Case Report: The use of del Nido Cardioplegia During Bypass on a Pediatric Sickle Cell Patient
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Perfusion Student
MUSC CVP Program

Disclosures
I have no disclosures.

Overview
- Sickle Cell Disease
- Del Nido Cardioplegia & the Sickle Cell Patient
- Case report of sickle cell patient undergoing CPB at MUSC
  - Preoperative
  - Intraoperative
  - Postoperative
- Conclusion/Future Studies

Sickle Cell Disease
- Recessive gene abnormality
  - Adenine --> thymine mutation causing glutamic acid → valine = Hemoglobin S
- SCD affects approximately 100,000 Americans
  - Most common inherited blood disorder
- Six most common types:
  - HbSS, HbSC, HbS beta thalassemia, HbSD, HbSE, HbSO
Sickle Cell Crisis

- Low oxygen tension and acidic states lead to structural modifications that affect transit through the body and cause sickling:
  - Infection
  - Dehydration
  - Acidosis
  - Changes in temperature
  - Excessive exercise, shortage of oxygen
  - Stress
  - High Altitudes
- When sickling occurs, blood flow to organs can become obstructed and leads to complications:
  - Vaso-occlusive crisis
  - Splenic sequestration crisis
  - Acute Chest Syndrome
  - Aplastic Crisis
  - Hemolytic Crisis

How Bypass Can Cause Sickle Cell Crisis

Cooling ➔ Hypothermia

Inadequate O2 delivery ➔ Hypoxemia

Inadequate pump flow ➔ Hypoperfusion

Improper blood management ➔ Acidosis

Pros & Cons of using Del Nido on a Sickle Cell Patient

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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</thead>
<tbody>
<tr>
<td>Cold blood infusion</td>
<td>Cold blood infusion</td>
</tr>
<tr>
<td>May require additional RBCs</td>
<td>May require additional RBCs</td>
</tr>
<tr>
<td>Single dose</td>
<td>Other options: warm induction with del Nido, 1NaCl:4delNido, other cardioplegia solutions (cold crystalloid)</td>
</tr>
<tr>
<td>Quick arrest</td>
<td>Achieve good myocardial protection</td>
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<tr>
<td>Achieve good myocardial protection</td>
<td>No change to current practice</td>
</tr>
<tr>
<td>No change to current practice</td>
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**Patient Background**

- 4 year old girl
- Sickle cell + beta thalassemia
  - No sickling events noted
- Mitral regurgitation and dilated cardiomyopathy
- Patent foramen ovale
- Height: 121cm, Weight: 21.9kg, BSA: 0.85m²
- Hemoglobin S: 60%

**Preoperative Management**

- Partial Exchange Transfusion Performed
  - Used a quinton catheter to decrease circulating Hgb S to less than 30%
  - 5 units exchanged in a 1:1 fashion
  - Calculated PBV: 1752ml (65ml/kg) / 5 units * 100% = 70% blood volume exchanged

- Pre-exchange transfusion hemoglobin variants:
  - Hgb S: 60%
  - Hgb F: 25%
  - Hgb A: 15%

- Post-exchange transfusion hemoglobin variants:
  - Hgb S: 13.7%
  - Hgb F: 5.5%
  - Hgb A: 77.6%

**Intraoperative Management: Surgical Technique**

- Full Sternotomy
- Aortic (14Fr) and Bicaval Cannulation (14 &16Fr)
- Cross Clamp
- Antegrade Cardioplegia
- Right atriotomy to repair PFO
- Left atrium opened to repair Mitral Valve

**Intraoperative Management: CPB Pump Prime**

- Initially primed with 1L Plasmalyte A and 25mEq NaHCO₃

- Prime constituents:
  - 257ml washed RBCs (1 unit)
  - 100ml 25% Albumin
  - 2000IU heparin
  - 5.475gm mannitol
  - 657mg tranexamic acid

- Post prime gas adjustments:
  - Additional 12mEq NaHCO₃

**Intraoperative Management: CPB Pump Prime (Continued)**

<table>
<thead>
<tr>
<th>Prime Constituents</th>
<th>Prime</th>
<th>Time (min)</th>
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<tbody>
<tr>
<td>257ml washed RBCs</td>
<td>1 unit</td>
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<td>2000IU heparin</td>
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<tr>
<td>5.475gm mannitol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>657mg tranexamic acid</td>
<td></td>
<td></td>
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<tr>
<td>Additional 12mEq NaHCO₃</td>
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</tbody>
</table>
Intraoperative Management: Exchange Transfusion with CPB Pump

- Not performed due to previous day partial exchange and low circulating Hgb S levels
- Had we performed it:
  - Draining of 65-70% of patients blood volume into reservoir
  - Simultaneous reinfusion of new red blood cells (~4-5 units)
  - Set-up similar to image on right


Intraoperative Management: Temperature Management

- Goal - maintain body temp >35° C
  - Bairhugger was used as needed
  - OR temp kept as warm as possible
- Lowest temp on CPB: 35.3° C
- Highest temp on CPB: 36.0° C

Intraoperative Management: ABGs

Goals
- pO2 >270mmHg
  - Normal institution protocol: 150mmHg – 250mmHg
- SvO2 >70%
  - Normal institution protocol: >65%
- HCT goals post CPB: >30
  - Normal institution protocol: >24
- pH 7.40 – 7.45
  - Maintain a slightly alkalotic state to prevent acidosis

ABG monitoring
CDI throughout CPB
iStat Q 30 minutes

Intraoperative Management: Anticoagulation

- No changes from institution anticoagulation protocols
- Heparin:
  - 500IU heparin/kg (11,000IU)
  - ACT > 400 seconds
  - iStat ~ Q 30 minutes
  - No additional heparin given on CPB
- Protamine
  - 60% of ACTD = heparin in Prime (78mg)

ACT Levels
Baseline
0715 148 seconds
Post Heparin
0814 >1000 seconds
0849 >1000 seconds
0914 >870 seconds
0947 798 seconds
Post Protamine
1027 139 seconds
Intraoperative Management: **Cardioplegia**

- Team Discussion to use blood versus crystalloid
  - 1 full dose of 1:4 cold Del nido was given (30ml/kg)

  Cardioplegia return was diverted to wall suction to prevent mixing of cold blood

  During delivery we monitored:
  - EKG
  - Line pressures
  - Patient pressures
  - $SvO_2$
  - $pO_2$

  Prior to XC removal, cardioplegia line was flushed to wall suction. 84mL hot shot (warm blood) was given

Intraoperative Management: **Volume Management**

- **Cell Saver**
  - Not used to prevent return of hemolyzed cells
  - Wall suction was used in its place

- **Ultrafiltration**
  - Performed while on CPB to remove hemolyzed cells and plasma water to optimize HCT
  - 1050mL of ultrafiltrate was removed

- **Urine Output**
  - Good indicator of sickling
  - Monitored continuously throughout bypass
  - 100mL of urine reported

- **Red Blood Cells**
  - 3 units of RBCs were given to manage patients volume status
  - 1 unit at:
    - 1 prior to XC
    - 1 prior to hot shot/removal of XC

- Esper et al., Blood Transfusion. 2011;9(2):139-47

Postoperative Management

- Hourly blood gases
- Hemoglobin variants not performed
- Epinephrine and milrinone started in OR and weaned POD1
- Uneventful course
- Patient discharged POD3
- No sickling events reported/observed

Conclusion/Future Studies

- Del nido provided myocardial protection and safe ischemic time with diversion to wall suction
  - Sickling events not observed

- More research should be performed on the effects of del Nido cardioplegia during CPB with SC patients
Thank you!
Purpose

- A training program to create a field ECLS experience was developed because evidence suggests that early initiation of ECLS in select patients with refractory pulseless cardiac rhythms may improve survival.

Background

- Out-of-hospital cardiac arrest (OHCA) is a prominent public health dilemma, with an annual incidence of over 350,000 and 39.5% occurring in public places.
- Integrating layperson CPR and public-access defibrillation programs has improved outcomes but the underlying pathology may be refractory to this standard pre-hospital care.
- Some evidence suggests that early initiation of ECLS may improve survival.
Innovation

- We have implemented an ECLS-CPR (E-CPR) alert to prepare an ECLS team for arrival of an OHCA patient meeting specific inclusion criteria at UPMC Presbyterian.
- Providers are trained to identify patients during the first 10 minutes of prehospital resuscitation, activate the alert, and expedite transport to the ECLS facility.
- To expand this system, we developed a novel training program to create a field ECLS team.

Why Pittsburgh.....

- 24/7 University of Pittsburgh Department of Emergency Medicine MD Field Response
- Provide advanced procedures
- LucuS® Device
- Pittsburgh EMS
- 13 ALS & 3 BLS Ambulances
- 2 ALS Heavy Rescue Units
- 2 Supervisor Units
- Pre-hospital E-CPR Checklist
- Transportation to an ECLS facility

Simulation

- We demonstrated a student athlete suffering a witnessed OHCA refractory to standard ACLS care.
- The EMS physician was responsible for cannulating the patient and operating the circuit.
- One paramedic group was trained to assist the physician with cannulation while other paramedics continued high-performance resuscitation.
- The simulation was conducted at a pediatric ECLS conference using a high-fidelity gel model for cannulation.
- ECLS support was achieved in 28 minutes.

Femoral Simulation Model
Simulation

- Medical simulations offer a realistic opportunity to develop, master and maintain clinical skills.
- We are constantly improving our ECLS training models with a goal to improve and simulate the overall educational experience.
- Some evidence suggests that early initiation of ECLS may improve survival.

Conclusion

References

- https://www.clearballistics.com/
**Exit to ECMO: How we do it!**
The Children’s of Alabama experience

Joseph Timpa CCP,FPP
Perfusion Manager/ ECMO Co-Coordinator
Children’s of Alabama

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**Definition**

- Ex Utero delivery leaving umbilical cord connected until an airway is established
- Ex Utero delivery leaving umbilical cord connected until head is out a baby is cannulated jugular and carotid
- Ex Utero and separating from the umbilical cord, immediately taking baby to another area to assess if ECMO is urgently required to stabilize

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**Indications for EXIT**

- The EXIT procedure has been successfully used to intervene in several fetal disease states.
- These include but are not limited to congenital airway obstructions such as tracheal stenosis/atresia, neck masses, pulmonary and mediastinal masses, congenital diaphragmatic hernia, and congenital heart disease.
- In some instances, the EXIT procedure can be performed in order to transition the infant to extracorporeal oxygenation (ECMO) until further surgical interventions can be done, such as in hypoplastic left heart syndrome with intact atrial septum.

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**No Disclosures**
Coordination and Planning

Planning for an EXIT Procedure

- The planning and preparation for an EXIT procedure involves a multidisciplinary team of practitioners working together over an extended period of time leading up to the procedure itself.

- Depending on when the fetal disorder is discovered, this can occur over several weeks or months.

- Furthermore, the lesion being treated will often dictate the team members involved.

Multidisciplinary Roles

- Through regular meetings, this group of practitioners will develop a plan of action for the EXIT procedure.

- The roles of each individual involved in the case needs to be established as well, since different specialists often feel that they should take responsibility for the care of the neonate.

- Communication on who will be the primary team for neonatal intubation, obtaining intravenous access, and initiation of resuscitation, if it becomes necessary, must take place early to prevent confusion during the procedure itself.

Simulation /Walk Thru

- For a complicated procedure such as EXIT with many different individuals participating in various roles, simulation of the case can be used to guide participants about the different roles and how to manage them.

- Issues such as space, the large number of personnel, their physical location in the room, and equipment needs can all be determined as well.

- Blood product availability and regulations from one hospital to another.

- Equipment such as POC, Medications, Transducers, Air and Oxygen connections all need to be considered for a smooth transition from one hospital to the next.
Planning

- Mamas blood collected on the day of last clinic visit for needs at UAB & Baby's blood sent to COA for cross match to have after birth for possible upcoming procedures
- Emergency release in cooler for ECMO prime
- Mama’s consent and baby admitted in COA before birth

Personnel for Cardiac lesions

- Obstetric anesthesiology for the mother
- Obstetric surgery team
- Pediatric anesthesiology team for the fetus
- Pediatric Cardiac surgeon
- Neonatologist and intensivist (in the operating room or post delivery evaluation)
- Cardiologist to perform echocardiogram
- CVOR nurses/Perfusionists

Delayed Cord Clamping

Advantage of delayed umbilical cord clamping in newborn infant

- Advantage of delayed umbilical cord clamping is that it allows for additional placental blood to the newborn infant, which can provide the newborn with an additional 20% blood volume, thereby protecting it from anemia without increasing the risk of neonatal or complications related to hyperviscosity and oxyhemoglobin. Delaying perfusion represents only 1% of the total output during intrauterine life but increases to 40% immediately after birth, and the extra intravascular volume expansion then facilitates the cardiopulmonary transition. A delayed cord clamping also decreases the risk of fetal-maternal transfusion, which is of particular importance in women with negative women. In premature infants, the risk of cerebral hemorrhage is lowered. To retain the advantage of both immediate blood sampling for acid-base determination, and allowing placental blood transfusion to the newborn, the blood can be sampled without clamping of the cord.

UAB and COA Partnership

UAB and COA Partnership: UAB RNICU/L&D, COA Cath Labs, CVICU & CVOR
UAB Women & Infant Center

• Connected by a crosswalk to Childrens of Alabama CV Services
• All CV clinicians are credentialed at both hospitals
• We operate on cardiac patients from birth to 20 years of age at COA and above 20 years at UAB
• All adult congenital caths are performed at COA

Cardiac Exit to ECMO

• In neonates born with hypoplastic left heart syndrome or severe aortic stenosis, most of the blood flow to the body is pumped from the right ventricle through the patent ductus arteriosus (PDA).
• Therefore, there must be an opening or intra-cardiac lesion that allows the oxygenated blood from the left side of the heart to mix with the right and be delivered to the body.

Cardiac Exit to ECMO

• Smaller disposables and portable ECMO pumps have allowed clinicians to increase the versatility of ECMO.
• In addition, the emergence of multidisciplinary ECMO teams has helped standardize patient care and made the therapy more predictable and reliable.
• We have started to use exit to ECMO strategies for early intervention in children born with complex cardiac lesions with intact septum.

Criteria for ECMO and Planned Procedure post ECMO

• The child is born in the delivery operating room via cesarean section
• The child is taken to the resuscitation area where the ECMO intervention team is mobilized
• The intensivist puts in umbilical artery monitoring while cardiovascular anesthesiologist intubates the patient
• The intensivists and surgeon will determine whether the patient needs ECMO
• If ECMO is needed, the procedure will be handed off to the CVOR team.
Goals EX UTERO

• SaO2 > 70 – Transport to COA for Conventional Care in the CVICU
• SaO2 50-70 – Transport to COA Hybrid Cath Lab for septostomy
• SaO2 <50 – ECMO cannulation in post delivery area, transport to COA Hybrid Cath Lab for septostomy and evaluation of next stage (wean off ECMO after fluid removal, Hybrid Norwood, Conventional Norwood)

Perfusion Prep

• Perfusionist has a size appropriate pump built for possibility of CPB if needed in Hybrid
• Perfusionist mobilized at UAB with clear primed ECMO circuit
• COA ECMO team also has a back up circuit built
• Cath lab and CVOR open that day

CV Perfusion - Exit to ECMO Checklist

- Supplies needed before patient is born
  - Delivery: Hospital emergency release blood (O) or cross-matched units from mother.
  - ECMO medications: Heparin 100 U/mL, Sodium Bicarbonate 1 Mq/mL, Calcium Chloride 100 mg/mL.
  - Pressure monitoring setup with portable monitor for transport
  - Two pump circuits: one ECMO outside of delivery room and one CPB ready in sterile connection room
  - ECMO cart with all connection supplies and POC devices
  - Portable room air and oxygen tanks (with quick connect)

- Priming the ECMO circuit
  - The ECMO circuit is primed with Flumeadon and drugs before the child is born
  - The donor and blood cells are added once it has been determined ECMO will be required
  - Talk with surgeon to determine appropriate cannula size

- Postnatal patient parameters
  - Subject to change based on each patient’s needs
  - Guidelines agreed upon at first team meeting prior to birth
  - SaO2 > 90 – Immediate care at the CVICU
  - SaO2 70-90 – Take to cath lab for a follow-up arterial oxygen
  - SaO2 < 70 – Exit to ECMO and take to cath lab for a follow-up arterial oxygen

Post Natal Evaluation Area
Our Patients #1

- HLHS w IAS
- ECMO standby at UAB stabilized and transported to cath lab for septostomy and PA banding
- 2 weeks later brought to OR for a Norwood w Sano
- Eventually went for BDG d/t complicated ICU course with PHTN and eventually expired from multi organ failure
Our Patients #2

- HLHS w/ IAS
- ECMO initiated outside delivery room and transported to cath lab for emergent atrial septostomy.
- ECMO was weaned the next day of life
- 2 weeks later received Hybrid Norwood in the cath lab.
  This patient was transplanted and doing well!

Our Patients #3

- Known HLHS w/ IAS in utero
- Placed on ECMO immediately after birth at UAB and transported to COA for Hybrid Norwood
- Patient suffered AKI and persistent PHTN and LCOS with rising lactate. Family chose no further interventions and patient expired.

Our Patients #4

- HLHS w/ IAS
- ECMO was initiated immediately after birth at UAB and transported to COA for Septostomy, Balloon valvuloplasty, and Hybrid Norwood
- This patient was transplanted and doing well!

Our Patients #5

- Critical Aortic Stenosis/Shones w/ IAS
- ECMO standby, stabilized, and transported to COA for Balloon valvuloplasty and atrial septostomy.
- Norwood cancelled in OR after measuring systemic PA pressures and LCOS in the CVICU. Family chose not to pursue ECMO and patient expired.

Other Cases

- Coarctation/ECMO initiated in UAB/RNICU, transported to COA and received ductal stent
- TAPVR/ECMO standby—received BT shunt and ECMO after surgery
Results

- 4 patients with HLHS / IAS - 50% survival
- 3 other patients with Various CHD / ECMO mobilization and emergent cath lab interventions – 67% survival
- Survival for total patients that ECMO was either mobilized or initiated at UAB with Emergent Cath lab interventions at COA-58%

Fetal Intervention and Prenatal Diagnosis with Intervention

Difficult Subset of Patients

- We do not have a fetal intervention program
- In the past, these patients would have died soon after birth
- Exit to ECMO mobilization has shown potential to save patients that would otherwise expire
- This population continues to be a complex group to treat even after early interventions
Grazie per Vostra Attenzione!

Children’s Cardiac Services
How I: Teach Pediatric Perfusion

Kerry L. Fair, BS, CCP, LCP

2019 AnSECT International
March 8-10th Nashville, TN
Gaylord Opryland Resort and
Convention Center

Background

- Attended Vanderbilt University Perfusion Program
  - Graduated 2004
  - Class of three, no outside rotations
  - Monroe Carell Jr. Children’s Hospital at Vanderbilt
    opened in 2004
  - Hired at Vanderbilt after graduation...never left.

Why Pediatrics??

- Immediately interested
- Easy access/exposure
- Surgeon support
- Trusting and respected preceptors
Vanderbilt Transitions...

- Transitions within Vanderbilt Perfusion program
- VCH had students come for observation but didn’t pump cases
- No formal guidelines for being a preceptor
- Significant changes in 2012: New Program Director!

An ever-evolving process

- How do we best get students prepared for the rigors of pediatric perfusion??
  - Intense didactic courses
    - 13 weeks of congenital lectures
  - Observation
    - Junior students come ASAP to start observing cases
    - Can often get hands on experience if opportunity is there
  - Simulation
    - Once a week for 9 weeks the students practice our pediatric setup, priming, and MUF techniques

9 week rotations, 10 students: you do the math!

- Which students get rotations?
  - Sometimes easy, sometimes not
- When do they start?
  - Usually under the direct guidance of the Program Director
  - Pros and Cons
  - Timing is everything...
Getting started
As they are completing the checklist

- Working on proficient charting
- Learning ancillary duties
- Eventually hands on
  - Suckers and vents
  - Cardioplegia
  - Sweep/FiO2...

First Case....

First case (or two...or three...)

- Primary Perfusionist handles communication with surgeon
  - Helps surgeon feel more comfortable
  - Helps “prompt” student
- Student runs the arterial head, cardioplegia, etc
- Primary or assist Perfusionist handles ancillary duties.

Briefing and Debriefing

- Student finds out the night before (if not earlier) case assignment and instructor
  - Students responsibility to reach out to instructor for instruction and plans
- Morning of: brief with goals for the case
  - Based on level of progression, areas in need of improvement etc
- After case: debrief with constructive criticism
  - Critical feedback for positive progression
Evaluation process

• We evaluate each student at the end of the rotation
• They also evaluate us
  – Receive great feedback for each instructor
• End of rotation interview
  – What does the student like?
  – Areas of improvement?

Preceptor Workshop

• Yearly Training for all Clinical Instructors
• Highlights some information about adult learning
  – Specific information about each student
• Standards and Guidelines set forth by the AC-PE

What we do well

• Very supportive learning environment
  – Surgeon and anesthesia support
• Nice mix of staff members and personalities
  – Most teammates have been teaching for years
  – New graduate gives great perspective
• Detailed progression
• Good communication within team about student’s progression
Where can we improve?

• Making students feel more like a member of the team
  – Strong introductions
• More inclusion into discussion and decisions
  – Pediatrics introduce many new decision-making skills to students
• Teaching about ancillary tasks
  – So much to learn, how do we include it all?

The numbers don’t lie!

• For reference: I pumped 37 pediatric cases as a student (and 125 adults)
• Students from 2015-2018 pump as many as 250 adult cases and up to 50 pediatric cases
  – Multiple rotation sites now
  – Two (and soon to be three) pediatric rotations available to Vanderbilt students.
My personal mantras

• You don’t HAVE to learn pediatrics, but it will make you a better perfusionist if you do.
• It’s much easier for me to do this myself than to teach you; show up ready to learn and have a good attitude.
• Most of the students are harder on themselves than I ever could be…no need to be a jerk.

THANK YOU!!
Why and how I use Nitric Oxide on Bypass
Clarke Thyss CCP FANZCP.

• No Disclosures

NO & Cardiopulmonary Bypass

• Why do we need nitric oxide?
• Adult cardiac surgical patients had preoperative increased levels of oxidative stress and decreased levels of antioxidants. Increased levels of nitric oxide inhibitor asymmetric dimethylarginine were also detected, suggesting arginine/nitric oxide pathway impairment.

Oxidative stress and nitric oxide pathway in adult patients who are candidates for cardiac surgery: patterns and differences.
Viviana Cavalca, Elena Tremolada, Benedetta Pomo, Fabrizio Veglia, Veronika Myasoedova, Isabella Squelleni, et al.
Interactive Cardiovascular and Thoracic Surgery 17 (2013) 923–930

Endogenous

http://www.reading.ac.uk/cellmigration/synthesis.htm
Is there a difference?

- NO derived from NO donors or eNOS, mediated mechanisms responsible for neuroprotective replicating the effects of therapeutic hypothermia.

- NO synthesized from iNOS contributes to further damage.


Nitric Oxide Gas

What does it do?

- Selective PVR
- Platelet deactivation
- Leukocyte deactivation
- Inhibit apoptosis
- Decrease myocardial injury
- Neuroprotective agent
- Reduce acute renal injury
- Anti Biofilm

How does it PVR

Platelet Inhibition


Leukocyte Deactivation

Leukocyte capture, rolling, adhesion, and transmigration through the endothelial cell barrier.


Apoptosis

University of Reading
Nitric Oxide Research Group
http://www.reading.ac.uk/nitricoxide/intro/no/apoptosis.htm

Apoptosis

• Ischaemic-Reperfusion Injury:
  • Ischaemia set up the cells for apoptosis.
  • Reperfusion is the killer.


Myocardial Injury:

- Ischaemic-Reperfusion Injury
  - The endothelial trigger
  - Loss of NO release by endothelial cells
  - Neutrophil amplification
    - Leukocytes adhere to the endothelium
    - Capillary plugging and oedema
    - Reduced coronary flow

- “No-reflow”
- Myocardial necrosis/apoptosis
- Reduced contractility

Effects of NO on cardiac arrhythmias

- Coronary endothelial dysfunction and NOS inhibitors reduce the coronary effluent NO levels and increase the incidence and severity of ventricular arrhythmias in rat models of ischaemia-reperfusion, whereas L-arginine and NO donors, even at subvasodilatory doses, reduce ischaemia/reperfusion-induced ventricular fibrillation (VF) in rats and dogs.

- Cardiac electrophysiological effects of nitric oxide.
- Juan Tamargo, Ricardo Caballero, Ricardo Gomez, and Eva Delpon
- Cardiovascular Research (2010) 87, 593–600

Cerebral Neuroprotection

- NO donors exerted a neuroprotective effect against cerebral ischemia-reperfusion injury at different levels by influencing cellular oxidative status.
- Pre- and postischemic administration of an NO donor attenuates the ischemia-induced increase of caspase-3 at 6 h of reperfusion and downregulates neuronal apoptosis.

Nitric oxide synthase in hypoxic or ischemic brain injury
Haiting Liu, Jiao Li, Fengyan Zhao, Huiqing Wang, Yi Qu, Dezhui Mu

Acute Renal Injury

- exposing blood to NO gas in the CPB oxygenator and after surgery for an additional 24 hours by inhaling at a dose of 80 ppm NO prevented the depletion of plasma NO, which was associated with a decrease in AKI rate and transition to stage 3 chronic kidney disease at 90 days and 1 year after surgery.

- Lei, Berra, Rezazad, et al.
- Nitric Oxide Decreases Acute Kidney Injury and Stage 3 Chronic Kidney Disease after Cardiac Surgery
- Am J Heart Fail Care Med; 198(10):1279–1287, Nov 15, 2018

Anti Biofilm

- Potent bactericidal activity was observed at 200 ppm NO with an average of 4.1 ± 1.1 h to completely stop bacterial growth.

- therapeutic levels of nitric oxide released from nanoparticles inhibits candida biofilm formation, destroys the extracellular polysaccharide matrices of mature fungal biofilms and hinders biofilm development on surface biomaterials such as the lumen of catheters.

- Mohammed Ahmadi, Hiu Ham Lee, David A. Sanchez, Adam J. Friedman, Moses T. Tar, Kelvin P. Davis, Joshua D. Nosanchuk, and Luis R. Martinez
- AAC Accepted Manuscript Posted Online 25 January 2016

- Nitric oxide synthase in hypoxic or ischemic brain injury
RCH Study

- 198 patients randomised to NO or control.
- All patients < 1.5 lpm blood flow on bypass
- Changes to normal sweep gas flow
- NO 20 ppm
- ICU blinded

- Nitric Oxide During Cardiopulmonary Bypass Improves Clinical Outcome: A Blinded, Randomized Controlled Trial
- Christopher S James, Stephen Horton, Christian Brizard, Charlotte Molesworth, Johnny Millar and Warwick Butt

Primary Outcome

A diagnosis of LCOS, defined as any of the following at any time during the first 48 hours:

- lactate > 4 mmol/l with central venous saturation level < 60% (or SaO₂-ScvO₂ difference >35% with single ventricle physiology)
- ECMO support
- Vasoactive Inotrope Score (VIS) >10

Vasoactive Inotropic Score

\[ \text{VIS} = \text{dopamine dose (g/kg/min)} + \text{dobutamine dose (g/kg/min)} + 100 \times \text{adrenaline dose (g/kg/min)} + 10 \times \text{milrinone dose (g/kg/min)} + 10,000 \times \text{vasopressin dose (U/kg/min)} + 100 \times \text{noradrenaline dose (g/kg/min)} \]
### Incidence of LCOS within first 48 hours of ICU admission between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Nitric Oxide (n=101)</th>
<th>Control (n=97)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>15/101 (15%)</td>
<td>30/97 (31%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age subgroups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>6/30 (20%)</td>
<td>14/27 (52%)</td>
<td>0.012</td>
</tr>
<tr>
<td>6 weeks – 2 years</td>
<td>2/13 (8%)</td>
<td>10/43 (24%)</td>
<td>0.026</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>7/36 (19%)</td>
<td>6/29 (21%)</td>
<td>0.901</td>
</tr>
<tr>
<td>RACHS classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>10 (14%)</td>
<td>19 (26%)</td>
<td>0.074</td>
</tr>
<tr>
<td>4–6</td>
<td>5/29 (17%)</td>
<td>11/23 (48%)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

### Cost Impact of LCOS

- **ICU stay** - $5000 /day (2015)
- **Shared ward stay** - $910/day (2016)
- **Peritoneal dialysis** - $1600/day
- **Ventilator support** - $1600/day

NO cost - $150/hr

### The Bottom Line

- **LCOS cost per 100 patients without NO**
- **1 day PD + 5.8 days ICU + 5 days Ventilator + 2 days shared ward stay**
  - ($1600 + $29000 + $8000 + 1820) x 30 patients
  - $1,212,600
- **LCOS cost per 100 patients with NO**
  - $606,300 (15 patients)
  - Cost of NO = 100 x $150 x 3 (Hours cpb)
  - $450,000

Savings $156,300 per 100 patients

At RCH 350 patients = $546,000
NO for every patient?

- Beating heart cases?
- MAPCAs (Major aortopulmonary collateral arteries)
- Anatomical Shunts
- Adults?

Adults

Kamenshchikov, Mandel, Podolskova, et al. Nitric Oxide provides myocardial protection when added to the cardiopulmonary bypass circuit during cardiac surgery: Randomized trial. JTCVS, 2018; in press.

Conclusion

Nitric Oxide for bypass? Yes, but not for every case.
How We Use $\text{DO}_2$ i at CCHMC

James A. Reagor, MPS, CCP, FPP
Assistant Professor
Director - Cardiovascular Perfusion
Cincinnati Children’s Hospital Medical Center

Current Publications

**Oxygen Delivery During Cardiopulmonary Bypass and Acute Renal Failure After Coronary Operations**

Marco Ranucci, MD, Federica Romiti, MD, Giuseppe Isgro, MD, Mauro Cottra, CCP,
Simonetta Bruschi, CCP, Alessandra Boncilli, CCP, and Antonio Ditta, CCP
Departments of Cardiothoracic Anesthesia and Intensive Care and Cardiovascular Protection, Policlinico Sant’Orsola, Milan, Italy

**Background.** The degree of hemodilution during cardiopulmonary bypass has recently been identified as an independent risk factor for acute renal failure after determining acute renal failure was subsequently included in the model.

**Results.** The best predictor for acute renal failure and
Goal-directed perfusion to reduce acute kidney injury: A randomized trial

Marco Raveci, MD, FESC; Ian Johnson, CCP; Timothy Wilkens, CCP; Robert A. Baker, PhD, CCP; Christina Boer, MD, PhD; Andrea Baumann, MD; George A. Jenkins, CCP; Filipe de Sousa, CCP; Paul Evans, BS (Hon), CCP; Sumeet Agarwal, FRCA; Richard F. Newland, CCP; Renald G. Stanislaus, CCP; Dirk Beckwoldt, PhD, CCE; Nathan Wester, MD; Rajivnigvan Venkateswaran, MD, FRCPC(CH); Federico Ambroggi, PhD; and Valeria Pontini*

ABSTRACT

Objective: To determine whether a goal-directed perfusion (GDP) strategy aimed at maintaining oxygen delivery (DO2) at >200 ml/min/m² reduces the incidence of acute kidney injury (AKI).

Methods: This multicenter randomized trial enrolled a total of 369 patients undergoing cardiac surgery at 9 institutions. Patients were randomized to receive either GDP or conventional perfusion. A total of 352 patients completed the study and were analyzed. Patients in the treatment arm were treated with a DO2 target of >200 ml/min/m².

Current Publications

Current Publications

Time-dose response of oxygen delivery during cardiopulmonary bypass predicts acute kidney injury

Hiroshi Mekada, MD, CCF; Satoshi Mano, MD, PhD; Kenji Kawaki, MD, PhD; Takahiro Iinuma, CCP; Yukinobu Mimura, BS, CCP; Akira Sugiyama, BS; and Atsushi Amato, MD, PhD

ABSTRACT

Objective: Previous studies have reported that nadir oxygen delivery during cardiopulmonary bypass is associated with the occurrence of postoperative acute kidney injury (AKI). However, these measurements only considered the bottom point of the oxygen delivery (DO2) but did not consider the duration of DO2. We aimed to examine whether the time-dose response of DO2 during cardiopulmonary bypass can be used to examine the risk for postoperative AKI.

Methods: We evaluated 112 patients who underwent cardiac surgeries with cardiopulmonary bypass. The time-dose response of DO2 was calculated for each patient. Akizawa et al. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.
### CCHMC Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>PS1 (N=155)</th>
<th>PS2 (N=80)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean], (years)</td>
<td>1.46(0.38, 6.29)</td>
<td>3.59(0.379, 10.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>7390(171)</td>
<td>8204(176)</td>
<td>0.36</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>9.1(5.5, 20.3)</td>
<td>13.5(18.3, 24.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>BSA [m²]</td>
<td>0.42(0.29, 0.4)</td>
<td>0.57(0.28, 1.14)</td>
<td>0.61</td>
</tr>
<tr>
<td>PreOp Creatinine [mg/dL]</td>
<td>0.3(0.21, 0.47)</td>
<td>0.365(0.28, 0.52)</td>
<td>0.11</td>
</tr>
<tr>
<td>STAT Mortality Category</td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>.   1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.   2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.   3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.   4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSA Mortality Category</td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Avg Cardiac Index (ml/m²/beat)</td>
<td>2.39 ± 0.059</td>
<td>2.93 ± 0.078</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre CPB Hct [%]</td>
<td>33.3(23, 42)</td>
<td>35.3(23.1, 40.2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Min Hct [%] on CPB</td>
<td>27(23, 30)</td>
<td>29(23, 27.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Minimum Core Temperature [°C]</td>
<td>36.5(33.3, 42.7)</td>
<td>35.5(33.3, 42.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>CPB Time (minutes)</td>
<td>170(181, 191)</td>
<td>150(181, 181)</td>
<td>1.00</td>
</tr>
<tr>
<td>Total PRBC (mcL)</td>
<td>420(235, 520)</td>
<td>430(245, 527)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

### CCHMC Study

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</tr>
</thead>
<tbody>
<tr>
<td>Min DO₂ (3 minutes)</td>
<td>264 ± 47.2</td>
<td>314 ± 47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Min DO₂ (5 minutes)</td>
<td>276 ± 47.2</td>
<td>326 ± 49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Min DO₂ (10 minutes)</td>
<td>301 ± 48.8</td>
<td>355 ± 48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Min DO₂ (15 minutes)</td>
<td>311 ± 49.5</td>
<td>366 ± 47.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Max DO₂ (3 minutes)</td>
<td>413 ± 76.2</td>
<td>441 ± 70.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Max DO₂ (5 minutes)</td>
<td>405 ± 74.9</td>
<td>433 ± 66.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Max DO₂ (10 minutes)</td>
<td>389 ± 75.6</td>
<td>420 ± 62.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Max DO₂ (15 minutes)</td>
<td>377 ± 74.6</td>
<td>405 ± 64.1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### CCHMC Study

<table>
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<tr>
<th>Variable</th>
<th>PS1 (N=155)</th>
<th>PS2 (N=80)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine [ml/kg/hr]</td>
<td>1.3(0.514, 2.34)</td>
<td>2.26(1.03, 4.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AKI Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.   No AKI</td>
<td>98(63.2)</td>
<td>66(83.3)</td>
<td>0.014</td>
</tr>
<tr>
<td>.   Stage 1</td>
<td>44(28.4)</td>
<td>11(13.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>.   Stage 2+</td>
<td>13(8.39)</td>
<td>6(7.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>
TURN IT UP

Management

Monitoring

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Group</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
</table>
| CDI 500 vs ABL 90 Hgb| ≤1 g/dL  | 498 | 79%
|                       | 1.1-2 g/dL | 98  | 15%
|                       | >2 g/dL   | 45  | 6%
| M4 vs ABL 90 Hgb     | ≤1 g/dL  | 467 | 63%
|                       | 1.1-2 g/dL | 158 | 21%
|                       | >2 g/dL   | 151 | 15%
| CDI 500 vs ABL 90 SvO2| ≤3%     | 251 | 60%
|                       | 3.1-5%    | 215 | 52%
|                       | >5%       | 85  | 21%
| M4 vs ABL 90 SvO2    | ≤3%     | 215 | 52%
|                       | 3.1-5%    | 176 | 34%
|                       | >5%       | 69  | 14%

Real Time Alerts
Practice Performance Metrics

Current CCHMC Study

- 785 patients
- KDIGO Criteria
  - 1.5 X increase Stage 1 or >0.3 mg/dl
  - 2.0 X increase Stage 2
  - 3.0 X increase Stage 3 or >4.0 mg/dl
- Comparison
  - Lowest 7 day prior to surgery Cr
  - Highest 48 hour post surgery Cr
  - No urine

Thank you!

It is amazing what you can accomplish if you do not care who gets the credit.

Harry S. Truman