ABSTRACT: Heart transplantation has emerged as the definitive therapy for patients with end-stage cardiomyopathy. The two most common forms of cardiac disease that lead to transplantation are ischemic cardiomyopathy and dilated cardiomyopathy, which together comprise approximately 90% of cases. The other less common forms of heart disease include viral cardiomyopathy, infiltrative cardiomyopathy, postpartum cardiomyopathy, valvular heart disease and congenital heart disease.

KEYWORDS: Anesthetic management; Cardiomyopathy; Cardiopulmonary bypass; Heart failure; Heart transplantation; Pulmonary artery hypertension;

INTRODUCTION: Heart transplantation has emerged as the definitive therapy for patients with end-stage cardiomyopathy. The two most common forms of cardiac disease that lead to transplantation are ischemic cardiomyopathy and dilated cardiomyopathy, which together comprise approximately 90% of cases. The other less common forms of heart disease include viral cardiomyopathy, infiltrative cardiomyopathy, postpartum cardiomyopathy, valvular heart disease and congenital heart disease.

The introduction of cyclosporine in 1981 and monoclonal antibody okT3 in 1983 for heart transplant patients greatly accelerated the progress of organ transplantation.¹ The peak period of heart transplantation was mid-1980s. The pace slowed down due to the limitations in the availability of donor organs. We have performed five heart transplant surgeries at Rajiv Gandhi Government General Hospital, Chennai, India during 2009 to 2011.

The corresponding author was a member of the team during three cardiac transplant surgeries while the co-author was a member during all the five transplant surgeries. This article is intended to share our experiences and anesthetic challenges during cardiac transplantations.

INDICATIONS FOR HEART TRANSPLANTATION:
1. New York Heart Association class III-IV symptoms despite maximal therapy
2. End-stage heart disease refractory to medical or surgical therapy
3. Age below 60 years
4. Prognosis for 1 year survival <75%
5. No other significant medical problems that might independently deter survival
6. Patient characteristics – mentally stable, motivated, compliant and with supportive family.

CONTRAINDICATIONS FOR HEART TRANSPLANTATION:
1. Age >65 years.
2. Fixed pulmonary vascular resistance > 6 wood units.
3. Brittle diabetes with end organ damage.
4. Active infection.
5. Major debilitating co-morbid disease.
6. Active or recent malignancy (< 2 years).
7. HIV seroconversion.
8. Morbid obesity (BMI > 35).
9. History of severe mental illness or psychosocial instability.
10. Evidence of active tobacco, alcohol or drug abuse.

RECIPIENT SELECTION: Heart transplant recipient selection is based on an extensive multidisciplinary evaluation intended to assess the patient’s disability and prognosis without transplantation and their ability to survive the procedure and comply with the required postoperative management. The patients are evaluated for significant pulmonary disease (including severe, irreversible pulmonary hypertension which is considered a contraindication to heart transplantation), renal dysfunction, hepatic dysfunction and active infectious disease before being listed for transplantation.

Cardiac conditions amenable to other surgical procedures, such as valve repair and comorbid conditions that would exclude long term survival after transplantation, should not be present. Appropriate sized heart and ABO type donor organ matching should be done. The heart transplant candidate is maintained on near maximal regimens of conventional (diuretics, beta blockers, calcium channel blockers, nitrates, angiotensin converting enzyme (ACE) inhibitors, inotropes and vasodilators) and second line therapies such as phosphodiesterase inhibitors and heart – assist devices for chronic congestive failure.\(^2,3\)

The patient population currently eligible for surgical management consists of those patients with end stage heart disease (NYHA functional class IV), a predicted life expectancy of less than six to twelve months and an ejection fraction less than 20% on maximal medical therapy.\(^4\)

DONOR SELECTION: Candidates who donate their hearts for transplantation must fulfill the criteria for brain death. Age less than 55 years is usually preferred but older hearts are also occasionally used because of the shortage of donor hearts. In older donors, assessment with echocardiography or angiography can be helpful. Donors should not have any serious cardiac disease or refractory ventricular arrhythmias. They should not have evidence of an active infectious process or malignancy and should not have had a prolonged cardiac arrest or required resuscitation. The final decision to accept a heart for transplantation is made at the time of harvesting after direct examination for previous myocardial infarction, trauma and coronary calcifications.

CONCERN OF THE ANAESTHESIOLOGISTS: The goal of the clinical anesthesiologist in preoperative care is to maintain the balance of pharmacologic and medical therapy in an attempt to support the patient’s status until surgery.\(^4\) Heart transplantation remains a challenge for the cardiac anesthetist as it requires a sophisticated monitoring and management of circulation, ventilation and homeostasis. It is important to remember metabolic acidosis, hyperkalemia and hypocalcemia as the most common acid-base and electrolyte disorders seen in low cardiac output status.\(^5\)

The patient with end-stage heart disease for heart transplantation presents formidable anesthetic challenges. The pathophysiology is one of severe cardiomyopathy marked by varying degrees of both systolic and diastolic dysfunction. The former is reflected by reduced stroke volumes and elevated end-diastolic volumes and the latter by chronically elevated diastolic filling pressures.
To this is added the well-recognized sequelae of heart failure like increased salt and water retention secondary to increased rennin and aldosterone production, impaired visceral, splanchnic and renal perfusion and increased catecholamine levels, which in time produce significant down regulation of beta receptors and diminished myocardial catecholamine stores.

**PREOPERATIVE MANAGEMENT:** The timing of heart transplant is determined by donor availability and hence occurs on an emergency basis at all hours. The anesthesiologist is left with little time for detailed pre-anesthetic evaluation. An examination focusing on current symptoms, level of activity, medications, prior surgical and anesthetic history, last oral intake and review of organ systems involved is performed. A complete physical and airway evaluation along with a complete review of blood tests, radiologic and echocardiographic studies is also essential. These patients range from completely ambulatory out patients to critically ill patients on multiple infusions, intra-aortic balloon counterpulsation and ventricular assist devices. Using a fresh sterile breathing circuit is recommended as is the use of a bacterial filter in the circle system.

There should be a close communication between the team harvesting the donor heart and the team preparing the recipient. To minimize the ischemic time, the recipient will be on cardiopulmonary bypass, with the recipient heart resected when the donor heart arrives. However, induction of anesthesia and making the incision in the recipient should not occur until the harvesting team has actually examined the donor heart to be certain it is suitable. Factors to be considered in timing the recipient operation include the distance and time it will take to transport the donor heart to the recipient and the time it will take to prepare the recipient (eg; whether the patient has had previous heart surgery and will take more time to open).

Induction of anesthesia and insertion of monitoring lines must be performed rapidly, which however can be a problem who often has experienced multiple previous punctures of arteries and central veins. The transplant recipient usually arrives into the anesthesia induction room before the organ is finally accepted. A large bore intravenous access (typically more than one) and an arterial catheter are inserted. The placement of an arterial catheter can be difficult in patients with an axial flow left ventricular assist device as no arterial pulse can be palpated.

Imaging of the radial artery by ultrasound devices and image guided puncture of the radial artery is helpful in this regard. Induction of anesthesia normally starts just with the final acceptance of the donor organ. A rapid-sequence induction with high dose of opioids is recommended as patients are in a stressful situation and sometimes with full stomach. Preoperative use of agents such as metoclopramide to promote gastric emptying and drugs to raise gastric pH like 30 ml of 0.3 molar concentration of non-particulate sodium citrate solution should be considered. If the hemodynamic status is marginal or tenuous, initiating or increasing inotropic support before induction should be considered.

The induction sequence is of critical Importance as these patients are highly dependent on endogenous sympathetic drive and the combination of anesthetic agents, which ablates the latter combined with drug induced reductions in heart rate, inotropic function, and preload can produce sudden cardiovascular collapse. Regardless of the agents used for the induction of anesthesia, care must be taken at all times to minimize the effects of negative inotropes, maintain heart rate and intravascular volume and avoid reductions in systemic vascular resistance (SVR). Opioids are the mainstay of induction: Fentanyl 10 to 15 µg/kg (upto 60 - 75µg/kg) is used depending upon the...
recipient’s hepatic and renal function. Amnesia is usually accomplished using titrable doses of Midazolam in the moribund patient. Maintenance of anesthesia is achieved with further continuous intravenous administration of opioids and Propofol or volatile anesthetics.

After induction, a triple lumen central venous catheter and an introducer set with a pulmonary artery catheter are placed in the right or left internal jugular vein. We preferred to use the left internal jugular vein leaving the right side free for future access to perform endocardial biopsies. We also preferred to place the arterial cannula and pulmonary artery cannula before induction itself so that a complete hemodynamic assessment can be made before and during induction of anesthesia.

A long sterile sheath should be placed over the pulmonary artery catheter to allow its withdrawal from the heart before SVC cannulation for CPB. Placement of these access lines before the final approval of the organ should be avoided if possible to save the vessels in case the donor heart is not acceptable for transplantation.

Transoesophageal echocardiography is routinely employed and is invaluable in assessing the ventricular function, contractility, volume status and the detection of intracardiac thrombi in the pre-bypass period. Manipulation of the heart in the pre-pump phase is minimized to avoid possible embolism of intracardiac thrombus if present. Before initiation of CPB, the pulmonary artery catheter should be shortly placed into the pulmonary artery to measure the actual pulmonary artery pressures (PAP) and cardiac output.

The calculation of the pulmonary artery vascular resistance (PAVR) follows the equation:

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\text{PAVR} = \left[ 80 \times (\text{mean pulmonary artery pressure} - \text{pulmonary capillary wedge pressure}) / \text{cardiac output} \right] \text{ Normal value is 100 dynes cm}^{-5}\]

Under hyperoxygenation and deep anesthesia the Transpulmonary gradient (TPG) is calculated by TPG = Mean Pulmonary artery pressure - Pulmonary capillary wedge pressure. Normal value is approximately 6 mm Hg. After measuring, before cannulation for CPB, the catheter should be removed into the upper venacava. Patients with an increased systolic PAP of >60 mm Hg and/or a PAVR >200 dynes cm\(^{-5}\) and/or a TPG of >15 mm Hg are considered to be of high risk to develop early perioperative right ventricular failure.9

Following cannulation of the venacavae and aorta, CPB is instituted and the diseased heart is excised leaving an atrial cuff containing the cavae, pulmonary veins and remnants of the pulmonary artery and aorta. On CPB, patients are cooled as for other conventional cardiac procedures. The four major anastomoses of the procedure are the left and right atrial anastomoses and the end to end aortic and pulmonary anastomoses. Prior to cross clamp release, Methyl Prednisolone 1 gm is routinely administered.

Following removal of the cross clamp, some electromechanical activity usually ensues. Rewarming is completed in the usual fashion and the weaning process is begun. Shortly before weaning from CPB, Transoesophageal echocardiography probe should be inserted to evaluate RV and LV function during and after weaning from CPB. It is of practical importance that during this period and the following weaning period, the patient is deeply anaesthetized as pain and awakening can result in excessive increase of the PAP and RV afterload. The examination should focus on the RV function as well as ejection fraction and diastolic function.

Inotropic therapy should be initiated with Isoproterenol in doses ranging from 0.005 to 0.05 µg/kg/min to ensure adequate heart rate and contractility. A combination of beta adrenergic agents such as Dobutamine (3 to 8 µg/kg/min) or Epinephrine (0.05 to 0.4 µg/kg/min) can also be used
according to the requirement. The beta adrenergic drug therapy should be combined with a Phosphodiesterase-3 inhibitor such as Milrinone (bolus of 50µg/kg over 10 minutes and continuous infusion of 0.5 – 0.75µg/kg/min). Both classes of agents improve contractility by increasing intra cellular levels of cyclic adenylylate monophosphate (cAMP).  

Some patients may need temporary epicardial pacing to wean from bypass and into the immediate post-operative period. The heart rate may be elevated by pacing to a frequency of approximately 110 – 120 beats per minute in order to increase RV output and “overpace” possible arrhythmias. If further arrhythmias are observed, cautious treatment with Amiodarone (150-300mg) over 10- 20 minutes should be initiated. Ventilation should be started with an inspired oxygen concentration of 100%, small inspiratory tidal volumes (6ml/kg) and a moderate positive end expiratory pressure (PEEP) of 5-6cm H2O. The intention is to prevent mechanical compression of the pulmonary capillary blood flow and increase PAVR, since RV failure or dysfunction is the most common etiology of failure to wean from CPB.  

Moderate hyper ventilation, high oxygenation and moderate alkalosis are basic strategies to reduce PAP and basic conditions before starting the weaning process from CPB and for the further course of the operation. Preemptive ventilation with inhaled Nitric oxide (NO) (20-40ppm) or inhalation of aerosolized prostaglandins (20-30µg Iloprost/15 minutes, repeated after 4 hours) before complete termination of CPB should be initiated for patients with an increased TPG. Both drugs have been shown to be effective means to reduce PAP in heart transplantation. The inhalation of these agents appears to be superior to a systemic administration of prostaglandins or other pulmonary vasodilators as the pulmonary artery bed is widened more selectively and systemic vasodilation and consequent systemic hypotension can be prevented.  

The newly transplanted heart needs appropriate filling pressures, being completely preload dependent. However high central venous pressures and right ventricular overdistension should be avoided. After 10 to 15 minutes of inhalation and optimization of ionotropic support, cautious separation from CPB can be completed. The remainder of the post bypass management is similar to other cardiac procedures: maintenance of adequate hemodynamics, reversal of heparinisation, administration of blood products as indicated and preparation for transfer to the intensive care unit. When cardiac failure after heart transplantation is severe and refractory to medical intervention, mechanical assist devices may be needed.  

Although it is usually believed to be a left heart assist device, intra – aortic balloon counterpulsation may be helpful in acute right heart failure by improving perfusion to the right ventricle and may provide the support needed until the donor heart function improves. In cases with extremely poor ventricular function after transplantation, right, left or biventricular assist devices may be needed to support the circulation depending on which ventricle is failing.  

Coagulopathy remains an ever present concern, especially in the redo patient. Aprotinin in the conventional high – dose regimen is frequently used and has been found to significantly reduce the quantity of blood products transfused. At present the standard of care is the use of epsilon amino caproic acid or Tranexamic acid, which is potent antifibrinolytics instead of Aprotinin, with the use of Factor 7a for emergency salvage in the case of uncontrolled bleeding. Administration of an antifibrinolytic agent during CPB, such as Tranexamic acid (10mg/kg bolus, 500 mg in the CPB prime, continuous infusion of 1 mg/kg/hour until chest closure), to attenuate hemostatic activation and perioperative blood loss is
The patient should be rewarmed to 36 – 37 degree centigrade before weaning from CPB and all infusions and transfusions should be given via fluid warming systems since a physiological body temperature is a pre-requisite to establish sufficient coagulation after CPB.

In patients with a higher risk of excessive hemorrhage, the hemoglobin level should be elevated to 12 to 14 gm/dl before weaning from CPB.

Even if hemodynamics are acceptable with open chest, the closure of the chest and compression of the swollen heart by the lungs or small intrapericardial cavity sometimes has a tamponade like effect and might impair particularly right heart function. Therefore, chest closure has to be done cautiously.

**POSTOPERATIVE:** Postoperative management of the cardiac transplant recipient combines the concerns both of the post –pump as well as the transplant status. Meticulous attention is paid to the maintenance of adequate oxygenation and ventilation, intravascular volume, pulmonary and systemic pressures, normothermia and coagulation. Appropriate anti-rejection and immunosuppressive regimens are instituted (typically Prednisolone, Tacrolimus, Azathioprine and Cyclosporine combinations). Once the patient has achieved stable hemodynamics and there is no significant bleeding, consideration can be given to decreasing sedation and weaning ventilator support. Most patients are maintained on ionotrophic and chronotropic support for 36 – 75 hours.

Exstubation is typically achieved when hemodynamics is stable and bleeding is no longer a risk. Ionotrophic support is withdrawn gradually and invasive monitoring is removed; chest tubes are usually taken out after 24 hours. The uncomplicated patient is usually discharged from the ICU within 72 hours. Postoperative care in the hospital involves continuation of anti – rejection therapy and careful observation for signs of acute rejection, which is best diagnosed by endocardial biopsy and treated by increasing immunosuppression until the rejection subsides. Biopsies are routinely performed every 1 or 2 weeks for the first few months after transplantation.

Complications in the early postoperative period include hyperacute and acute rejection, pulmonary and systemic hypertension, cardiac arrhythmias, respiratory failure, renal failure and infection in the immunocompromised patient. Opportunistic infections become a more likely problem because of chronic suppression of the immune system.

Allograft coronary artery disease is the major limiting factor for the long term outcome. Factors that predispose to this include older donor age, male sex, hypertension in the donor, hypertension in the recipient, immunosuppression and CMV infection. Panvasculopathy occurs as an insidious process. It is usually diffuse and involves the vessel circumferentially.

Overall survival has improved over the past 40 years climbing from a five year survival rate of 70% in the early 1990’s to 77% in 2004. Post-transplant renal dysfunction is common and is primarily the result of cyclosporine nephrotoxicity. Hypertension is common, occurring in approximately two – thirds of all cardiac transplant recipients, attributed to the use of cyclosporine and corticosteroids – both mainstays of immunosuppression is associated with an increased incidence of malignant neoplastic disease.

**CONCLUSION:** Although being a standard surgical procedure since decades, heart transplantation remains a challenge for the cardiac anesthetist as it requires sophisticated monitoring and management of circulation, ventilation and homeostasis. The challenge is mainly because the donor
heart often cannot easily adapt to the increased PAP and PVR of the recipient after prolonged ischemia and reperfusion injury. The anesthetic challenge involved in the perioperative management of these complex patients must be well understood.

Limitations in the availability of donor organs have served to slow the pace of heart transplantation surgeries.

REFERENCES:

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