Surgery Research Conference

2017 We Care Award Updates:
Optimizing Cardiopulmonary Bypass to Support Cerebral and Somatic Perfusion During Aortic Arch Reconstruction

To receive 1.0 credit for this session, text the SMS code: KEFYES to 414-206-1776. This code will expire in 5 days

ACCME Accreditation Statement: The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. AMA Credit Designation Statement: The Medical College of Wisconsin designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Hours of Participation for Allied Health Care Professionals: The Medical College of Wisconsin designates this activity for up to 1.0 hours of participation for continuing education for allied health professionals.
Research Highlights
MCW Research Day 2019 Awardees

**Department of Surgery Poster Session Awardees:**

- Guillermo A. Urrutia, MD, Surgery  
  (Lomberk Lab)

- Romica Kerketta, PhD, Surgery/ GSPMC  
  (Urrutia Lab)

- Tim Stodola, PhD, Surgery/GSPMC  
  (Urrutia Lab)

- Young-In Chi, PhD, Surgery/GSPMC  
  (Precision Medicine Discovery Laboratory)

**Department of Surgery Poster Session Honorable Mentions**

Jennifer Geurts, MS, CGC, GSPMC: Genetic Counseling/ Surgery
Congratulations on the 2019 CTSI Translational and Clinical Studies Program Pilot Start-Up study

*Bioengineered Heart Tissue in Congenital Heart Disease*

Drs. Aoy Mitchell, PhD  
Professor, Pediatric Congenital Cardiac Surgery  
Mitchell Lab

Brandon Tefft, PhD  
Assistant Professor, Biomedical Engineering  
Cardiovascular Regenerative Engineering Laboratory
Pancreatic Cancer Translational Science Symposium

A Return to the ABC's Advancing Science Building
Collaborations Convert Discoveries into Cures

October 25th, 2019 | 9:00am-4:00pm
HUB A5520/A5628
Reception: HUB A9030/A9070
Med Student Scholarly Pathways

Interested in serving as a Pathway Advisor for Med Students?

Your role as Faculty Advisor:
• Approve student’s Individual Learning Plan (ILP)
• Guide the student to achieve ILP goals
• Assess the student’s progress on achieving ILP goals (5 question evaluation) 2 times per year

Students should complete an average of 6 hours/month and meet with advisors at least 3 times per year

Complete the Faculty Pathway Project Proposal Form
Handbook for Faculty
Pathway Advisor Expectations
Publications

**September 2019**

**Transplant**

**Surgery in Patients with Portal Hypertension.** *Clinics in Liver Disease. (M. Wong & R. Busuttil)*

**Trauma & Acute Care Surgery**

**Enteric Fistula Treatment and Management: Results of an Institutional Inpatient Treatment Protocol.** *Wisconsin Medical Society.* (Kugler NW, Boateng S, Webb TP, Trevino CM)

**Pediatric Surgery**

**Pediatric Congenital Cardiac Surgery**
*Decreased OLA1 (Obg-Like ATPase-1) Expression Drives Ubiquitin-Proteasome Pathways to Downregulate Mitochondrial SOD2 (Superoxide Dismutase) in Persistent Pulmonary Hypertension of the Newborn. Hypertension.* (Schultz A, Olorundami OA, Teng RJ, Jarzembowski J, Shi ZZ, Kumar SN, Pritchard K Jr, Konduri GG, Afolayan AJ)

**Surgical Oncology**
*Prevalence and scope of advanced practice provider oncology care among Medicare beneficiaries with breast cancer.* *Breast Cancer Research & Treatment.* (Yen TWF, Laud PW, McGinley EL, Pezzin LE, Nattinger AB)
Overview of the Research Compliance Office

Matt Richter, JD, MA, is Manager of Research Compliance at the Medical College of Wisconsin. He started his research administration career in 2007 as a pre-award specialist and has since held research compliance positions in central policy and grants offices at the University of Wisconsin-Madison and the University of Wisconsin-Milwaukee. Matt completed his MA in English at the University of Wisconsin-Milwaukee (2009) and his JD at the University of Wisconsin Law School (2012).
Surgery Division of Research is collecting items for Keep Greater Milwaukee Beautiful

Science Supplies & Shoe Drive
October 14-November 27

These products help support our programming:

- School Supplies (Markers, colored pencils, glue sticks, card stock paper, etc.)
- Craft Supplies (Pipe cleaners, Puff Balls, tissue paper)
- Clear, plastic storage containers
- Tape (all types)
- Children's books with environmental themes
- Gently used SHOES
- NO flip flops (plastic), slippers, ski/winter boots, ice skates, roller skates/blas.
Optimizing Cardiopulmonary Bypass to Support Cerebral and Somatic Perfusion During Norwood st. I Palliation

Principal Investigators:
Viktor Hraska, MD & George Hoffman, MD

Co-Investigators:
Ronald K. Woods, MD & Michael E. Mitchell, MD & William K. Johnson, PhD, MSc
Outline

• Clinical background
  – St. I palliation for HLHS
• Study design
• Current study data
Introduction

- **Incidence**
  - 7-9% of all CHD

- **Diagnosis**
  - Hypoplastic LV + AA
  - AS/AA ± MS/MA
  - IVS

- **Physiology**
  - PDA dependent circulation
## Natural History of HLHS

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st week of life</td>
<td>70% of patients died</td>
</tr>
<tr>
<td>1st month of life</td>
<td>90% of patients died</td>
</tr>
<tr>
<td>1st year</td>
<td>No survivals</td>
</tr>
</tbody>
</table>
Treatment Options

- Reconstructive surgery
- Comfort care
- Htx
Reconstructive Approach

1\textsuperscript{st} stage
Norwood st I

2\textsuperscript{nd} stage
BDG

3\textsuperscript{rd} stage
Fontan
Surgical Approach to St. I Palliation

• Demanding operation which may require prolonged repair

• Flexible circulatory support options during repair should address both the physiologic needs of the patient and the requirements for surgical access
Norwood St. I Palliation
Challenges

• Operative paradox
  – Demanding procedure w/o significant improvement of hemodynamics
  – Circulation inherently instable

• Cerebral and somatic protection
Neurological Injury in Neonates

- Congenital Brain Anomalies & Intrauterine Accident: 60% incidence
- Preoperative Hemodynamic & Iatrogenic Insult: 10-20% incidence
- Introperative Insults & Accident
- Postoperative Hemodynamic & Iatrogenic Insults: 20-30% incidence
Arch Reconstruction in HLHS

DHCA

ACP
DHCA

- Deep hypothermia is widely accepted method for neuro-protection
  - @18°C, the rate is only 12% to 25% of its metabolism at normal temp
  - yet achieving lower temps increases risks of sequelae related to profound hypothermia and prolonged duration of CPB

Yan TD “Consensus on hypothermia in AA” Annals 2013
Safe Duration of DHCA

Brain temperature ($^\circ$C)

Duration of circulatory arrest (minutes)

"Safe" Harmful


DHCA Summary

• Organ injury remains a feature of prolonged circulatory arrest

• Complex surgical arch reconstruction cannot always be performed within the 25 to 40 minutes that constitute a reasonably safe duration for DHCA
Evaluation of Brain Protection

ACP at deep hypothermia with low flows (25-45 ml/kg/min)
Selective cerebral perfusion attenuates derangements in cerebral metabolism associated with DHCA
A randomized clinical trial of regional cerebral perfusion versus deep hypothermic circulatory arrest: Outcomes for infants with functional single ventricle

TABLE 3. Bayley Scales of Infant Development results; A comparison of RCP and DHCA groups

<table>
<thead>
<tr>
<th></th>
<th>RCP</th>
<th>DHCA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDI before 2nd stage</td>
<td>67.3 ± 13.8 (n = 23)</td>
<td>74.8 ± 15.0 (n = 29)</td>
<td>.07</td>
</tr>
<tr>
<td>MDI before 2nd stage</td>
<td>85.6 ± 15.4 (n = 23)</td>
<td>88.9 ± 13.3 (n = 29)</td>
<td>.41</td>
</tr>
<tr>
<td>PDI YR</td>
<td>74.0 ± 20.3 (n = 22)</td>
<td>79.6 ± 20.9 (n = 28)</td>
<td>.34</td>
</tr>
<tr>
<td>MDI YR</td>
<td>88.9 ± 21.6 (n = 22)</td>
<td>94.1 ± 20.0 (n = 28)</td>
<td>.39</td>
</tr>
</tbody>
</table>

RCP, regional cerebral perfusion; DHCA, deep hypothermic circulatory arrest; PDI, Psychomotor Development Index; MDI, Mental Development Index; YR, at 1 year.

Figure 2. Survival for the RCP and DHCA treatment groups at hospital discharge after Norwood operation, to second-stage operation, and to 1 year of age. RCP, retrograde cerebral perfusion; DHCA, deep hypothermic circulatory arrest.
• Study compared 2 techniques, neither of which reliably avoids cerebral hypoxia
• Flow rates used for ACP (10-20 ml/kg/min) shown insufficient for cellular metabolic needs
Evaluation of Brain Protection

ACP at deep/mild hypothermia (20-28 C) with high flows (60-80 ml/kg/min)
- MAP 40-50 mm Hg
- Cerebral sat 80-95%

ACP at deep hypothermia with low flows (25-45 ml/kg/min)

DHCA
Cerebral Goal-Directed Therapy

• High flow antegrade cerebral perfusion
• Continuous perioperative cerebral NIRS monitoring for organ-specific goal-directed therapy (rSO₂C)
Perioperative cerebral oxygen saturation in neonates with hypoplastic left heart syndrome and childhood neurodevelopmental outcome

George M. Hoffman, MD, a,b Cheryl L. Brosig, PhD, a,b,c Kathleen A. Mussatto, BSN, PhD, a,c,d James S. Tweddell, MD, a,b,c and Nancy S. Ghanayem, MD, a,b

Pediatr Cardiol

Neurodevelopmental Outcomes for Children With Hypoplastic Left Heart Syndrome at the Age of 5 Years

Cheryl Brosig · Kathleen Mussatto · George Hoffman · Raymond G. Hoffmann · Mahua Dasgupta · James Tweddell · Nancy Ghanayem
• Near-infrared spectroscopy (NIRS) monitoring provides continuous non-invasive estimation of regional tissue and venous oxygen saturation … thus, a candidate to supplement or replace systemic venous oxygen saturation (SvO₂) monitoring

• Authors concluded that continuous non-invasive measurement of regional cerebral and somatic NIRS saturations in the early postop period can predict outcomes of early mortality and ECMO use in HLHS cohort

• Because outcomes were strongly determined by NIRS measures @ 6 hours, early postop NIRS measures may be rational targets for goal-directed interventions

NIRS in conjunction with SM22 and I-FABP biomarkers can prove diagnostically useful as an additional tool in the detection of somatic ischemia
ACP Caveats

- Some collateral flow occurs to non-cerebral organs
  - Physiologically poor somatic support (renal morbidity)
  - Hypothermia is still required to avoid somatic injury
Evaluation of Brain Protection

- DHCA
- ACP at deep hypothermia with low flows (25-45 ml/kg/min)
- ACP at deep/mild hypothermia (20-28 °C) with high flows (60-80 ml/kg/min)
- Whole body perfusion strategy at mild hypothermia (32 °C)

Optimization of cerebral and somatic perfusion
Goal-directed Dual Perfusion Strategy

• Whole body perfusion
Our Hypothesis

• An alternative (near normothermic) dual perfusion bypass technique both maintains cerebral & organ $O_2$ intra-operatively without significant post-operative decline
• 1st step – feasibility study
• 2nd step – prospective study funded by We Care
Feasibility Study
Near-normothermic goal-directed

innominate and femoral perfusion for Norwood palliation of HLHS

George Hoffman, Viktor Hraska, John Scott, Caleb Varner, Michael Mitchell, Ronald Woods, Eckehard Stuth
Herma Heart Institute
Children's Hospital and Medical College of Wisconsin
Milwaukee, WI, USA
Methods

• Anesthetic management
  – Balanced anesthesia with fentanyl 5-10 mg/kg/hr, dexmedetomidine 0.5-1 mcg/kg/hr, 0.5 MAC sevoflurane (isoflurane on CPB)
  – Hydrocortisone (0.1 mg/kg/hr) and bumetanide (6 mcg/kg/hr)
  – Milrinone, epinephrine, norepinephrine to SVRI 12-16 during warming and to wean from CPB

• Goal-directed targets:
  – PP (MAP – CVP) ~40 mmHg
  – SpO2 80%, rSO2C >50%, rSO2S>60%

• Selective primary chest closure
Methods - perfusion

• Percutaneous femoral artery access with 3.3 or 4 Fr sheath

• Perfusion steps
  – Innominate artery was perfused via a 4.0 or 3.5 mm PTFE graft, with 3.2 L/min/m² bidirectional flow for cooling to 32°C, then antegrade at 60-80 ml/kg/min
  – The femoral artery was perfused retrograde, flexibly before and during isolation of proximal arch, septectomy, and cardioplegia
  – Dual aortic perfusion (DAP) for arch repair with flow adjustments based on NIRS and BP
  – CPB Rewarming and myocardial reperfusion via 8 Fr neoarticular canula
  – Modified ultrafiltration after separation
Methods - monitoring

- Arterial saturation (GE Masimo SET)
- Arterial pressure UAC, R Radial
- Atrial/venous pressure (UVC, RA line)
- Regional saturation (Medtronic/INVOS 5100) with neonatal cerebral and T12-L2 somatic probes
- Bypass flows calculated by RPM and ultrasonic flow probe on arterial lines (Transonic systems)
Methods - data

• Data from all patients undergoing Norwood palliation of HLHS with this near-nomothermic perfusion strategy were included in this report
• Demographic and management variables extracted from EHR and perfusion records
• Physiologic data extracted from electronic anesthesia records at 5 min intervals
• Renal injury classification from renal function measures and eGFR according to Schwartz formula
• Parametric and nonparametric summary measures
• Associations by chi-squared and panel regression methods with significance determined at p < 0.05 after multiple comparison correction
## Patients Characteristic (N=18)

<table>
<thead>
<tr>
<th>variable</th>
<th>Mean ± sd</th>
<th>Median (iqr)</th>
<th>Min - Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (kg)</td>
<td>3.22 ± 0.47</td>
<td>3.15 (0.78)</td>
<td>2.53 – 4.32</td>
</tr>
<tr>
<td>Gest Age (wk)</td>
<td>38.9 ± 0.71</td>
<td>39.1 (0.2)</td>
<td>37.1 – 39.6</td>
</tr>
<tr>
<td>Age S1P (days)</td>
<td>5.89 ± 1.78</td>
<td>6 (1)</td>
<td>4 – 11</td>
</tr>
<tr>
<td>Wt S1P (kg)</td>
<td>3.32 ± 0.52</td>
<td>3.17 (0.63)</td>
<td>2.55 – 4.46</td>
</tr>
<tr>
<td>BSA (m2)</td>
<td>0.22 ± 0.02</td>
<td>0.21 (0.02)</td>
<td>0.19 – 0.26</td>
</tr>
<tr>
<td>aAo Diam (mm)</td>
<td>2.5 ± 0.7</td>
<td>2.0 (1.0)</td>
<td>2.0 – 4.0</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>10/18 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic Syndrome</td>
<td>4/18 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoch</td>
<td>Mean ±sd</td>
<td>Median (iqr)</td>
<td>Min - Max</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>CPB cooling time</td>
<td>35 ±17</td>
<td>33 (16)</td>
<td>4 – 70</td>
</tr>
<tr>
<td>ACP time</td>
<td>64 ±34</td>
<td>49 (33)</td>
<td>36 – 164</td>
</tr>
<tr>
<td>RFP time</td>
<td>59 ±39</td>
<td>49 (19)</td>
<td>2 – 163</td>
</tr>
<tr>
<td>Clamp Time</td>
<td>61 ±32</td>
<td>51 (28)</td>
<td>20 – 164</td>
</tr>
<tr>
<td>Low Flow time</td>
<td>1 ±2</td>
<td>0 (1)</td>
<td>0 – 3</td>
</tr>
<tr>
<td>Dual Aortic Perfusion Time</td>
<td>58 ±26</td>
<td>46 (22)</td>
<td>36 – 137</td>
</tr>
<tr>
<td>CPB warming time</td>
<td>46 ±3</td>
<td>34 (22)</td>
<td>25 – 138</td>
</tr>
<tr>
<td>CPB total support time</td>
<td>145 ±71</td>
<td>117 (45)</td>
<td>89 – 372</td>
</tr>
<tr>
<td>Surgical time</td>
<td>326 ±106</td>
<td>290 (130)</td>
<td>215 – 656</td>
</tr>
<tr>
<td>Anesthesia time</td>
<td>469 ±110</td>
<td>443 (75)</td>
<td>339 – 758</td>
</tr>
</tbody>
</table>

**Support Timeline**

<table>
<thead>
<tr>
<th>CPB Cooling</th>
<th>ACP</th>
<th>RFP</th>
<th>LF</th>
<th>DAP</th>
<th>RFP</th>
<th>CPB Warming</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>33</td>
<td>33</td>
<td>46</td>
<td>1</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>
### Hemodynamic and oximetric summary during DAP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ±sd</th>
<th>Median (irq)</th>
<th>Min - Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qacp (ml/kg/min)</td>
<td>63 ±12</td>
<td>70 (25)</td>
<td>45 – 80</td>
</tr>
<tr>
<td>Qrfp (ml/m²/min)</td>
<td>47 ±7</td>
<td>48 (10)</td>
<td>36 – 59</td>
</tr>
<tr>
<td>MAP Rrad (mmHg)</td>
<td>49 ±6</td>
<td>49 (5)</td>
<td>38 – 67</td>
</tr>
<tr>
<td>MAP UAC (mmHg)</td>
<td>36 ±8</td>
<td>34 (13)</td>
<td>24 – 47</td>
</tr>
<tr>
<td>ΔMAP (RR-UAC)</td>
<td>13 ±9</td>
<td>15 (15)</td>
<td>3 – 24</td>
</tr>
<tr>
<td>rSO2 Cerebral (%)</td>
<td>83 ±8</td>
<td>84 (17)</td>
<td>42 – 95</td>
</tr>
<tr>
<td>rSO2 Renal (%)</td>
<td>88 ±8</td>
<td>92 (20)</td>
<td>54 – 95</td>
</tr>
<tr>
<td>Δa-rSO2 Cerebral (%)</td>
<td>22 ±15</td>
<td>16 (17)</td>
<td>7 – 58</td>
</tr>
<tr>
<td>Δa-rSO2 Renal (%)</td>
<td>17 ±14</td>
<td>12 (20)</td>
<td>5 – 43</td>
</tr>
<tr>
<td>Temp (C)</td>
<td>31 ±1</td>
<td>32 (2)</td>
<td>28 – 33</td>
</tr>
</tbody>
</table>
Results: hemodynamic changes

- UAC MAP decreased during DAP, but no difference between preop and postop.
- Radial Artery MAP not different during DAP and postop.
- Radial MAP exceeded UAC during DAP. Postoperatively, this relationship was flipped.
Results: oximetric changes

- Cerebral oxygenation increased during DAP
- but cerebral da-rSO2C was not altered
- Renal somatic oxygenation increased during DAP
- Renal da-rSO2R was reduced during DAP and was maintained in the early post-CPB period
## Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean ±sd</th>
<th>Median (iqr)</th>
<th>Min - Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milrinone (mcg/kg/min)</td>
<td>18</td>
<td>0.53 ±0.08</td>
<td>0.5 (0)</td>
<td>0.5 – 0.75</td>
</tr>
<tr>
<td>Epinephrine (mcg/kg/min)</td>
<td>18</td>
<td>0.07 ±0.03</td>
<td>0.06 (0.05)</td>
<td>0.02 – 0.15</td>
</tr>
<tr>
<td>Norepinephrine (mcg/kg/min)</td>
<td>7</td>
<td>0.03 ±0.04</td>
<td>0 (0.05)</td>
<td>0 – 0.15</td>
</tr>
<tr>
<td>Vasoactive Inotrope Score</td>
<td>18</td>
<td>10.3 (5.9)</td>
<td>8 (9.8)</td>
<td>2.5 – 23.5</td>
</tr>
<tr>
<td>fiO2</td>
<td>18</td>
<td>0.49 ±0.12</td>
<td>0.5 (0.1)</td>
<td>0.35 - 0.90</td>
</tr>
<tr>
<td>PetCO2 (torr)</td>
<td>18</td>
<td>39 ±9</td>
<td>39 (9)</td>
<td>17 – 52</td>
</tr>
<tr>
<td>Open chest</td>
<td>14</td>
<td>78 ±10 %</td>
<td>52 – 93 %</td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>2</td>
<td>11 ±7 %</td>
<td>1.3 – 34 %</td>
<td></td>
</tr>
</tbody>
</table>
## Results: biochemical and renal measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Nadir Day</th>
<th>Median (IQR)</th>
<th>Min - Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base excess (mEq/L)</td>
<td>0</td>
<td>-2.5 (5.3)</td>
<td>-2 – 5</td>
</tr>
<tr>
<td>Creatinine (mg/L)</td>
<td>1</td>
<td>0.59 (0.11)</td>
<td>0.41 – 0.83</td>
</tr>
<tr>
<td>BUN (mg/L)</td>
<td>3</td>
<td>24 (9)</td>
<td>14 – 50</td>
</tr>
<tr>
<td>eGFR (ml/kg/min)</td>
<td>1</td>
<td>38 (6)</td>
<td>28 – 59</td>
</tr>
<tr>
<td>Creatinine ratio (peak/baseline)</td>
<td>(max)</td>
<td>1.3 (0.28)</td>
<td>1.0 – 1.8</td>
</tr>
<tr>
<td>pRIFLE (stage 1)</td>
<td>(max)</td>
<td>8/18 (44%)</td>
<td>0 – 1</td>
</tr>
<tr>
<td>AKIN (stage 1)</td>
<td>(max)</td>
<td>4/18 (22%)</td>
<td>0 – 1</td>
</tr>
<tr>
<td>KDIGO (stage 1)</td>
<td>(max)</td>
<td>4/18 (22%)</td>
<td>0 - 1</td>
</tr>
</tbody>
</table>
Results: early outcome milestones

- Survival 94%
  - 1 death POD 1 on ECMO
- Limb ischemia 0, Renal failure 0, early NEC 0

<table>
<thead>
<tr>
<th>Milestone (postoperative day)</th>
<th>Median (iqr)</th>
<th>Min - Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest closure</td>
<td>2 (4)</td>
<td>0 – 14</td>
</tr>
<tr>
<td>Extubation</td>
<td>6 (6)</td>
<td>2 – 30</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>7 (9)</td>
<td>2 – 25</td>
</tr>
<tr>
<td>Milrinone</td>
<td>21 (47)</td>
<td>5 – 94</td>
</tr>
</tbody>
</table>
• Early and mid-term outcomes
  – Hospital survival 94%
  – Current survival 94%
• Interstage events
  – 1 shunt event, rescued
  – 2 prolonged LCOS, late medical NEC
• Current status:
  – Bidirectional Glenn 12 (67%)
  – OHT or VAD 3 (17%)
  – 35% occlusion of femoral/iliac artery
Conclusions

• Modified dual aortic perfusion strategy with percutaneous femoral artery access pre-CPB permits flexible intraoperative perfusion strategy to avoid circulatory arrest with minimal periods of low flow and short total support time
• Physiologic measures indicated preserved cerebral blood flow and improved somatic blood flow compared to preoperative baseline
• **No limb ischemic events, but higher occlusion rate from percutaneous femoral access**
• Mid and longer term outcomes need to be determined
Prospective Study
Study Aims

• **Assess effectiveness** of the dual perfusion strategy in neonates to adequately deliver O₂ to brain & organ regions

• **Identify** optimal neurological/somatic protective perfusion parameters (flow rates, temperature)

• **Demonstrate the technical feasibility**, reproducibility, and safety of the full-body perfusion strategy & **approach via descending aorta**

• **Evaluate long-term neurodevelopmental outcomes** in neonates who underwent arch reconstruction...in comparison with a historical cohort
Experimental Design
Study Type
Non-randomly assigned control group study

- Similar to randomized clinical trial (RCT), except that patients are assigned to treatment groups in a non-random fashion.
- RCT would be ideal...but practical considerations (e.g., costs, unacceptability, etc.) make a high-quality trial infeasible.
Outcomes

- **Primary**
  - Neurological health
    - Freedom from adverse events, complications, etc.
  - Neurological development (long-term)
    - Developmental scores, etc.

- **Secondary**
  - Mortality
    - Survival to discharge; survival to Glenn procedure, etc.
  - Morbidity
    - Acute kidney injury (AKI), other complications, Interstage status (discharged prior to Glenn), etc.
Treatment vs Control Groups

- **Prospective cohort**
  - 5-10 HLHS pts/year
  - N = 20 pts

- **Retro-cohort**
  - HLHS 2006-2012
  - N = 40 pts

Retro-cohort will be compared with prospective @ 2 : 1 ratio
Norwood by Year

Survivor  Mortality  Still Inpatient  Mortality %

2009: 23
2010: 16
2011: 15
2012: 18
2013: 16
2014: 15
2015: 11
2016: 7
2017: 16
2018: 8
Prospective Cohort

- ACP via shunt & lower body perfusion via thoracic aorta
- Lowest temperature 32°C
- Flow rates
  - ACP flow – target of 60% of CO (60-80 ml/kg/min)
  - Systemic flow – target of 40% of CO (40-60 ml/kg/min)
- Target mean arterial pressure (MAP) < 45 mm Hg
- Constant NIRS monitoring
- Blood collected @ 5 time points & Urinalysis @ 4 time points
Inclusion Criteria

- All pts born with HLHS or variant of HLHS
- All pts who needs Norwood st. I palliation with BT
Exclusion Criteria

• Birth weight < 2.5 kg; or Gestational age < 32 weeks
• Pre-existing neurological or renal impairment
• Heterotaxy and hybrids
• Previous exposure to nephrotoxic drugs
• Identified genetic syndrome associated with abnormal neurodevelopment or renal development
• Pre-surgical sepsis, severe shock, or NEC
• Prolonged in utero exposure to psychoactive drugs
Retro-Cohort

• **Case matching criteria** will include:
  - Surgical weight (≥ 2.5kg)
  - Gestational & surgical age
  - 1° diagnosis & 1° surgical procedure

• **Additional matching criteria for analytical purposes** include:
  - Inotrope score
  - Patients who go to the OR extubated only
    - For purpose of comparing “equal” Norwood cases, prefer extubation to occur between D.O.L. 3 & 7

• Perfusion strategy – ACP w high flow and deep hypotemia
<table>
<thead>
<tr>
<th>TIME POINT</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Preoperative investigation (<em>ECHO, diagnostic catheterization, MRI, etc.</em>)</td>
</tr>
<tr>
<td>2</td>
<td>Indication for operation/diagnosis</td>
</tr>
<tr>
<td>3</td>
<td>Patient’s family approached – <strong>SURGICAL CONSULTATION</strong></td>
</tr>
<tr>
<td>4</td>
<td>Screening – patient considered for eligibility</td>
</tr>
<tr>
<td>5</td>
<td>Patient’s family approached – <strong>STUDY CONSENT OBTAINED</strong></td>
</tr>
<tr>
<td>6</td>
<td>Operation Scheduled</td>
</tr>
<tr>
<td>7</td>
<td>Pre-op visit (<em>24hrs prior to surgery</em>) – <strong>BASELINE VITALS COLLECTED</strong></td>
</tr>
<tr>
<td>8</td>
<td>Operation (pre-CPB baseline collection)</td>
</tr>
<tr>
<td>9</td>
<td>Operation (post-CPB collection)</td>
</tr>
<tr>
<td>10</td>
<td>ICU Admit</td>
</tr>
<tr>
<td>11</td>
<td>Postoperative (Day 1)</td>
</tr>
<tr>
<td>12</td>
<td>Postoperative (Day 2)</td>
</tr>
<tr>
<td>13</td>
<td>Prior to discharge...hospital follow-up</td>
</tr>
<tr>
<td>14</td>
<td>30 day post-operative follow-up (mortality, morbidity, discharge status)</td>
</tr>
<tr>
<td>15</td>
<td>6-month follow-up</td>
</tr>
<tr>
<td>16</td>
<td>12-month follow-up</td>
</tr>
<tr>
<td>17</td>
<td>18-month follow-up</td>
</tr>
<tr>
<td>18</td>
<td>Long-term follow up age 3 or 4 (consent will indicate 4 years for data collection authorization)</td>
</tr>
<tr>
<td>19</td>
<td>Study completion &amp; patient report</td>
</tr>
</tbody>
</table>

**Blood & urine collected for research purposes**

**Patient’s status recorded**

There will be **no extra visits** for research purposes.
Research sample collection time points...monitoring AKI & $O_2$

- **Urine Samples**
  - T0 (Pre-CPB (Baseline))
  - T1 (6hr after CPB)
  - T2 (12hr after CPB (Next morning))
  - T3 (24-36hr after CPB (following morning))

- **Blood Samples**
  - T0 (Pre-CPB (Baseline))
  - T1 (Post-CPB)
  - T2 (ICU Admit)
  - T3 (Post-op Day)
  - T4 (Post-op Day)

**LEGEND**
- S100b (Ca$^{2+}$ binding protein B of the S-100 protein family)
- GFAP (glial fibrillary acidic protein)
- Cystatin-C (cystatin 3; formerly gamma trace)
- Troponin I (cardiac and skeletal muscle protein)
- SM22 (protein that in humans is encoded by the TAGLN gene)
- I-FABP (Intestinal-type fatty acid-binding protein)
- NGAL (Neutrophil gelatinase-associated lipocalin)
- KIM-1 (Kidney injury molecule-1)

**Best AKI sensitivity windows after renal insult**
- Within 1-3 hrs (NGAL)
- Within 2-12 hrs (KIM-1)

**Best AUC (area under the curves):**
- NGAL: 2 hrs.
- KIM-1: 12 hrs.

**In hospital follow-Up**
- T4 (Post-op Day)
- T5 (Post-op Day)

**URINALYSIS**
(creatinine) will occur multiple days out as standard
Why these biomarkers?

<table>
<thead>
<tr>
<th>Protein of Interest</th>
<th>Clinical Justification</th>
<th>Sample Notes</th>
</tr>
</thead>
</table>
| S100B               | Neuro-injury           | ○ Reported to **rise prior to any detectable changes** in intra-cerebral pressure, neuroimaging, and neurological examination findings  
○ Elevations provide a sensitive measure for determining **CNS injury at the molecular level** before gross changes develop, enabling timely delivery of crucial medical intervention |
<p>| GFAP                | Neuro-injury           | ○ Study of 22 child patients undergoing ECMO, children with <strong>abnormally high levels of GFAP</strong> were 13 times more likely to die and 11 times more likely to suffer <strong>brain injury</strong> than children with normal GFAP levels (<strong>Johns Hopkins</strong>) |
| Cardiac Troponin I  | Renal failure/heart failure | ○ Patients with <strong>renal insufficiency may have increased serum troponins</strong> even in the absence of clinically suspected acute myocardial ischemia |</p>
<table>
<thead>
<tr>
<th>Protein of Interest</th>
<th>Clinical Justification</th>
<th>Sample Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystatin-C</td>
<td>Acute renal injury</td>
<td>○ It is not subject to any significant protein binding…can <strong>accurately indicate even small changes in the GFR</strong></td>
</tr>
<tr>
<td>SM22</td>
<td>Intestinal O2/ischemia</td>
<td>○ Literature shows that SM22 released into circulation upon severe ischemia of the intestinal muscle layers…plasma levels of SM22 useful in detection of transmural intestinal ischemia</td>
</tr>
<tr>
<td>I-FABP</td>
<td>Intestinal O2/ischemia</td>
<td>○ Rapidly released into circulation upon <strong>damage</strong>…<strong>highly sensitive marker for intestinal ischemia</strong>…short half-life…significantly <strong>elevated within 1hr of ischemia in only 1-2% of small intestine</strong></td>
</tr>
<tr>
<td>Protein of Interest</td>
<td>Clinical Justification</td>
<td>Sample Notes</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>NGAL</td>
<td>Acute renal injury</td>
<td>- Elevation precedes any increase in serum creatinine by 1-3 days (sustained throughout duration of AKI)…risks in proportion to the severity and duration of AKI…may enable more accurate prediction of cardiac surgery associated-AKI</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Acute renal injury</td>
<td>- Expressed in in trace amounts in proximal tubular cells…up-regulated dramatically after ischemic insult…easily detected in urine…clinical promise for early detection of subclinical tubular injury</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Renal injury/efficiency</td>
<td>- If glomerular filtration is deficient, levels rise…levels in blood and urine may be used to calculate clearance (CrCl)…which correlates approximately with GFR to assess renal function</td>
</tr>
</tbody>
</table>
## Minimum blood & urine volumes needed...

<table>
<thead>
<tr>
<th>Protein of Interest</th>
<th>Sample Type</th>
<th>Minimum volume (µL) needed per sample</th>
<th>Sample volumes (µL) in duplicate (Min. vol. needed (\times 2) for validation @ each assay time point)</th>
<th>Volume for each time point ((\times 5 \text{ for serum} &amp; \times 4 \text{ for urine}))</th>
<th>Total mL of blood or urine collected from each patient for research purposes</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100B Serum</td>
<td>Serum</td>
<td>50</td>
<td>100</td>
<td>Will collect 1.2 mL total @ each time point *See notes below</td>
<td>6 mL</td>
</tr>
<tr>
<td>GFAP Serum</td>
<td>Serum</td>
<td>100</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Troponin I</td>
<td>Serum</td>
<td>50</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystatin-C Serum</td>
<td>Serum</td>
<td>100</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SM22 Serum</td>
<td>Serum</td>
<td>100</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-FABP Serum</td>
<td>Serum</td>
<td>100</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGAL Urine</td>
<td>Urine</td>
<td>50</td>
<td>100</td>
<td>Will collect 1.5 mL total @ each time point *See notes below</td>
<td>6 mL</td>
</tr>
<tr>
<td>KIM-1 Urine</td>
<td>Urine</td>
<td>100</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>Will be measured as part of standard care; not assayed separately</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes

In the case of sampling error or mishandling:

- Will collect an **extra \(~0.2\) mL serum** \((above the 1 mL needed)\) at each of the 5 time points; thus, ↑ blood volume to **6 mL** total for each patient

Because the **urine** is discarded naturally, we will likely collect an extra \(~1.2mL\) \((above the 0.3 mL needed)\) at each of the 4 time points, bringing the total volume to **6 mL** for each patient; Only the minimum volumes are listed for proposed assay validation
Lack of active controls...so:

- Does the retrospective data have comparable variables (NIRS $O_2$ data, blood tests, etc.)
  - Yes...most physiological labs are available (NIR, etc.)...only missing research labs
  - Neurological outcomes and complications will be compared with prospective cohort @2:1 ratio...will also compare additional variables (NIRS, etc.)

- How far should we go back retrospectively? Mainly, what is the most meaningful data to gather if we propose a larger study in the future
  - Norwood data goes back to 1996; we will aim to select only cases back to 2012 to avoid era effect. If needed we will consider earlier cases
  - The new blood urine/research may potentially be useful diagnostically in future
Potential Limitations

• Reduction in patient consent in prospective arm of study
• Reduction in eligible cases that meet criteria
  • # of pts born w HLHS is decreasing
• Inadequate replication of CPB technique (flow rates, patient anatomical barriers, etc.)
Future Direction

- Potential to utilize the data for larger prospective study comparing outcomes in a near-normothermic cohort with hypothermic cohort

- **Multi-institutional collaboration**

- Procure additional funding...an adequate budget may allow for:
  - More frequent follow-up visits and family stipends
  - Increased imaging & examinations
  - Additional lab draws to monitor blood protein hemodynamics
  - MRI’s pre-surgery and during developmental follow-up visits
Cohort Details

Enrollment has been much lower than expected due to a fluctuation in cases the meet the inclusion criteria

5 patients (4 Males; 1 Female)

<table>
<thead>
<tr>
<th>Avg. Gestation (Wks)</th>
<th>Avg. Birth Weight (Kg)</th>
<th>Avg. Birth Length (Cm)</th>
<th>Avg. Age at Surgery (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.69 (Median=38.71)</td>
<td>3.33 (Median=3.34)</td>
<td>49.8 (Median=50)</td>
<td>6</td>
</tr>
</tbody>
</table>
Cohort Details

Index CPB Time (continuous)

- **121.6 minutes** (Avg. continuous CPB duration for index round)
• Millipore Sigma is building custom multiplex ELISA assays to measure concentrations of biomarkers in serum and urine samples that we’ve collected over various time points

• The assays will help us to detect subtle and significant changes in the regulation of certain biomarkers that could be indicative of acute kidney injury and hypoxia

• **Assay development is ongoing** and is expected to be complete around December *(or possibly earlier)*. We do have biomarker data for serial samples that were used to begin constructing the assays
Custom Immunoassay Development: Milestone Work-plan

1. Evaluation of Existing Analytes in Serum Samples
2. Custom MILLIPLEX Kit- New Analyte Development
3. Custom MILLIPLEX Multiplexing and Assay Verification
4. Custom MILLIPLEX Quality Control and Range
5. Assay/Kit Manufacturing

Current step: Custom MILLIPLEX Multiplexing and Assay Verification
The machine that we will use for analysis of the serum and urine samples is the **MAGPIX® System**.

The system utilizes **magnetic bead-based multi-analyte panels**; thus it allows for multiple analytes to be measured from each sample.

Some of its capabilities are:

- **Real-time analysis and accurate quantification** of antibody-antigen interactions
- **Can simultaneously measure up to 50 analytes in as little as 25 μL of sample**
We thank the MCW Department of Surgery and the We Care Fund for Medical Innovation and Research for supporting us in this endeavor.
Thank You
Biomarker Data

- S100B increased tremendously following CPB, but **dropped off significantly to below baseline within 6 hour period**

- Elevations in S100B may provide a **sensitive measure for determining CNS injury** at the molecular level

- Cerebral biomarker elevation may be an early indicator of injury and thus **may help guide strategies** that target cerebral oxygenation and hemodynamics

*Data is comprised of samples from one pt. used for analyte detection in construction of custom immunoassays*
Previous CHW (S100B) Research

- Study also demonstrated a rise in S100B concentration after bypass, and subsequent drop off.

- In this study, patients who spent any time with a cerebral arteriovenous difference (da-rSo2C) greater than 50 during CPB had significantly higher peak S100B, a marker of cerebral injury.

- Relatively short periods of cerebral desaturation were found to be associated with elevated S100B levels, suggesting that properly timed biomarker assays may be more sensitive than histologic assessment or clinical findings for detection of neuronal injury.
Sources report that glial scarring is a consequence of several neurodegenerative conditions, as well as injury that severs neural material; it is reported that the scarring is partially caused by up-regulation of GFAP.

Study by Johns Hopkins notes that high GFAP during ECMO is significantly associated with acute brain injury and death; thus, brain injury biomarkers may aid in outcome prediction and neurologic monitoring of ECMO patients to improve outcomes and benchmark new therapies.

*Data is comprised of samples from one pt. used for analyte detection in construction of custom immunoassays*