LLUCH Pediatric Orthotopic Heart Transplant Anesthesia Considerations

Background

- The International Society of Heart and Lung Transplantation (ISHLT) began a registry of pediatric heart transplant patients in 1982. Since then, >14,000 children have been registered and followed. Currently children account for 13% of total heart transplant recipients and have a higher mortality rate during the waiting period. Transplantation is considered when it offers a survival benefit over alternative management options; over 400 pediatric heart transplants are performed yearly in the US, with 12 pediatric heart transplants performed at LLUCH in 2018.

Indications

- Cardiomyopathies (CM)
  - Dilated- most common, accounts for 75% of transplantations for CM
  - Hypertrophic
  - Restrictive
- Congenital Heart Disease (CHD)
  - Primary therapeutic modality vs previously repaired/palliated CHD with poor ventricular function
  - Most commonly failed Fontan palliation, carries increased risk of bleeding—ensure good IV access!!
    - Underlying coagulopathies, redo sternotomies, aortopulmonary collaterals, need for PA reconstruction
- Re-transplantation (6-7%)

Contraindications

- Active malignancy, uncontrolled infection, multi-organ failure, psychosocial issues
- Irreversible pulmonary HTN (PVR >6 woods units)
- Severe organ dysfunction (cirrhosis, kidney failure, stroke, major neurodevelopmental disorder)

ABO-incompatible Heart Transplants

- Must be <15 months of age (necessitates an immature immune system) and have low/no isohemagglutinins levels
- Must receive only ABO-compatible blood products perioperatively (confirm with perfusionist and BB)
- At the outset of CPB, will receive two times blood volume exchange transfusion, which may be repeated depending on the level of isohemagglutinins (checked periodically)
  - Removed RBCs can be "washed" in the cell saver and retransfused

Pre-op Assessment

- Review available studies:
  - 12-lead ECG, echocardiography, cardiac MRI or CTA, CXR, right/left heart cath
- Inquire about recent deteriorations in cardiac or functional status
- Current level of cardiovascular support:
  - Oral medications, continuous inotrope infusion, mechanical assist devices
- Determine the presence/setting of any cardiac implantable electronic device (CIED)
  - Pacemaker or defibrillator
- Anatomical vascular pathology (thrombosed vessels, persistent left SVC, aberrant subclavian artery)
- Labs: T&C, CBC, Coags, CMP (renal and hepatic function may be affected by low CO or R heart failure)
- Anticoagulation/anti-platelet therapy and/or evidence of coagulopathy
- Allosensitization (present in nearly one third of pediatric OHT candidates):
  - Typically defined as having an elevated panel reactive antibody (PRA) >10%.
  - Treated with plasmapheresis, immunoadsorption, and complement inhibition (eculizamab)
  - Pre-op discussion regarding treatment plan
- NPO status (may need RSI)
- Need for pre-medication (typically beneficial)
- Past anesthetic records

Preoperative Preparation

- Standard pediatric cardiac setup (per rotation guide), NIRS sensors x 2
- Blood Products (discuss number of units with attending, order early, verify with the Blood Bank)
    - PRBCs (irradiated; washed if <10kg) and FFP: in room prior to sternotomy
    - Platelets and cryoprecipitate: release when rewarming
- Infusions: Epinephrine, Milrinone, Dopamine, Nitroglycerin
- Antifibrinolytics: Tranexamic Acid (dosing per rotation guide)
- Nitric Oxide: call LLUCH RT to set up
- Antibiotics: Ancef (unless contraindications or otherwise instructed)

Immunosuppression

- **Methylprednisolone** 10 mg/kg (max dose 500mg): unit dose and hand to perfusionist, will be administered with release of aortic cross clamp (dosing schedule in the transplant cardiologist's note)
- Any additional induction regimen to be requested by the transplant cardiologist and confirmed with the transplant surgeon during time out
    - **Thymoglobulin** typically started in 5800, but may be requested intra-op and given once stable after separating from CPB.
        - Pre-treat with IV diphenhydramine 1 mg/kg and Acetaminophen 12.5 mg/kg 30 min prior,
        - Must be given separately in a central line (consider infusing through CVP line) or peripherally (not recommended, requires concentration adjustment)
        - May cause cytokine release syndrome, serum sickness, and rarely anaphylaxis: slow/stop infusion if symptomatic (fevers/rigors/hypotension), discuss with transplant pharmacist

Induction (after confirmation of the donor organ)

- Potential full stomach/difficult airway
- Goal: Smooth induction of anesthesia and airway securement with minimal hemodynamic changes
- Continue pre-op inotropes (such as epinephrine and/or milrinone)
- Manage existing co-morbidities
    - Severely depressed cardiovascular function requiring ongoing inotropic and/or mechanical support
    - Pulmonary hypertension and RV dysfunction
    - Concurrent respiratory failure
    - Risk of malignant arrhythmias (history of VT, previous sternotomy—R2 pads required!)

Procedure Summary/Anesthetic management

- *Prior to sternotomy:*
    - Start antibiotics (consider starting vancomycin earlier, during line placement)
    - Confirm blood products are in the room and checked
- *Pre-CPB:*
    - Maintenance with high dose opioid for infants, inhaled halogenated anesthetics as tolerated for age >1 year
    - Provide analgesia and mitigate the stress response with opioids, ensure muscle relaxation
    - Continue and adjust inotropes/vasopressors as needed
    - Dissection: median sternotomy and pericardiotomy are performed
        - The dissection can be time consuming in patients with previous sternotomy/cardiac surgery and the urgency to finish the dissection and cannulate before the donor organ arrives is felt by both the surgical and the anesthesia teams
    - Once ascending aorta and bicaval venous cannulation are obtained, CPB is initiated and the aorta is cross clamped
- *On CPB:*
    - Cardiectomy: The recipient heart is removed, which usually includes much of the RA. Only the stumps of the SVC and IVC (bicaval technique, used if > 1 yo) and a single left atrial cuff containing all the pulmonary veins are preserved. Ideally, the recipient cardiectomy is completed just before arrival of the cardiac allograft to minimize the organ ischemic time (goal ≤4 hr). Any preexisting CIED leads will be cut and the distal tips removed with the heart. For patients <1 year old, a biatrial technique may be chosen, with the surgeons cooling these patient and using a single venous cannula.

    - The donor heart is placed in the chest and the left atrial anastomosis is performed first. This is typically followed by the anastomoses of the pulmonary artery and aorta. This will allow the reperfusion of the donor heart (after de-airing the LV and aorta) before finishing the rest of the anastomoses, therefore shortening ischemic time.
    - Methylprednisolone is given by the perfusionist after the aortic anastomosis is complete, just after release of aortic cross clamp and reperfusion (*must be documented in our anesthesia record!).*
    - The donor heart will start beating after the aortic cross clamp is released, but may require defibrillation. Epicardial pacing wires are placed if the need for pacing is anticipated.
    - The anastomosis of IVC and SVC are performed last (bicaval technique). This is slightly more time consuming than the standard ("biatrial") technique in which a part of the graft RA is excised in order to complete the anastomosis. "Bicaval" technique has been shown to result in lower RA pressure, less tricuspid regurgitation and higher likelihood of sinus rhythm in the graft heart
- *Weaning from bypass:*
    - Start **nitroglycerin** and **milrinone** with rewarming, release platelets and cryo.
    - Suction lungs and start to ventilate upon surgeon request, **start iNO**
    - Provide chronotropic support for the denervated heart in the form of inotropes (epinephrine, dopamine preferred for younger ages) and/or epicardial pacing.
        - The graft heart is denervated (no direct sympathetic, parasympathetic, or sensory innervation) and lacks swift heart rate responses to baroreceptor or volume status changes
    - The weaning may be prolonged due to ventricular dysfunction, most commonly RV failure
    - Zero the pressure transducers prior to separating from CPB
    - Draw frequent ABGs to track the degree of metabolic acidosis (may indicate hypoperfusion on CPB, graft dysfunction, low CO, or high dose vasoconstrictors)
- *Post-CPB and Hemostasis:*
    - Hemostasis is achieved with heparin reversal (protamine), targeted blood component transfusion, and surgical control. Continue to check ABGs frequently
    - During this period, surgical manipulation of the heart results in periodic hemodynamic fluctuations—temporize with pressors and keep the surgeons informed of these changes
    - Due to ischemia and reperfusion injury, the graft heart may have significant diastolic dysfunction and be very sensitive to preload, which should be monitored (by TEE and CVP) for optimal balance.
    - Thymoglobulin may be started at this time if hemodynamically stable (remember to pre-treat!!)
- *Chest closure:* There is a risk of RV compression during sternum approximation causing significant dysfunction and hemodynamic change. If this occurs, the chest may be left open.

Transfusion Goals Post-CPB

- Order irradiated blood, goal hematocrit should be discussed with the surgeon and perfusionist.
- Platelets and cryoprecipitate are transfused after the protamine administration
    - Platelet dysfunction (quantitative/qualitative) is the most common cause of non-surgical bleeding post-CPB.
    - Hyperfibrinolysis is also common despite routine anti-fibrinolytic use
- Check CBC, PT/INR, PTT, fibrinogen, TEG and/or BRISK to direct blood component therapy
- Factor VIIa is the *last resort* (full dose is 90mcg per kg), but remember to replace any platelet/factor deficiency *first*

ICU transport

- Prepare transport bucket with emergency medication/ equipment
- Complete interdisciplinary handoff sheet (perfusionist times, surgical portion)
- Notify LLUCH respiratory therapist to prepare iNO for transport
- Ensure adequate sedation if remaining intubated (most will):
    - Infants typically receive high dose fentanyl and do not require additional sedation, while those > 1 year old should be sedated with a dexmedetomidine (or low dose propofol) infusion during transport. Ensure ample fentanyl is available for administration during transport

References

1. Shure AY and Kussman BD. Pediatric heart transplantation: demographics, outcomes, and anesthetic implications. *Pediatric Anesthesia* 2011; **21**: 594-603.
2. Dipchand AI. Current state of pediatric cardiac transplantation. *Ann Cardiothorac Surg* 2018; **7**: 31-55.
3. Hsu DT and Lamour JM. Changing indications for pediatric heart transplantation. *Circulation* 2015; **131:** 91-99.
4. https://srtr.transplant.hrsa.gov/annual_reports/2017/Heart.aspx

Table 1 Heart failure staging in children. Modified from (25)

Stage	Interpretation	Clinical Examples
A	At risk of developing heart failure	Congenital heart defects Family history of cardiomyopathy Anthracycline exposure
B	Abnormal cardiac structure/function No symptoms of heart failure	Univentricular hearts Asymptomatic cardiomyopathy
C	Abnormal cardiac structure/function Past or present symptoms of heart failure	Repaired or unrepaired congenital heart disease Cardiomyopathies
D	Abnormal cardiac structure/function Continuous i.v. infusion of inotropes or PGE_1 Mechanical ventilatory and/or circulatory support	Same as stage C

Table 2 United Network for Organ Sharing allocation algorithm for pediatric medical urgency. Modified from (26)

Status 1A	I. At least one of the following devices/therapies Mechanical circulatory support Balloon pump Mechanical ventilation <6 months old, PGE, or pulmonary hypertension at >50% systemic pressures High-dose or multiple i.v. inotropes (Dobutamine or Dopamine >7.5 mcg·kg^{-1}·min^{-1}) Unresponsive, recurrent life-threatening arrhythmias (if all thoracic organ transplant center within the organ procurement organization agree) II. Heart status 1A Justification Form within 24 h of listing
Status 1B	At least one of the following Low-dose i.v. inotropes (Dobutamine or Dopamine <7 mcg·kg^{-1}·min^{-1}) <6 months old, not meeting criteria as Status 1A Falls of growth curve and exhibits poor systemic ventricular function, or has failed previous surgical intervention
Status 2	All other actively listed children

Table 3 Physiology of the transplanted heart. Modified from (54)

Elevated filling pressures
Low normal left ventricular ejection fraction
Restrictive physiology (stiff heart)
Increased afterload (hypertension)
Afferent denervation
Silent ischemia
Altered cardiac baro-and mechanoreceptors
Less stress-induced increase in systemic vascular resistance
Increased blood volume (decreased natriuresis and diuresis)
Efferent denervation
Resting tachycardia (loss of vagal tone)
Impaired chronotropic response to stress (dependent on circulating catecholamines)
Electrophysiology
Sinus node dysfunction in immediate postoperative period
Normal AV node conduction
Shift from β1 to β2 receptors
Altered response to medications
No heart rate response to atropine or glycopyrrolate
Decreased response to digitalis; possible severe bradycardia /cardiac arrest with neostigmine
Exacerbated response to Ca^{++}channel blockers, β-blockers, adenosine
Exacerbated response to direct acting sympathomimetic agents
Decreased response to indirect acting agents (dopamine, ephedrine)
Possible sympathetic reinnervation
Enhanced contractile response and exercise tolerance
Higher peak heart rates during exercise

Shure & Kussman *Pediatric Anesthesia* 2011