Anesthesia for Adult Heart Transplantation

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The following discussion focuses on the specifics of anesthetic management for heart transplantation in adults. Where not explicitly mentioned, room setup, equipment, drugs and anesthesia procedures are the same as for other cardiac cases and are covered elsewhere in this manual.

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General considerations

The important distinction in anesthetic management for cardiac transplantation is related to the unique characteristics of the recipients (including immunosuppression), and the physiology of the denervated heart (post-CPB).

Preoperatively, these patients have extremely poor intrinsic myocardial function. The unassisted physiology is usually that of a dilated cardiomyopathy, where myocardial function is critically dependent on relatively high heart rates, high preload, and reduced afterload. These patients have very low ejection fractions and are often dependent on inotropic infusions to maintain an adequate perfusion pressure. Some are maintained on anticoagulants such as warfarin to prevent intracardiac thrombus formation and embolization. Many patients will come to transplant after having had a left ventricular assist device (LVAD) placed. In general, patients with assist devices are in better physical condition and are easier to manage from a hemodynamic standpoint than transplant candidates without LVADs.
Coordination and timing are essential for the success of solid organ transplantation and every attempt should be made to adhere to the requested surgical time frame. On the other hand, delays in procurement, transportation and/or recipient preparation are quite common. Of course, the “redo” chest will take longer to open, and isolate the heart.

The recipients are admitted through the ICU or directly to the OR area. This “atypical admission route” means that certain preoperative interventions may be neglected or overlooked. The anesthesiologist should assist in making sure that the patient has been properly identified and consented and that they have received (or will receive) oral anti-rejection drugs and antibiotics according to local transplant protocols. Other routine preoperative studies and tests, if indicated, should not be neglected. Unless the patient is an inpatient, and has been kept NPO > 8 hours (rare situation!), all patients should be considered to have a “full stomach.” Some transplant recipients have been called in from home and thus may in fact have recently ingested a meal.

Pulmonary hypertension may be the limiting factor in the function of the donor heart. The right ventricle of the allograft is from a patient with normal pulmonary vascular resistance and will be prone to failure in the presence of a high fixed pulmonary vascular resistance. Irreversible pulmonary hypertension is also one of the two indications for a heterotopic heart transplant (most heart transplants are orthotopic), where the donor heart is grafted onto the recipient heart in parallel, in the right chest (the other indication being gross size mismatch between donor and recipient organ). Right ventricular failure after transplantation is a devastating complication, and every effort should be made to minimize the chances of it occurring. Once in place, it should be treated immediately (see section on pulmonary hypertension and right heart failure, below).

**Preoperative Checklist**

- Make sure the Heart Transplant Coordinator can reach you with information/changes regarding procedure times and patient information. The times agreed on usually include: OR arrival (of the recipient), skin incision, and arrival of the donor heart.
- Ensure surgical and anesthesia consents have been obtained.
- Review the History and Physical in the chart.
- Review the EKG and CXR.
- If available, check the most recent recipient echocardiogram and/or coronary angiography results.
- Check laboratory results (minimum labs: CBC, platelets, electrolyte panel, PT, PTT, type & screen).
- Add additional orders if necessary (e.g., ABG on an intubated patient).
- Order crossmatched PRBCs and make sure they are available prior to induction in the O.R., especially if a redo sternotomy will be performed. Important: Leukocyte-filtered and cytomegalovirus-matched blood products should be used to minimize recipient alloimmunization and CMV infection. CMV seronegative recipients should receive only CMV seronegative blood products, because there is evidence that CMV replication in the immunosuppressed recipient correlates with acute rejection and accelerated allograft vasculopathy [1-3]. If the donor heart is CMV positive, antivirals (e.g., ganciclovir) will likely be a part of the patient’s perioperative regimen and post-operative prophylaxis [4-5]. Check with the transplant team to see whether you need to administer any antivirals.
- Make sure that the antibiotics have been given. Check local protocol. Drugs in the protocol may include cefuroxime sodium (Zinacef) 1.5g IV or vancomycin 1g IV. Administer antibiotics slowly to prevent untoward reactions.
- Check applicable institutional protocols for initiation of immunosuppression. If called for, make sure cyclosporine PO has been administered preoperatively. Pre-operative azathioprine may also be part of the immunosuppression regimen.
- If the patient is not fasting, consider sodium biccitrate 30 ml PO. Metoclopramide and H2 blockers are not likely to be helpful, because there is too little time for the stomach to empty after the cyclosporine dose.
- Contact the electrophysiology service to deactivate ICD devices prior to operation, if indicated.
- If the patient is a VAD explant, the perfusion department should be contacted for assistance with the VAD(s). Typically, a perfusionist will help with patient transportation to the O.R. and will bring and install the VAD console. VAD batteries (if the VAD is electrically driven) should be charged before transportation, and additional batteries/supplies should be immediately available.
- If you are able to have a discussion with the recipient and/or his/her family, maintain donor anonymity.

**Anti-Fibrinolytics, Vitamin K, FFP**

- Consider the use of an antifibrinolytic (ω-aminocaproic acid – EACE,) for heart transplant operations. Elicit the surgeon’s preference as well.
- Vitamin K: 10 mg should be given IV, because the patient may have a tenuous nutritional status, may end up being NPO for days after the operation, and/or may arrive anticoagulated with warfarin. At some medical centers, vitamin K is infused IV throughout the case at 2 mg/hour [6].
- Patients on warfarin: order FFP. Administer only AFTER the final “go-ahead” has been received for transplantation.

**Line placement and hemodynamic monitoring**

- Aseptic technique is vital to prevent infections in the immunosuppressed patient. All lines should be inserted in an aseptic fashion, including aseptic prep and sterile gloves. In some institutions, if time allows and the patient has a pre-existing central line older than 1 day, it is removed and a fresh line is placed to reduce the chances of infection.
- Radial arterial catheters can be difficult to place in the heart failure patient with chronically low cardiac output, low systemic blood pressure, or recent radial a-line insertions where there may be a thrombus at the puncture site. In addition, patients who are being maintained on an axial (non-pulsatile) flow LVAD such as the DeBakey VAD® will often lack a radial pulse. If a radial a-line proves unusually difficult to place, most cardiac anesthesiologists and thoracic surgeons will elect to place a femoral a-line instead. Check with the surgical team if one groin is preferable to the other vis avis the potential for surgical cannulation of the femoral artery.
- At a minimum, all patients should have a central venous catheter placed and the CVP monitored. If possible, consider placing the central line in the left internal jugular vein in order to preserve the right internal jugular for future endomyocardial biopsies.

- Whether or not to use a pulmonary arterial catheter depends on the patient, local protocol and preference of the surgeon and anesthesiologist. The presence of preoperative diagnosis of pulmonary hypertension will be the primary indication for pulmonary arterial catheterization. In many institutions, the PAC will only be floated during completion of the graft anastomoses (with assistance by the surgeon). The rationale is that it can be time-consuming and difficult to float a PAC in the dilated recipient heart at the start of the case (when time is of the essence), and it may also be prudent to minimize the chance of triggering a malignant ventricular rhythm during catheter advancement.

**Pharmacological Agents**

- Many protocols call for a large dose of steroids to be given at some time during the operation (e.g. 0.5 - 1 gm methylprednisolone (Solu-Medrol) IV at the time of heparinization)
- If methylprednisolone is used, it needs to be reconstituted slowly, without shaking (to avoid foaming) and well before it is needed (to allow the foam to dissipate)
- Prepare isoproterenol, milrinone, vasopressin, NTG and norepinephrine drips
- Have available: dopamine, epinephrine and dobutamine drips
- Because of the poor cardiovascular reserve of these patients, it is advisable to have a dose of heparin drawn up in case the patient needs to “crash” on bypass (e.g., after induction, or sternotomy). A conventional dose will be 300 units/kg.
- The routine use of “renal dose” dopamine infusion (2-3 mcg/kg/min) for renal protection is ineffective based on current literature and cannot be recommended. Numerous studies and meta-analyses have failed to demonstrate any significant benefit [7-9].
- Nitric oxide may be needed post-CPB if there is significant pulmonary hypertension and/or right heart failure. An ICU ventilator may be needed (see below).
- Insulin may be required to maintain normoglycemia.

**Induction and maintenance**

- Nasal cannula oxygen is advisable throughout the preoperative period.
- Premedication should be light, especially in unassisted patients.
- Pre-existing maintenance drips should be continued until initiation of bypass, and titrated as necessary.
- For the redo chest, consider placing defibrillation pads prior to induction.
- The induction should be tailored to maintain hemodynamic stability while achieving rapid control of the airway. Cricoid pressure should follow preoxygenation. An agent or combination of agents that maintain CO and a reasonable SVR is recommended, e.g. etomidate followed by a slow titration of a narcotic (e.g. fentanyl, sufentanil). Some cardiac anesthesiologists will induce by titrating midazolam instead of etomidate.
- Muscle relaxation can be achieved with a cardiostable muscle relaxant such as rocuronium. Succinylcholine can also be used, unless otherwise contraindicated [10].
- When administering anesthetic and vasoactive medications, it is important to recognize that their pharmacologic effect may be dramatically delayed because of the slow circulation time.
- Hypotension may complicate induction in the patient dependent on high sympathetic tone and/or inotropic infusions. Maintain high preload, appropriate afterload and high heart rates in the pre-CPB period.
- Maintenance of anesthesia is frequently accomplished with a narcotic-based technique. A low-dose potent inhalational agent in 100% oxygen, benzodiazepine, or a combination of both should be titrated as tolerated to avoid awareness.
- A BIS monitor (Aspect Medical Systems, Norwood, MA) can be used. A discussion of the pros and cons of BIS-monitoring is outside the scope of this manual. Nevertheless, it should be noted that spurious BIS values during CPB have been reported [11].

**Transesophageal echocardiography**

The benefits of TEE monitoring during heart transplantation are multifold. TEE:

- may reveal the presence of mural thrombi in the dilated heart, which in turn should lead to minimal manipulation prior to CPB.
- can provide information about the extent and location of atherosclerosis in the ascending aorta and arch. This may be useful to the surgeon in determining the optimal site for cannulation. Epiaortic scanning is also beneficial in this respect.
- is helpful in deairing the allograft.
- can adequately assess left and right ventricular function and filling, and may provide early signs of right ventricular failure, before hemodynamic collapse has become manifest.
- is helpful in verifying normal function of VAD inflow and outflow conduits (see chapter on VADs, below). This may be useful should RV failure ensue and an RVAD become necessary as a rescue measure (rare but possible outcome, esp. in poorly matched donor hearts).

Before placing a TEE probe, it is advisable to pass an orogastric tube and suction the stomach. Air in the stomach can be particularly detrimental to the generation of good TEE images. The orogastric tube must be removed before attempting to insert the TEE probe.

**CPB during heart transplantation**

- During the period of CPB, the atria of the donor heart are sutured to the atrial cuff of the recipient. Then the aortic anastomosis is performed. A bubble-free irrigation of the left side of the donor heart is carried out during the aortic anastomosis to remove residual air. The aortic cross-clamp is released after completion of the aortic anastomosis, and the pulmonary arterial anastomosis is then completed.
- Upon completion of all anastomoses, check that the PAC is not caught in a suture (if floated) by gently pulling it back 2-3 cm. If resistance is met, do not apply force. Inform the surgeon.
Post-CPB

The post-CPB period is remarkable for the physiology of the denervated heart:

- There may be two P waves on the ECG tracing – one from the atrial cuff of the recipient, and one from the donor heart.
- Maintaining an adequate heart rate is vital. Traditionally this has been accomplished with direct-acting β-adrenergic agents, especially isoproterenol. In addition to its chronotropic effect, isoproterenol is a potent inotrope and pulmonary vasodilator. The use of temporary epicardial pacing is much more controllable and predictable, and will not produce undesirable tachycardia or ventricular irritability as is often seen with isoproterenol.
- Indirect sympathomimetics (ephedrine) will not have an effect on the denervated heart, nor will drugs that indirectly act on the parasympathetic nervous system (atropine, pancuronium). Drugs with mixed action will also not display their indirect effects, e.g. no tachycardia will be seen with norepinephrine, or bradycardia with neostigmine. There will be no response to vagal maneuvers and no carotid baroreceptor reflex mediated changes in heart rate.
- Many transplant recipients are maintained preoperatively on amiodarone and ACE inhibitors. These long acting medications often result in significant vasodilation in the post-CPB period. Where necessary, vasopressin is the preferred vasoconstrictor in this setting because it may not significantly increase pulmonary vascular resistance (as do alpha agonists).
- For right and/or left ventricular failure, milrinone – a potent inodilator – is a good choice.
- Protamine should be administered with the same caution as in any other CPB case. Remember that many of these patients have been exposed to protamine in the past.
- If the patient remains coagulopathic after an adequate protamine dose, consider the empiric administration of platelets, followed by FFP and cryoprecipitate as needed. The administration of these products can be guided by coagulation studies, but time is rarely sufficient to obtain results intraoperatively. Point-of-care testing may be invaluable in these circumstances. Since right ventricular failure from pulmonary hypertension is a common cause of post-transplant hemodynamic instability, it imperative to weigh the risk of increasing pulmonary vascular resistance with injudicious hemostatic transfusion versus life-threatening coagulopathic bleeding.
- There is anecdotal evidence of successful use of recombinant factor VIIa as a salvage therapy in refractory post-CPB bleeding [12]. The use of rFVIIa is FDA-approved only for patients with hemophilia A or B with inhibitors to Factor VIII or Factor IX, or for patients with congenital factor VII deficiency. Nevertheless, if all other treatment modalities fail to control bleeding and the situation is life-threatening, in the estimate of the anesthesiologist and surgeon it may be worthwhile to administer rFVIIa “off-label”.

Managing Pulmonary Hypertension and/or Right Heart Failure

If the transplant recipient develops severe pulmonary hypertension and/or right heart failure as evidenced by PAC readings and TEE, then several steps should be taken to treat this problem.
Hyperventilate the patient and optimize oxygenation

Avoid high intrathoracic pressures. In severe cases, the chest may be left open for 24 – 48 hours (albeit at an increased risk of infection)

Optimize RV preload guided by CVP and TEE.

Provide inotropic support to the right ventricle and optimize perfusion pressure (to avoid RV ischemia). First-line drugs in this respect are milrinone (0.25-0.5 mcg/kg/min) and vasopressin (3-6 units/hr). If necessary, epinephrine, dobutamine and norepinephrine may be added.

Administer a pulmonary vasodilator, ideally inhaled nitric oxide (see below), or inhaled epoprostenol [23]. Reports of the successful use of inhaled milrinone and inhaled nitrates are also in the literature. The transplant program and hospital should have a pre-existing plan for inhalational treatment of acute right ventricular dysfunction. This is not a good time to try something new.

Intravenous Prostaglandin E1 infusion (0.05-0.15 mcg/kg/min) is also effective in lowering pulmonary vascular resistance. Compared with NO, however, it is not selective for the pulmonary vasculature, and produces more systemic hypotension [13].

Ensure the patient is not hypothermic.

Deepen the anesthesia.

Magnesium sulfate (5-10 mmol) can also be given for its pulmonary vessel spasmolytic properties.

As a last resort, the surgeon may place an intra-aortic balloon pump (coronary perfusion pressure), or a right ventricular assist device.

Nitric Oxide Therapy

Nitric oxide is a potent and specific pulmonary vasodilator with minimal systemic effects [14-15]. It is a gas that is commonly delivered by a special delivery apparatus, the INOvent (GE Healthcare, formerly Datex-Ohmeda). The latter is attached to the proximal inspiratory limb of the anesthesia circuit or ICU ventilator, with a gas monitoring line attached approximately 6 inches proximal to the Y-piece in the inspiratory limb (via an extension). When used with an ICU ventilator, the INOvent has been shown to deliver the set dose of NO reliably over a wide range of ventilation modes [16]. With an anesthesia circuit, there is the potential for rebreathing. This setup has been studied and it is recommended to keep the fresh gas flow greater than or equal to minute ventilation in order to ensure accurate delivery of the desired NO dose [17]. Check with the surgeon or perfusionist as to the local NO delivery mode.

If nitric oxide therapy is necessary:

- Notify respiratory therapy (or whoever supplies the NO) prior to the termination of bypass to bring the nitric oxide machine (and ICU ventilator, if necessary) to the OR.
- If an ICU ventilator is to be used, prepare an intravenous anesthetic technique to replace the volatile.
- Connect the NO delivery system and ICU ventilator circuit to the patient’s endotracheal tube; leave end-tidal CO2 monitoring in place.
- Suggested dosing (or use local protocol): Start the nitric oxide at 80 ppm (parts per million) and wean by 20 ppm each 10 minutes until a dose of 20 ppm. Leave at 20 ppm.
A Note on Rejection

Hyperacute rejection is a rare but devastating complication in the immediate post-transplantation period [18-19]. It is mediated by pre-existing recipient cytotoxic antibodies against donor antigens, e.g. in the ABO system. If hyperacute rejection occurs, the allograft becomes cyanotic from microvascular thrombosis and ceases to function. The situation can lead to intraoperative death unless the patient can be supported with a VAD until a new donor heart can be found. Acute rejection is a constant threat during the first 6 months after heart transplantation. It frequently presents with low CO, arrhythmias and other derangements of heart function. Serial endomyocardial biopsies are used to detect its presence. Due to the time frame of presentation and the lesser degree of hemodynamic impairment, it is unlikely that the anesthesiologist will be involved in its management in the intraoperative period.

References