

Post-cardiac transplant recipient: Implications for anaesthesia

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ABSTRACT

The annual heart transplant rate is gradually increasing worldwide. A proportion of this patient population present for an elective or emergency surgery which may or may not be related to the transplanted heart. A MEDLINE search for heart transplant, anaesthesia, adult, paediatric and surgery was conducted to review anaesthetic management for heart transplant recipients. Anaesthesia and perioperative management are different in these cases. A thorough understanding of the physiology of denervated heart, post-transplant morbidities and pharmacology of immunosuppressants is essential for best perioperative management and improved post-operative outcome.

Key words: Adult, anaesthesia, heart transplant recipient, paediatric, surgery

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/ija.IJA_390_17

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INTRODUCTION

According to international registry of heart–lung transplant, the annual cardiac transplant rate worldwide varies between 5000 and 10,000 and this number is expected to increase.^[1] These patients may require anaesthesia for elective or emergency surgery in hospitals where specialised anaesthesiologists may not be available. Therefore, the anaesthesia team must be aware of the physiological effect of denervation, the unique anaesthetic implications of a transplanted heart, potential patient risks such as rejection and infection as well as the effect of immunosuppressants. This review elaborates the anaesthetic management of a post-heart transplant patient who can present for various surgeries. A Medline search for heart transplant, anaesthesia, adult, paediatric and surgery was conducted and 38 relevant literatures are added to this review.

CONDITIONS FOR WHICH A POST-HEART TRANSPLANT PATIENT MAY REQUIRE ANAESTHESIA AND SURGERY

The heart transplant recipient may require surgery for procedures related to the transplant or to

non-transplant-associated conditions [Table 1]. The need for surgery for different problems has been documented from 2 h to >10 years post-transplant. The incidence of significant general surgical complications developing within the 30-day post-transplant period has been reported between 4.8% and 7%.^[2]

PHYSIOLOGY OF THE TRANSPLANTED HEART

Heart transplant involves the removal of the diseased heart, in which the aorta and main pulmonary arteries (PA) are transected, the cardiac plexus is interrupted, and the heart is partially denervated. The atria of recipients remain innervated, but conduction does not occur across the atrial suture line. In spite of the fact that the transplanted heart is a denervated organ, the intrinsic cardiac mechanisms are preserved. The heart is extremely sensitive to

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How to cite this article: Choudhury M. Post-cardiac transplant recipient: Implications for anaesthesia. Indian J Anaesth 2017;61:768-74.

Table 1: Conditions for which a post-heart transplant patient may require anaesthesia and/or surgery

Heart transplant-related conditions	Non-heart transplant-related conditions
Complications of diagnostic procedures (e.g., endomyocardial biopsy leading to right ventricular perforation, pneumothorax and haemothorax)	Aortic aneurysm repair; continuing atheromatous disease
Complications of transplant surgery itself (bleeding and allograft vasculopathy)	Laparoscopy
Complications related to immunosuppressive therapy (malignancy, cholelithiasis, etc.)	Pregnancy and labour
Systemic thromboembolism	Fracture and dislocation Other organ dysfunction or transplant

changes in loading conditions, and the Frank-Starling pressure volume relationship becomes paramount in adjusting contractility. It is commonly said to be 'preload dependent' as cardiac output (CO) depends on the venous return. In comparison to normal, the transplanted heart has a higher resting heart rate (HR) (90–110 beats/min), similar maximum HR, higher minimum HR and reduced HR variability in a 24 h Holter monitoring study.^[3] This is due to the absence of parasympathetic innervation. Most of the transplanted heart recipients have normal sinus rhythm with an increased refractory period of the sinus node; thus, many have first-degree heart block and a higher rate of pacemaker implantation. The possible reasons of heart block include biatrial anastomosis, organ rejection, nodal ischaemia and inadequate myocardial preservation.

Clinically, significant atrial and ventricular arrhythmias are infrequent although ectopic beats are common. Presence of fatal ventricular arrhythmias usually indicates severe acute rejection or allograft coronary artery disease.^[2] The resting electrocardiogram (ECG) is usually altered showing two *P* waves; one is from recipients' own sino-atrial (SA) node and other is from donor's SA node. Tachycardia in response to physiological stress, for example, pain and hypovolaemia is blunted as it depends on circulating catecholamines. Carotid sinus massage and Valsalva manoeuvre have no effect on HR.^[4] These patients are at higher risk of developing atrial flutter or fibrillation a few years later. This is because of the onset of some degree of reinnervation. Complete neuronal control has been described 15 years after transplantation. This explains the frequent complaint

of angina, vasovagal episodes and cardiac arrest after neostigmine administration in these patients.^[5] Coronary autoregulation remains intact. Immediately after transplant, left ventricular dysfunction is due to anoxic injury during graft transfer, acute withdrawal of sympathetic support or after load mismatch. There is a rapid improvement of ventricular function, and CO becomes normal within few days. The PA pressure and pulmonary capillary wedge pressure remain elevated during the 1st-month after transplant and become stable by 1 year. The systemic vascular resistance is frequently elevated; however, a 15% increase in blood volume following transplant may explain the high normal CO through the Frank-Starling mechanism of increasing preload in the setting of cardiac denervation.^[2] There is well-preserved systolic function and mild diastolic dysfunction. Mild-to-moderate mitral and tricuspid valve regurgitation may be present. The myocardial function is subnormal during stress and exercise with a low peak HR, low peak CO and maximum oxygen uptake. This is expected to result from lack of efferent cardiac innervations, either due to HR change alone or together with a submaximal inotropic response.^[6]

PERIOPERATIVE CONSIDERATIONS

This can be discussed in the following headings:

Immunosuppressants and their interaction with commonly used drugs in the perioperative period

The commonly used immunosuppressive agents are cyclosporine A, azathioprine, antilymphocyte globulin, monoclonal antibodies and corticosteroids. Recently, tacrolimus and mycophenolate have replaced cyclosporine and azathioprine, respectively, in some immunosuppression protocols.^[7] The blood level of both cyclosporine and tacrolimus must be kept within the indicated therapeutic range to get the desired effect. The perioperative fluctuation of the plasma level of these two drugs should be strictly monitored as there is a significant reduction of blood level by dilution with volume infusion or cardiopulmonary bypass.^[8] Both these drugs are metabolised by cytochrome P-450 system of liver, and therefore many of the drugs administered perioperatively can affect their plasma levels^[9,10] [Table 2]. Data on cyclosporine A and tacrolimus interaction with major anaesthetic agents are lacking. Fever, anaemia, leucopenia, thrombocytopenia, hypertension, diabetes, renal dysfunction, neurotoxicity, osteoporosis leading to high rate of fractures and anaphylaxis are some major side effects of immunosuppressants which

Table 2: Drugs that interact with cyclosporine A and tacrolimus

Drug class	Drug	Effect on blood level	Intervention ^[7-12]
BZP	Diazepam, midazolam, alprazolam, flurazepam and clonazepam	↑ BZP	Consider for BZP dose alteration
Antibiotics	Erythromycin, clarithromycin Co-trimoxazole, metronidazole, norfloxacin, levofloxacin	↑ cA and T level	Consider substitute (azithromycin) Monitor cA and T concentration and adjust the dose
Antimycobacterial	Rifampin	↓ cA and T level	Monitor cA and T concentration
Antimalarial	Chloroquine, mefloquine	↑ cA and T level QTc prolongation in patients with T therapy	Monitor cA and T concentration as well as QTc interval
Antifungal	Ketoconazole, fluconazole, itraconazole and voriconazole	↑ cA and T level QTc prolongation in patients (fluconazole or voriconazole therapy)	Decrease the dose of antifungals by 40%
Anti-retroviral	Ritonavir, atazanavir, darunavir, cobicistat, delavirdine	↑ cA and T level	Monitor cA and T concentration Consultation with retroviral therapist is mandatory
Cardiovascular drugs (antiarrhythmics and CCBs)	Amiodarone, lidocaine, quinidine, verapamil, diltiazem, amlodipine, felodipine	↑ cA and T level QTc prolongation by amiodarone and quinidine	Monitor cA and T concentration Avoid QTc prolonging agent Avoid simvastatin
Statins	Simvastatin, atorvastatin, lovastatin, pravastatin	↑ statin concentration	Avoid using maximum dose of other statins
Anticoagulants	Apixaban, dabigatran, rivaroxaban	↑ anticoagulant concentration	Monitor for signs of excessive anticoagulation Avoid these anticoagulants in patients receiving cA and T with renal insufficiency
Hypoglycemic	Both sulfonylureas and biguanides	↑ cA level	
GI	Metoclopramide, omeprazole, lansoprazole, octreotide	↑ cA and T level Octreotide with T leads to QTc prolongation	Monitor QTc interval
Hormones	Estrogen and testosterone preparation	↑ cA and T level	
Antipsychotics	Haloperidol, desipramine, fluoxetine, trazadone	↑ cA and T level	↑ pimozone level
Others	Bosentan Carbamazepine	↓ cA and T level	Avoid pimozone if QTc prolongation is present

BZP – Benzodiazepines; cA – Cyclosporine A; T – Tacrolimus; QTc – Corrected QT; CCBs – Calcium channel blocker; GI – Gastrointestinal

have some impact on perioperative management and choice of anaesthetic agents. Withdrawal of azathioprine in patients taking warfarin may precipitate bleeding.^[11] Although the exact mechanism is not known, it is assumed that 6-mercaptopurine, a metabolite of azathioprine, induces hepatic microenzymes that metabolise warfarin. Azathioprine and allopurinol combination can lead to serious adverse effects (severe bone marrow suppression, pancreatitis and hepatotoxicity) that can be reduced with close monitoring of metabolites and blood levels.^[12] Prednisone has a similar side effect profile like tacrolimus. However, its action is different because it has anti-inflammatory actions on organ systems. Mycophenolate mofetil has similar efficacy and side effects as azathioprine with the added advantage of lower incidence of fungal infection.^[13] A better understanding of pharmacokinetic changes with age now allows a reduction of dose of immunosuppressants in old age while maintaining the therapeutic level.^[14]

Table 3 describes the effect of various anaesthetic agents on immunosuppressants and vice versa.

Knowledge regarding post-transplant complications and their implications in anaesthetic practice

Apart from the burden of old age and co-morbidities, post-transplant patients have a high incidence of the following problems which need to be identified and managed perioperatively.

- Infection: A high incidence of post-operative wound infection is observed in patients receiving tacrolimus. Strict aseptic techniques during handling of such patients, minimum use of indwelling catheters and earliest removal of invasive lines are mandatory. Fungal infection may need prolonged treatment. The patients should receive cytomegalovirus (CMV) negative blood transfusion. Microbiology advice should be strongly sought for prevention as well as strict control of infection. Any infection should

Table 3: Effect of anaesthetic agents on various chemotherapeutic agents in heart transplant patients and vice versa

Anaesthetic agent	Resultant effect with immunosuppressants
Inhalational agents	
Isoflurane	The clearance of oral cA decrease with isoflurane anaesthesia and a steady state level maintained with IV cA ^[15,16] Most of the inhalational anaesthetic agents are well tolerated unless there is significant heart failure
Thiopentone	Nil
Midazolam	↑ Blood level of BZP. Needed dose modification ^[9,10]
Propofol	Nil ^[17]
Etomidate	Nil
Opioids	
Muscle relaxants	Most of the muscle relaxants can be used safely. Atracurium and cisatracurium are the preferred agents because their elimination is not affected by renal or hepatic function ^[17]
Neostigmine	Neostigmine usually has no effect on transplanted heart. Special concern should be taken when reinnervation is anticipated (>1-year post-transplant) because there is evidence of bradycardia and cardiac arrest with neostigmine despite the concurrent use of an antimuscarinic agent ^[18]
Opioids	Cyclosporine increases the analgesic effect produced by fentanyl
Local anaesthetics	Bupivacaine can be safely used through regional routes without any side effects

BZP – Benzodiazepines; cA – Cyclosporine A; IV – Intravenous

be treated preoperatively. It is important to realise that immunocompromised patients may not present with typical signs and symptoms of infection i.e., fever and leucocytosis. A high index of suspicion is essential and microbiological tests can rule out the diagnosis^[19,20]

- b. Rejection: Allograft rejection may occur at any time during the post-transplant period, especially with discontinuation of immunosuppressants. Unexplained weight gain, fever, dyspnoea and peripheral oedema are the usual features of rejection. Urgent endocardial biopsy is needed to confirm the diagnosis;^[21] however, a negative biopsy does not exclude rejection. The episodes of acute rejection necessitate, emergency management with increased immunosuppression, for example, intravenous (IV) immunoglobulin and plasmapheresis. At times, the patient may need mechanical circulatory support. The presence of any degree of rejection should be ruled out

and managed preoperatively, as post-operative morbidity rate is high if it remains untreated before surgery^[22]

- c. Allograft vasculopathy: Cardiac allograft vasculopathy is the atherosclerotic obstructive disease of coronary vessels. It may result from a variety of causes, for example, immune-mediated vascular injury, ischaemic endocardial injury before transplant, immunosuppressive agents, CMV infection, hyperlipidaemia, smoking and hypertension. It occurs within 1st year of transplantation in 10%–20% of patients and in nearly 50% cases within 5 years^[2,23,24]
Even in angiographically normal coronary arteries, luminal narrowing may develop insidiously. The lack of afferent innervations renders episodes of myocardial ischaemia silent in these patients. Intravascular ultrasound is the most sensitive technique to detect early changes. Angioplasty is used for focal proximal lesions. At times, disease is wide spread, and distal revascularisation by any means is impossible
- d. Miscellaneous: Apart from the above said specific problems, post-transplant patients may also suffer from diabetes, epilepsy, hypertension (50% patients with cyclosporine A therapy), cholelithiasis and pancreatitis.^[25-28]
Because haemodynamic changes during stress and exercise are dependent on circulating catecholamines, beta blockers are best avoided in these patients for treatment of hypertension.^[29]

Pre-operative assessment and premedication

The transplant team as well as the attending anaesthesiologist and surgeon should have a good coordination during perioperative period of a major surgical procedure. The following investigations should be available preoperatively.

1. ECG (to assess graft function and arrhythmias if any). About 5% of the patients may present with pacemaker
2. Endomyocardial biopsy (to rule out the evidence of rejection)
3. Echocardiography (ventricular function assessment and detection of allograft vasculopathy)^[30]
4. Coronary angiography: Reserved for patients with suspected allograft vasculopathy^[31]
5. Laboratory parameters

- a. Complete haemogram (rule out bone marrow depression)
- b. Electrolytes
- c. Renal function tests: In therapeutic doses, both cyclosporine and tacrolimus may cause dose-related decrease in renal blood flow and glomerular filtration rate due to renal vasoconstriction^[32]
- d. Liver function tests
- e. Biomarkers: Brain natriuretic peptide may have a role in the detection of allograft rejection and coronary vasculopathy.^[33]

These patients tolerate similar premedication as those without a transplant. However, dose adjustment for some drugs as well as adjuvants is needed [Table 2]. Assess stress test findings to establish patients exercise tolerance and if necessary obtain a review from cardiologist. The dose of immunosuppressants should not be altered and should be continued post-operatively to reduce the risk of rejection. Daily monitoring of the steady state blood level is recommended. Oral cyclosporine should be administered 4–7 h before surgery to maintain therapeutic blood levels. The alteration of dose of other immunosuppressive drugs is not required unless the route of administration need to be changed from oral to iv. The oral and iv dose of azathioprine is approximately equivalent, and oral dose of prednisolone is equal to the similar iv dose of methylprednisolone. Supplemental steroids are not necessary for stress coverage except in post-transplant recipients in whom steroids are recently withdrawn.

Intraoperative concerns and anaesthesia techniques

A variety of anaesthetic techniques (local, regional, neuroleptic and general) have been used successfully in these patients. Between general anaesthesia (GA) and regional anaesthesia, no technique has been demonstrated to be better as long as care is given to maintain the preload.^[34] GA is usually preferred by many as there is a possibility of impaired response to hypotension after spinal or epidural anaesthesia. The type of intraoperative monitoring depends on the type of surgery as well as the availability of monitoring. In case of major surgery, invasive blood pressure, urinary catheter and transoesophageal echocardiography may be required to monitor vital organ and volume therapy. Oral endotracheal intubation is always preferred to nasotracheal intubation because of the potential risk of infection caused by nasal flora. Gingival hyperplasia at times is present in patients taking

cyclosporine. This may lead to bleeding and aspiration during airway manipulation. Airway obstruction may be encountered in patients with diabetes and lymphoproliferative disorders. Avoid hyperventilation in patients taking cyclosporine and tacrolimus because of a decrease in seizure threshold with these two drugs. There is a loss of sympathetic response to laryngoscopy and intubation.^[35] Laryngeal mask airway is not contraindicated. The denervated heart has a blunted HR response to inadequate anaesthetic depth or analgesia. Non-steroidal anti-inflammatory drugs should be avoided for pain control because of the risk of bleeding.

In a post-transplant heart, the catecholamine response is different from that of normal heart because intact sympathetic nerves are required for the normal uptake and metabolism of catecholamines. The receptor density, however, remains unchanged, and the transplanted heart can respond to direct acting drugs, for example, sympathomimetics. Dopamine is a less effective inotrope, whereas isoprenaline and dobutamine have similar effects in both transplanted and normal heart. Because atropine has no effect on a transplanted heart, isoprenaline and epinephrine should be readily available to manage bradycardia and hypotensive emergencies.^[35] Table 4 summarises the haemodynamic response of some commonly used drugs for resuscitation.

Post-operative care

In addition to the routine care as those for non-transplant recipients, increased attention should be paid to the preload status, renal function and prevention of infection. The immunosuppressants should be continued postoperatively and blood level is to be monitored.

ANAESTHESIA MANAGEMENT IN SPECIAL CASES

Pregnancy and delivery

Pregnancy is possible in heart transplant recipients without affecting allograft survival. Currently used immunosuppressants are not teratogenic and need not be discontinued during pregnancy. The risk of preeclampsia, eclampsia, premature labour and allograft rejection is high in these patients; therefore, there is a need for more caution. No matter what anaesthesia technique is followed, maintenance of haemodynamic stability is important. Neuraxial block is preferred by many authors because it produces less impact on baby compared to GA.^[36]

Table 4: Response of denervated heart to various cardiovascular agents drug

Drugs	SA node rate	AV conduction	SVR	BP	CO	Remark
Atropine	-	-	-	-	-	Cannot be used in bradycardia emergency
Dopamine	↑	↑	-	~	↑	
Dobutamine	↑	↑	-	↑	↑	Effect on HR is more than normal heart Can be used in detection of coronary insufficiency
Epinephrine	↑	↑	-	↑	↑	
Norepinephrine	↑	↑	-	↑	~	
Isoprenaline	↑	↑	-	↓	↑	
Phenylephrine	-	-	-	↑	~	
Digoxin	-	↓				

AV – Atrioventricular; SVR – Systemic vascular resistance; BP – Blood pressure; CO – Cardiac output; - – No effect; ~ – Equivocal; HR – Heart rate; SA – Sino-atrial

The following points need to be remembered during neuraxial blockade: control appropriate block level because^[37] too high a level of block may inhibit sympathetic nerves and cause vasodilatation which is unfavourable for a transplanted heart; too low a level is not suitable for surgery as resultant pain may lead to increased myocardial oxygen consumption. Strict maintenance of preload is mandatory, and one should not forget that too much of fluid is also deleterious for the denervated heart as it can lead to heart failure. Phenylephrine is the vasoconstrictor of choice to maintain haemodynamic stability. Strict asepsis and antibiotic prophylaxis should be used for all operative, and instrumental delivery and immunosuppressants continued postoperatively.

Laparoscopic surgery

Pneumoperitoneum is well tolerated. The occasional hypertensive response to pneumoperitoneum can be tackled by increase in analgesic dose.^[38]

CONCLUSION

A good understanding of the changes in physiology of a heart transplant recipient is essential for the best perioperative management. Some important factors must be addressed including changes in haemodynamic status, pharmacological management of denervated heart and prevention of cardiac allograft rejection postoperatively.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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