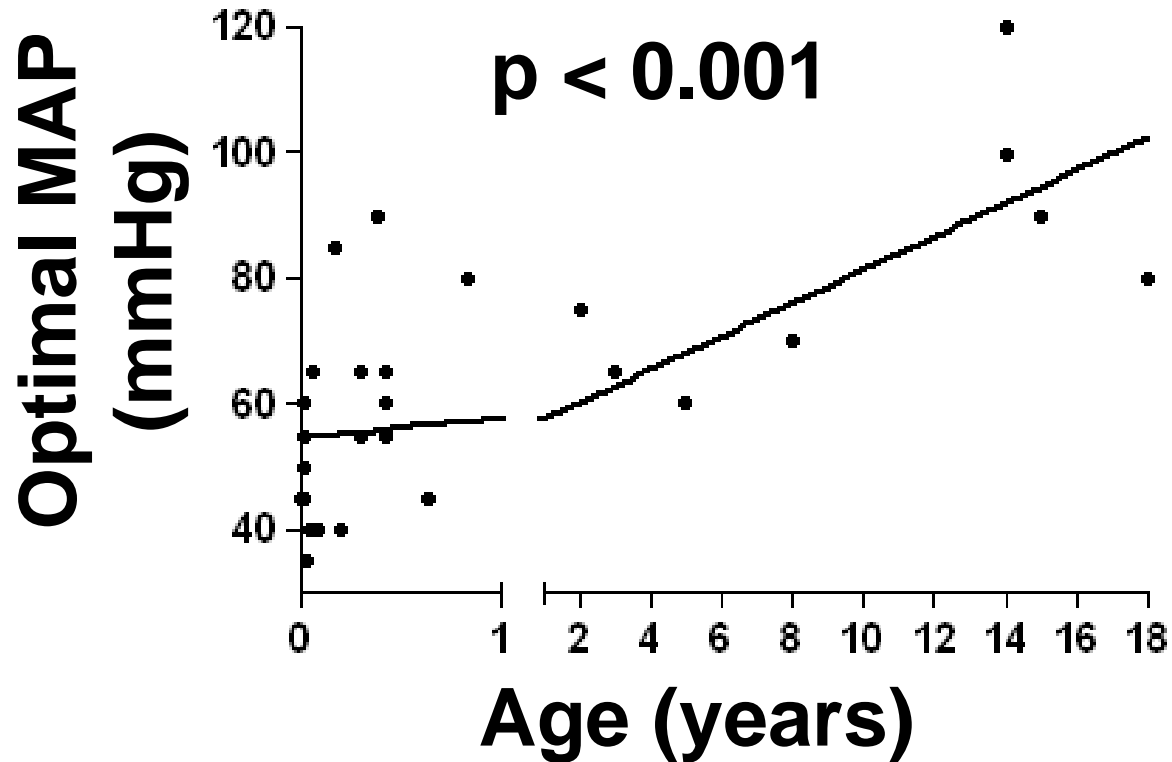
Circle = one patient



Pediatric Cardiac Arrest

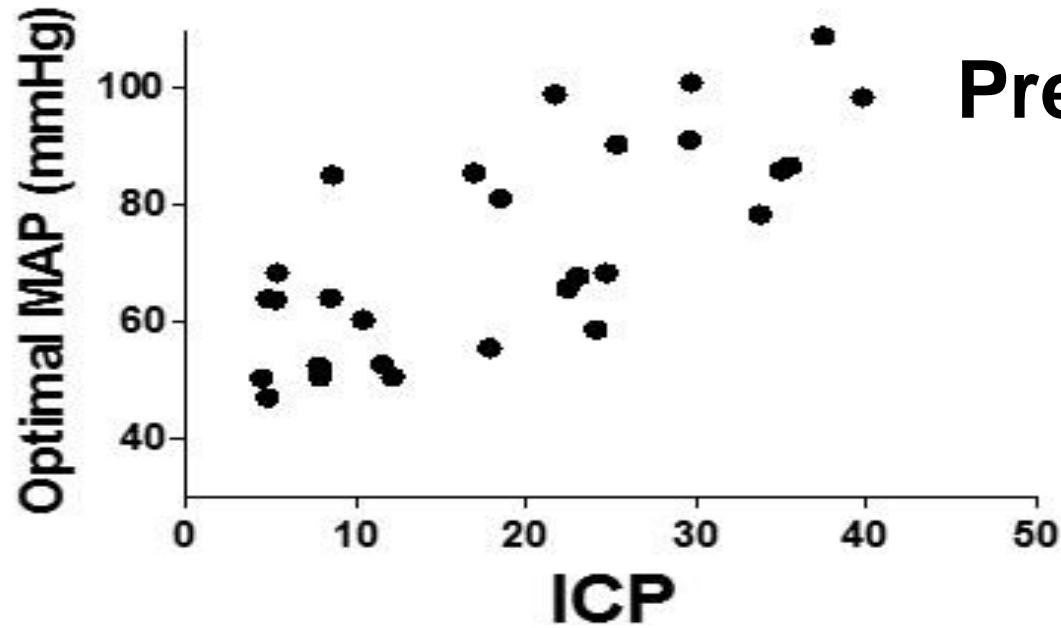
- More time and greater blood pressure deviation below optimal MAP
 - During the 2nd 24 hours after return of circulation
 - **New tracheostomy or gastrostomy**
(n = 28; p = 0.04)
 - During the 1st 48 hours after return of circulation
 - **Declaration of brain death or withdrawal of support for neurologic futility**
(n = 29; p = 0.04)

Pediatric Cardiac Arrest (n = 29)



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

Piglet Controlled Hydrocephalus: optimal MAP from ICM+

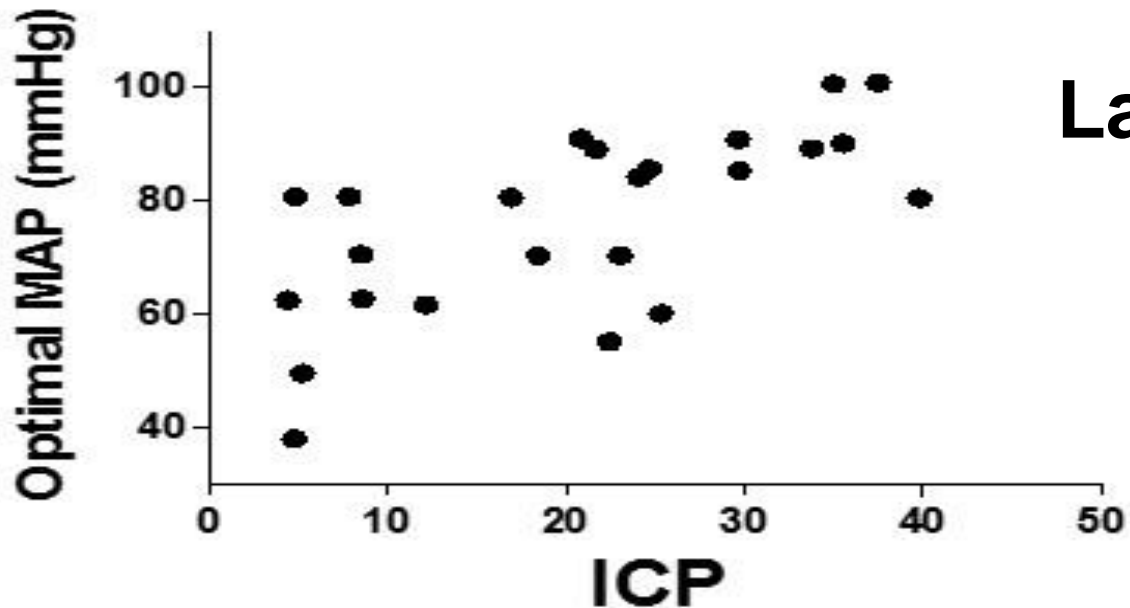


Pressure Reactivity index (PRx)

$n = 29$

$p < 0.001$

$r = 0.80$ (95% CI: 0.52, 0.88)



Laser Doppler flowmetry (LDx)

$n = 24$

$p = 0.002$

$r = 0.61$ (95% CI: 0.26, 0.82)

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

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)

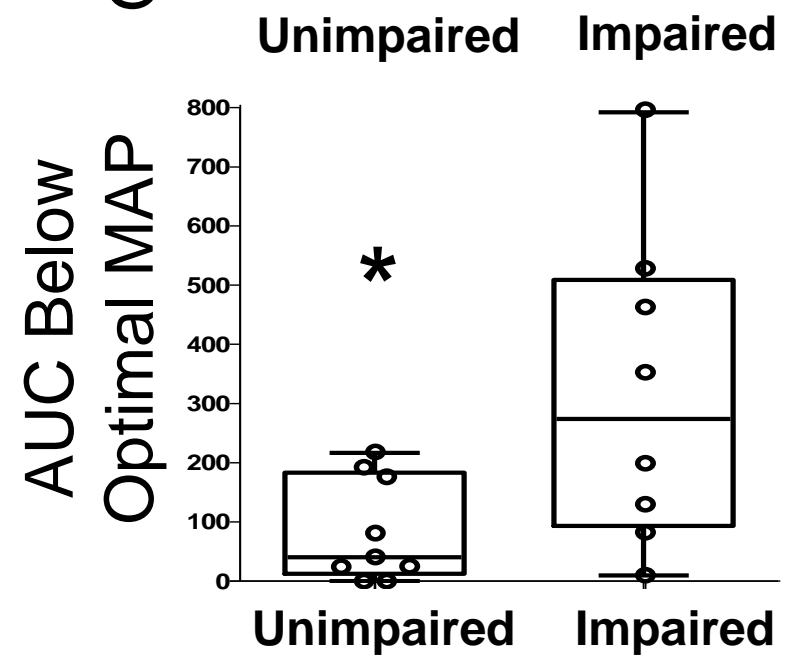
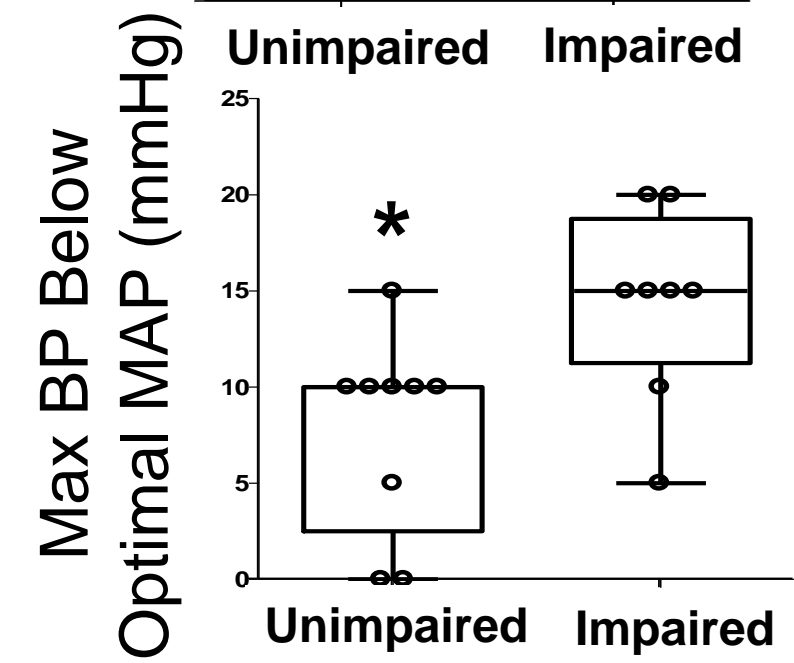
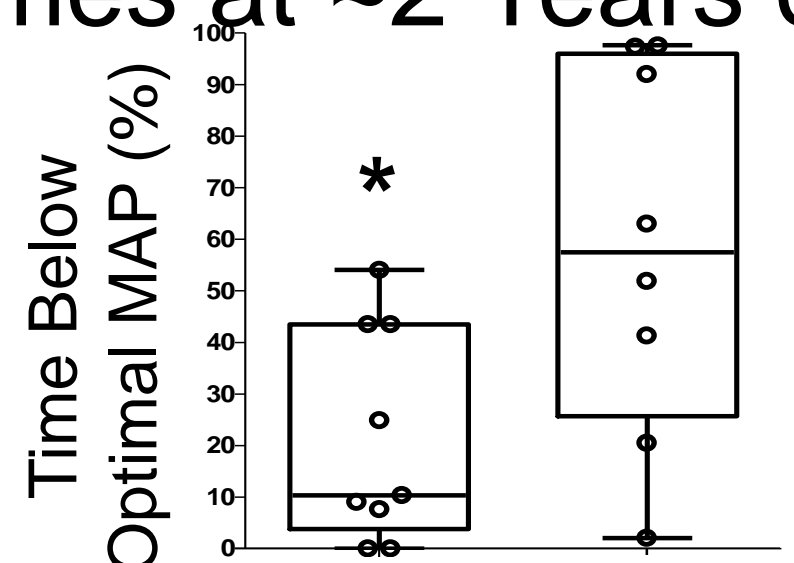
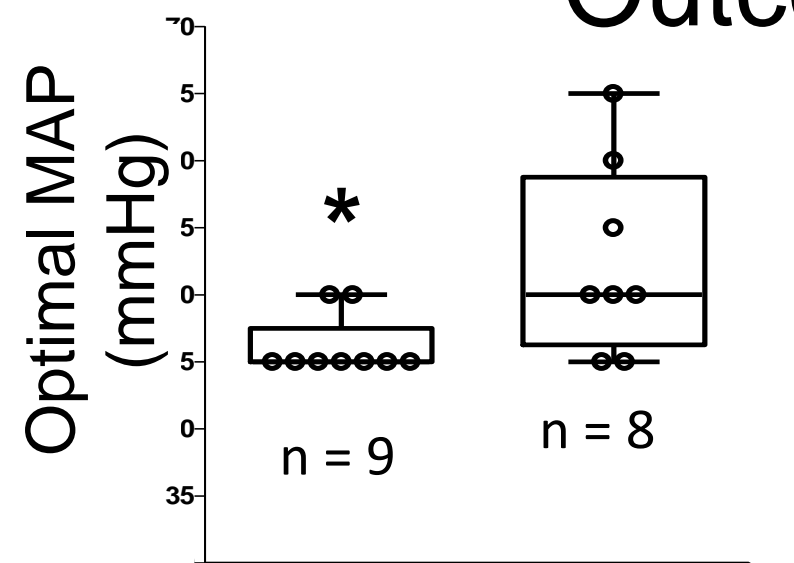
Neonatal Hypoxic Ischemic Encephalopathy and Brain MRI at 1-2 weeks (n=64)

- 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 MAP_{OPT} during rewarming and normothermia
 - Lesser injury in the white matter, putamen and globus pallidus, and brainstem
- Blood pressure above MAP_{OPT} (maximum 75 mmHg) during hypothermia
 - Lesser injury in the paracentral gyri

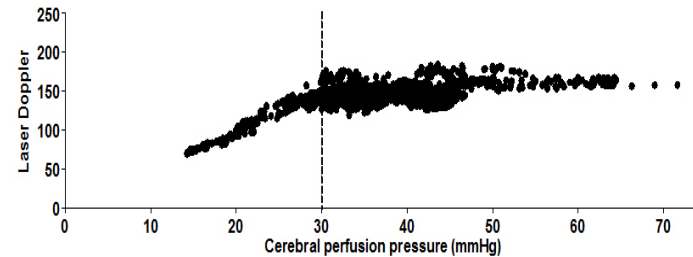
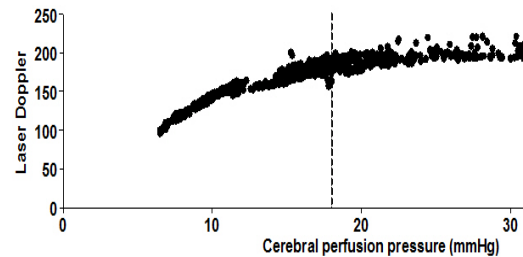
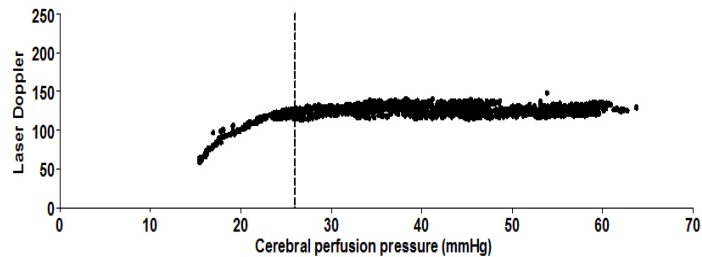
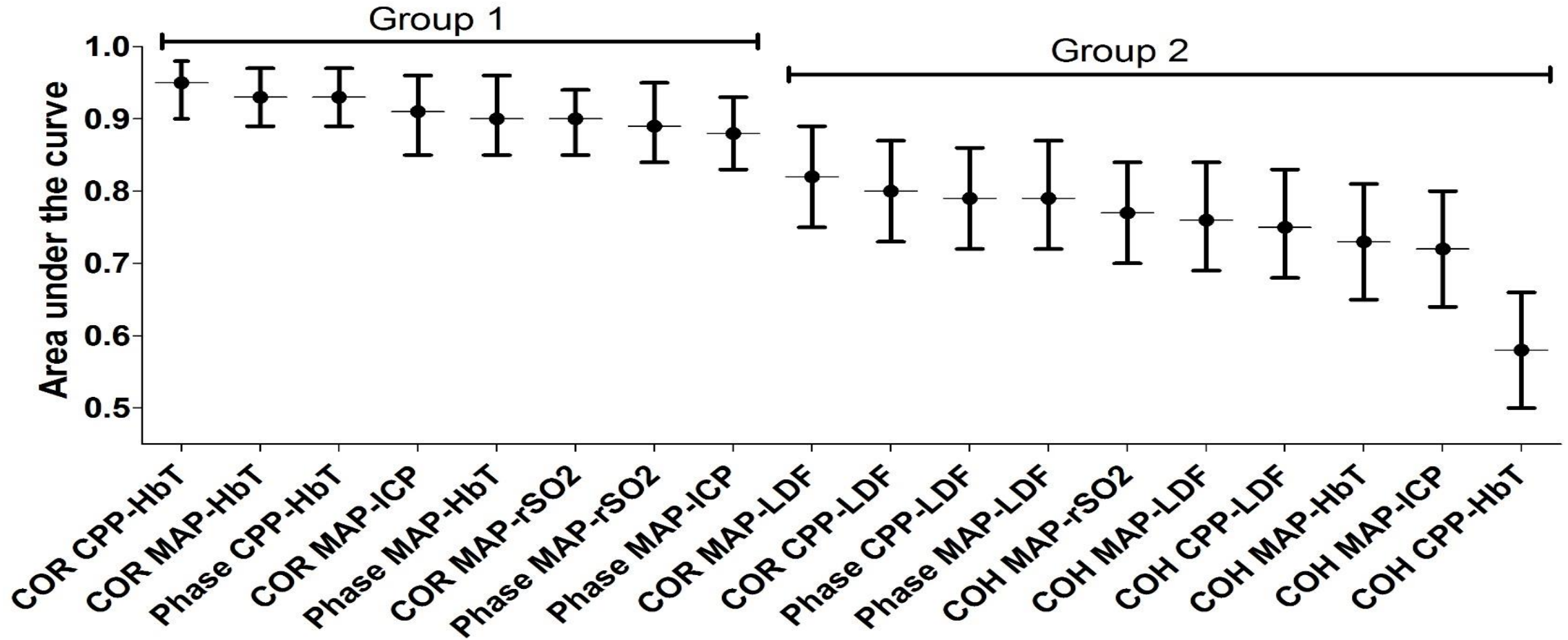
Neonatal HIE and Rewarming – Neurodevelopmental Outcomes at ~2 Years of Age



* $p < 0.05$

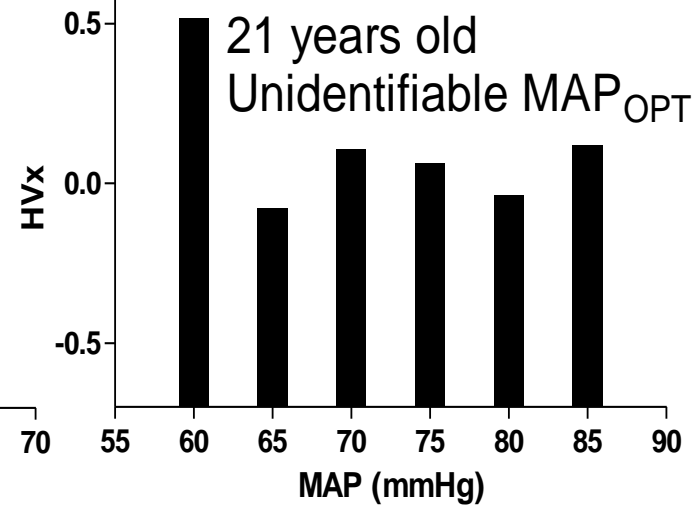
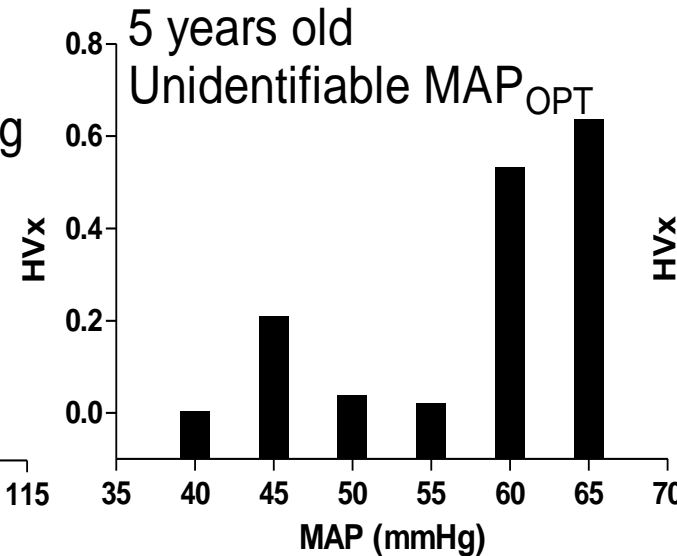
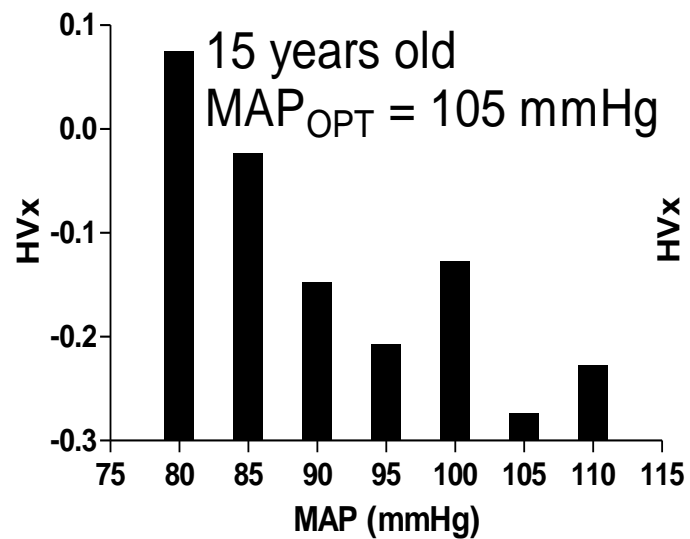
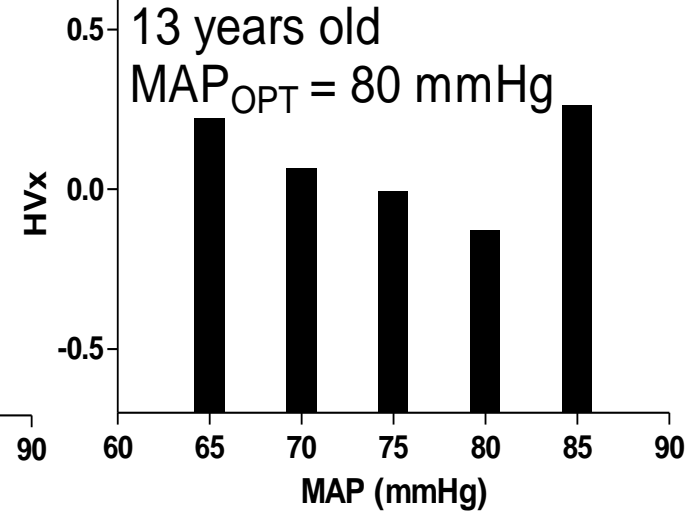
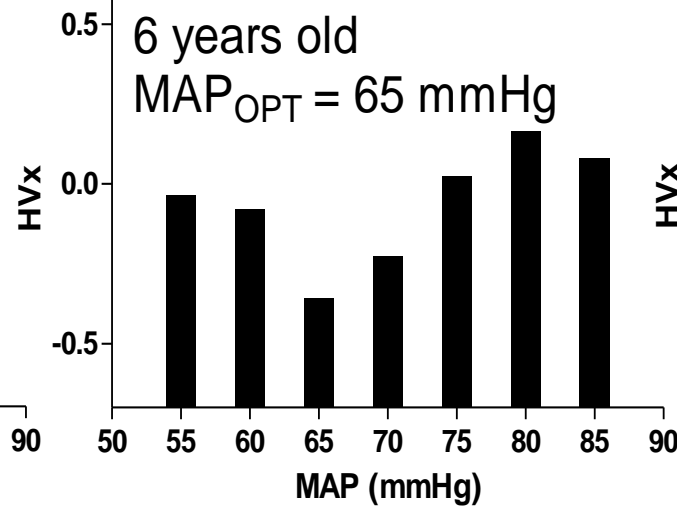
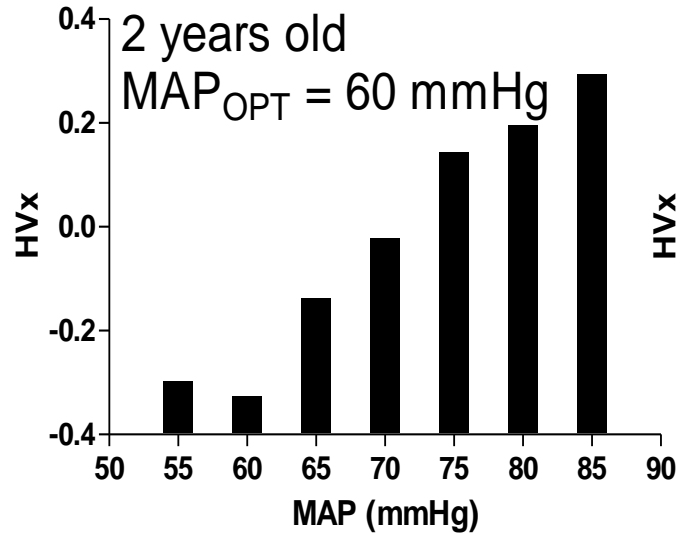
- Mullen Scales of Early Learning
- Gross Motor Function Measure testing
- Capute developmental & motor quotients

Comparison of indices: 66 *historic* HI and sham piglets

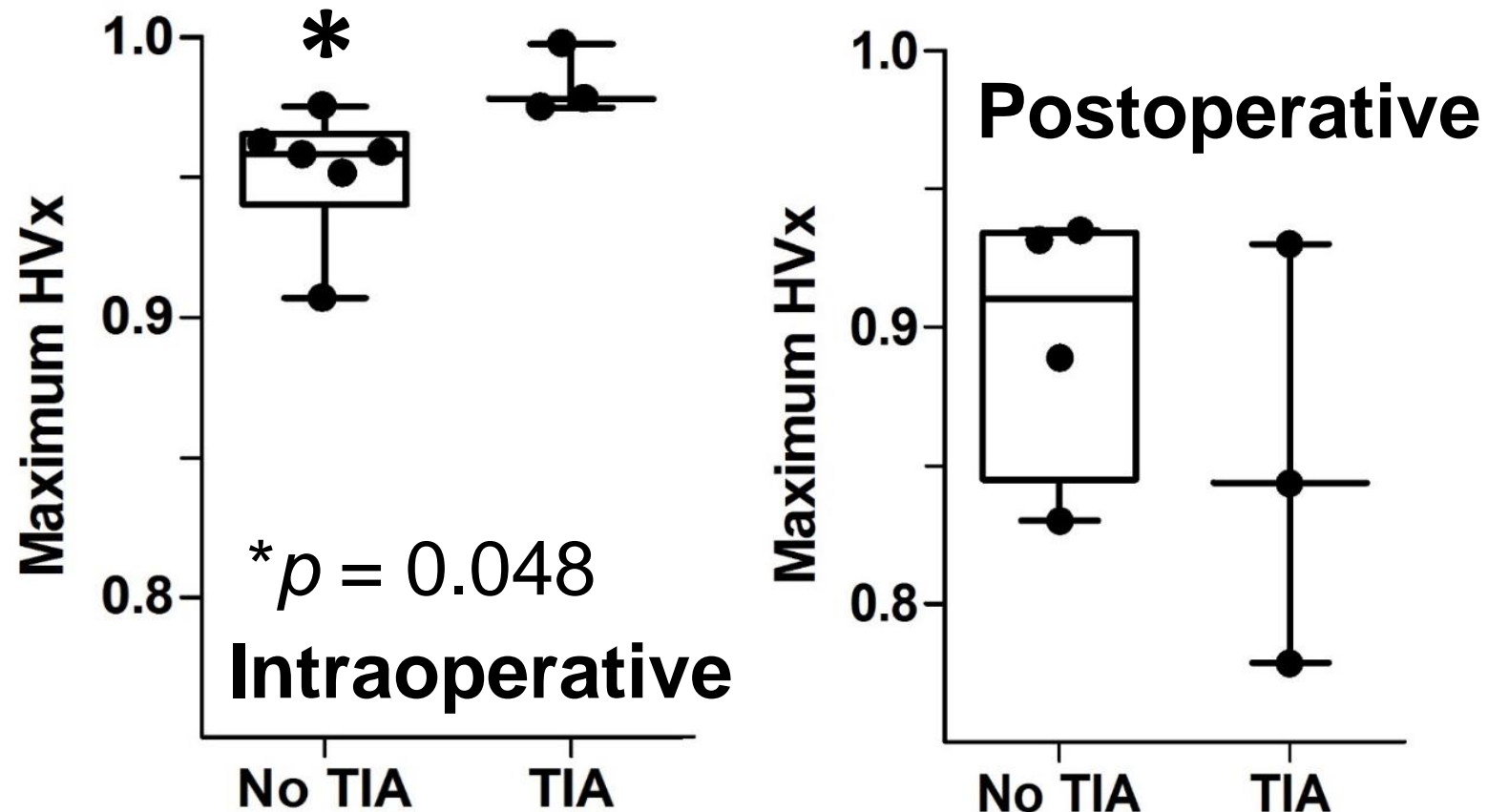


Moyamoya Revascularization (Pial Synangiosis)

Autoregulation curves during surgery

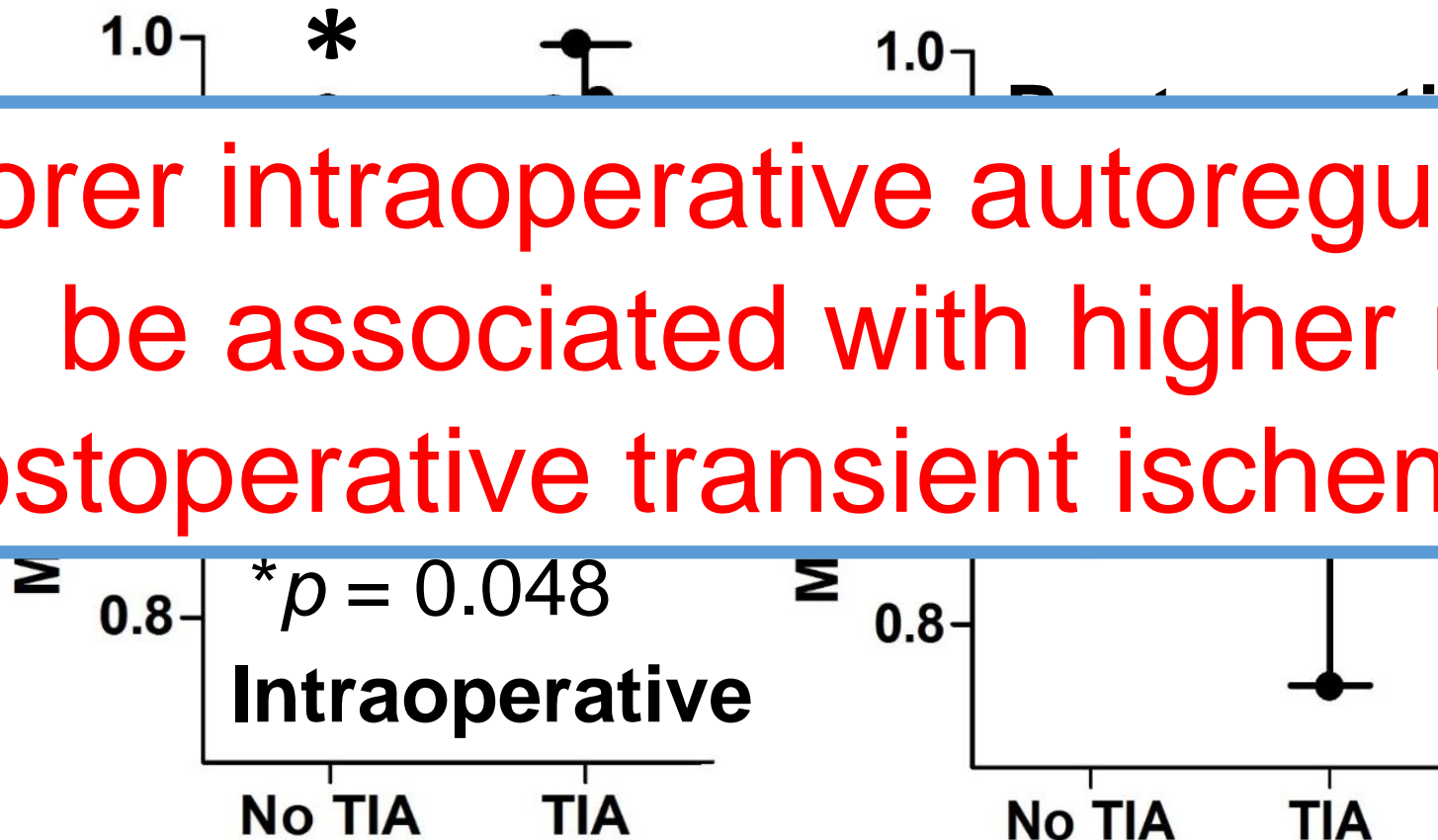


Moyamoya Revascularization (Pial Synangiosis) Bilateral Vasculopathy Ages 2 - 21 years old (n=9)



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



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