Review Article

Perioperative Care of Heart Transplant Recipients Undergoing Non-Cardiac Surgery

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ABSTRACT

The life expectancy of patients with end-stage heart disease undergoing Orthotopic Heart Transplantation (OHT) has increased significantly in the recent decades since its original introduction into the medical practice in 1967. Substantial advances in post-operative intensive care, surgical prophylaxis, and anti-rejection drugs have clearly impacted survivability after OHT, therefore the volume of patients presenting for non-cardiac surgical procedures is expected to continue to escalate in the upcoming years. There are a number of caveats associated with this upsurge of post-OHT patients requiring non-cardiac surgery, including presenting to healthcare facilities without the resources and technology necessary to manage potential perioperative complications or that may not be familiar with the care of these patients, facilities in which a cardiac anesthesiologist is not available, patients presenting for emergency procedures and so forth. The perioperative care of patients after OHT introduces several challenges to the anesthesiologist including preoperative risk assessments different to the general population and intraoperative management of a denervated organ with altered response to medications and drug-drug interactions. The present review aims to synopsize current data of patients presenting for non-cardiac surgery after OHT, surgical aspects of the transplant that may impact perioperative care, physiology of the transplanted heart as well as anesthetic considerations.

Keywords: Anesthesia, heart transplantation, non-cardiac surgery, outcomes, perioperative care

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Submitted: 11-Sep-2019 **Accepted:** 26-Sep-2019 **Published:** 19-Apr-2021

INTRODUCTION

Orthotopic heart transplantation (OHT) constitutes the gold standard intervention for the definitive management of patients with end-stage heart disease despite the striking development of short-term and long-term mechanical circulatory support in the form of ventricular assist devices.[1-4] Globally, 1% of patients with end-stage heart disease undergo OHT and this procedure is performed approximately in 3500 patients annually worldwide—2500 of these made in the United States.[1,5]

Significant improvement in surgical techniques, intra- and postoperative care, immunosuppressant therapies and infection prophylaxis have directly influenced graft survival after OHT, currently reported to be approximately 75%–80% after 1 year, 50% after 10 years, and a median life expectancy around 10.7–11.9 years following OHT.[3,5-8] Due to increase awareness for organ donation

Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.ACA_130_19

How to cite this article: Navas-Blanco JR, Modak RK. Perioperative care of heart transplant recipients undergoing non-cardiac surgery. Ann Card Anaesth 2021;24:140-8.

and survival of these patients after OHT, the likelihood of anesthesiologists to encounter these patients for non-cardiac surgery is expected to increase in the upcoming years.

The perioperative care of heart transplant recipients presenting for non-cardiac surgery may be challenging, based on its convoluted and exclusive physiology, intricated pharmacologic responses, and complex drug interactions. The purpose of this review is to synopsize the current data regarding the perioperative risk of heart transplant recipients presenting for non-cardiac surgery, summarize fundamental anatomic and physiologic concepts, as well as peri-operative considerations.

DATA ON HEART TRANSPLANT RECIPIENTS PRESENTING FOR NON-CARDIAC SURGERY

The International Society for Heart and Lung Transplantation Registry described that roughly 118.788 heart transplants have been performed worldwide until 2015.[7] The immediate postoperative mortality has been reported to be around 1%–2%, with a superb 1-year survival rate of 75%–80% and almost half of these patients surviving after 10 years.[3,7,9] The introduction of improved immunosuppressant therapy in the form of Cyclosporine A in the 1980s, lead to a significant increase in the survival rate after OHT.[2,10,11] However, the postoperative morbidity of these patients has been reported to be between 9%-10%, mostly due to risk of postoperative infection secondary to chronic immunosuppressive therapy.[9,11]

Despite of post-OHT improvement of outcomes, the body of literature describing the perioperative care of these patients, as well as morbidity and mortality rate for non-cardiac surgery is scarce. Overall, the incidence of non-cardiac surgery has been described to be approximately around 15%-47% [Table 1].[2,3,6-9,11-14] Marzoa *et al.* in a retrospective analysis of 207 heart transplant recipients, described that malignancy was the most common indication for non-cardiac surgery after OHT (33.6%). A significant portion of these patients had a mortality rate of 16.6% when presenting for emergency procedures ($P = 0.012$) and surgical site infection was the most common postoperative complication (6.9%).[6]

Retrospective data analysis obtained from our institution (Henry Ford Hospital, Detroit, Michigan, US) for patients who underwent OHT from December 2013 to April 2018, demonstrate a similar trend regarding the incidence of non-cardiac surgery after heart transplant. In average, these patients presented for non-cardiac surgery within 16 months after OHT [Table 2]. The procedures most commonly performed were ventral hernia repair, laparoscopic cholecystectomy and exploratory laparotomy (general surgery procedures: 31%) and the incidence of surgical site infection was 3%.

ANATOMY OF THE TRANSPLANTED HEART

The surgical technique employed during heart transplantation plays an important role in the perioperative outcome of these patients and has a paramount impact in the anesthesia care when they present later for non-cardiac surgery. A brief overview of the most common surgical techniques employed for OHT and its anesthetic implications is described:

The *biatrial technique*, introduced by Lower and Shumway, aims to preserve the posterior portion of the right atrium attached to the vena cava as well as the posterior inter-atrial septum and posterior left atrium—preserving the entrance of the pulmonary veins.[5,15] Authors advocating for this technique, highlight a decreased allograft cold ischemic time and cardiopulmonary bypass time, since preserving both right and left atrial cuffs facilitate re-implantation of the donor heart.[16] Conversely, several authors have emphasized the presence of enlarged atrial chambers as major disadvantage of this technique which leads to a higher rate of atrio-ventricular valve dysfunction, atrial arrhythmias, and permanent pacemaker implantation.[5,15,17,18]

The *bicaval technique* was introduced by Dreyfus and Sievers, as a modification of the biatrial procedure, where the anastomosis is performed directly at the level of the superior and inferior vena cava, pulmonary artery and aorta, and preserving the posterior portion of the recipient's left atrium as well as most of the donor right atrium.[5,16] Authors supporting this technique highlight its favorable 30-day mortality and improved overall survival when compared with the biatrial technique, in addition to improved preservation of atrial geometry, lower mean pulmonary arterial pressures, decreased incidence of tricuspid regurgitation, atrial arrhythmias, and permanent pacemaker requirement.[5,16-20] The major disadvantage related to this technique has been longer cold ischemic, operative time, and cardiopulmonary bypass use.[17]

The total orthotopic heart transplantation technique ("bicaval, bipulmonary venous technique"), introduced by Dreyfus and seldom employed, where both atria are excised entirely, leaving only two small

Table 1: Incidence of Non-Cardiac Surgery (NCS) after Orthotopic Heart Transplant

Author	Year	Total of heart recipient patients	Number of patients requiring for NCS	Number of NCS performed	Most common performed NCS	Perioperative Adverse Outcomes
Yee *et al.*[14]	1990	78	14 (18%)	16	Emergent Exploratory Laparotomy (44%), Elective Abdominal (19%)	No immediate postoperative mortality reported, surgical wound infection (13%)
Melendez *et al.*[13]	1991	124	28 (23%)	35	Biliary Tract (23%), Other Abdominal (14%), Thoracic (14%)	No immediate postoperative mortality reported
Cheng *et al.*[2]	1993	86	18 (21%)	32	Ophthalmologic (28%), Abdominal (16%)	No immediate postoperative mortality reported
Bhatia *et al.*[12]	1997	349	54 (15%)	94	Biliary tract (15%), Orthopedic (8%), Colorectal (7%)	Mortality was 45% in transplant-related thoracic procedures
Mueller *et al.*[11]	1999	94	44 (47%)	75	Abdominal (23%), Vascular (18%), Urologic (11%)	Postoperative complication rate was 9% (8 of 75)
Marzoa *et al.*[6]	2007	207	72 (35%)	116	Urologic (30.2%), Abdominal (25%), Vascular 12.1%)	Mortality 4 of 72 (5.6%)

Table 2: Statistics of Non-Cardiac Surgery (NCS) after Orthotopic Heart Transplant (OHT) at Henry Ford Hospital

Total of Heart Recipient Patients	95
Number of patients requiring for NCS	28 (29.4%)
Number of NCS performed	59
Most common performed NCS	General Surgery (31%), Otolaryngology (19%), Plastic Surgery (14%)
Perioperative Adverse Outcomes	2 Surgical Site Infection (3.3%), 2 post-operative respiratory distress (3.3%)
Average Age (range)	52 (27-69)
Average number of days for NCS after OHT (range)	503 (1-1812)

Data from December 2013 to April 2018. Data obtained from the Department of Statistics of Henry Ford Hospital

pulmonary vein cuffs which are anastomosed with the donor left atrium.[21] Rivinius *et al.* demonstrated a lower incidence of atrial fibrillation when this technique was employed ($P = 0.0012$), although longer operative times seem to be the major disadvantage of this technique.[18,19]

PHYSIOLOGY OF THE TRANSPLANTED HEART

The following sections present an overview of the most commonly encountered physiologic modifications in post-OHT patients [Table 3].

Changes in atrial geometry

Regardless of the surgical technique employed, all patients are expected to develop a variable degree of increased atrial size after OHT, as remaining cuffs of the atria are usually preserved depending on the technique employed.[2,8] In regards to atrial sizing after OHT, several authors have advocated for the *bicaval* technique to preserve better the architecture of the atria, in despite to be more surgically challenging and with longer bypass and ischemic time, when compared to the *biatrial* technique.[17]

Riberi *et al.* demonstrated a larger left atrial surface in patients who underwent a biatrial technique when compared to those who received a bivacal technique (33+/- 4 cm^2 biatrial group *vs.* 20+/- 3 cm^2 bicaval group; $P = 0.01$).[22] Similarly, Dell'Aquila *et al.* performed cardiac magnetic resonance imaging follow-up in post-OHT patients, and revealed larger right and left atrial sizes among those who received a biatrial technique when compared to the bicaval group ($P = 0.001$), as well as higher left and right atrial end-diastolic and end-systolic volumes in the former group.[15] Likewise, Aziz *et al.*, in a retrospective analysis revealed that patients who underwent the bicaval technique had lower right atrial pressures (4.3+/- 4.0 mmHg *vs.* 10.9+/- 4.8 mmHg in the biatrial technique group), lower mean pulmonary artery pressures and higher left ventricular ejection fraction ($P = 0.005$).[20]

Donor-recipient size mismatching leading to atrial enlargement has also been associated to functional regurgitation of either atrio-ventricular valve, with the tricuspid valve being most commonly affected.[17] Numerous authors have cited a much higher incidence of functional tricuspid and mitral regurgitation in patients who received a biatrial OHT when compared to those who receive a bicaval technique.[17,20,23-25]

Changes in pacemaker function and electrophysiology

During the first year after OHT, the prevalence of dysrhythmias is around 50%, likely due to unopposed sympathetic tone and increased sensitivity to circulating catecholamines.[1,2] The baseline heart rate is higher compared with non-OHT patients (average 90–110 beats per minute).[3,26] Similarly, the presence of tachycardia as an ominous sign of underlying physiologic distress (e.g. pain, hypovolemia, etc.), may be blunted as well

Table 3: Physiologic Changes of the Transplanted Heart

Changes in Atrial Geometry
Larger right and left atrial end-diastolic and end-systolic volumes
Larger right atrial pressure
Functional atrio-ventricular valve regurgitation (tricuspid valve most commonly affected)
Changes in Pacemaker function and Electrophysiology
Resting heart rate 90-110 beats per minute
Blunted tachycardia response to physiologic stress
Presence of "*two p-waves*" in electrocardiogram
Lack of functional efferent systemic vaso-motor input
Changes in Cardiac Function
Preserved Frank-Starling Mechanism (normal contractile response to preload)
Heart rate responsive to increased circulating catecholamines
Accentuated orthostatic hypotension
Greater left ventricular mass
Diastolic compliance and relaxation abnormal
Lower maximal heart rate and cardiac index during exercise
Changes derived from Cardiac Denervation
Heart Rate unresponsive to Systemic Blood Pressure changes (Absent Baroreceptor Reflex)
Heart Rate unresponsive to Carotid Massage
Lack of Heart Rate change to Valsalva Maneuvers and Respiratory Changes
Slower Heart Rate response to postural changes
Lack of Angina Pectoris during myocardial ischemia ("*silent ischemia*")

since the response of the grafted tissue to intrinsic catecholamines is variable.[2,26]

After OHT, the grafted tissue possesses its own sino-atrial node which is initially denervated and completely devoid of functional efferent systemic vaso-motor input, therefore is unable to partake in many physiologic reactions such as response to systemic blood pressure changes (lack of baroreceptor reflex), lack of response to carotid sinus massage, Valsalva maneuvers, respiration and positional body changes.[2,3,5] The presence of "two P waves" on the electrocardiogram is not uncommon, due to co-existing portions of the native and donor sino-atrial node tissues, though activity from the former is not conducted as it gets interrupted due to the mid-atrial suture line.[2,5,10]

The incidence of first-degree atrio-ventricular block is common, and up to 30% of patients may develop right bundle branch block. Totally, 76% of patients develop atrial premature beats, 18% may progress to atrial fibrillation or flutter, and the majority of patients after OHT develop ectopic ventricular beats unrelated to rejection.[5,27] Overall, the bicaval technique is associated with lower incidence of post-OHT tachyarrhythmias and lower incidence of permanent pacemaker (PPM) placement. Meyer *et al.* in a retrospective analysis of 105 patients undergoing OHT, demonstrated a significant decline in PPM requirements at 30 days (13% biatrial group *vs.* 0% bicaval group; $P = 0.008$) and 90 days (17% *vs.* 1.8%; $P = 0.01$).[17,28]

Changes in cardiac function

After OHT, the denervated organ relies on its normal Frank-Starling mechanism as a response to stress and exercise. The graft contractile reserve, preserved preload response and myocardial metabolism, coupled to an increased heart rate secondary to circulating catecholamine surge, play a paramount role to accomplish an adequate cardiac output during exercise.[5] Similarly, postural variations in these patients lead to an accentuated change in the systemic blood pressure, as cardiac output relies on an adequate venous return.[29]

Bovard *et al.* demonstrated in a study between post-OHT patients and matched controls undergoing exercise stress echocardiography, that the former group had a left ventricular (LV) wall thickness ($P < 0.01$) and LV mass-to-volume ratio ($P = 0.01$) greater than the control group. Stroke volume measures in this study were similar between groups during exercise as the heart rate increased analogously, although as exercise progress, both heart rate and cardiac index increase to a lesser extent in the post-OHT group.[30] Commonly, systolic ventricular function remains normal, while diastolic compliance and relaxation may be impaired during the first year after OHT, leading to a transient higher filling pressures that normalizes over time, unless severe graft rejection ensues.[5,31]

Cardiac plexus "reinnervation"

Extrinsic denervation of both components of the cardiac plexus (parasympathetic vagal fibers and post-ganglionic sympathetic nerve fibers – originated from the stellate ganglion –) is anticipated after OHT. The degree and extent of this denervation, as well as the rate of regeneration of these nerve fibers is variable and unpredictable.[32,33] Clinically, cardiac denervation leads to a devoid neural input to the sino-atrial node, impaired

reflex responses (loss of cardiac baroreflexes in response to tracheal intubation, surgical pain, or vasodilation), and loss of efferent feedback from the graft, which has been hypothesized as the reason by which post-OHT patients are unable to experience angina pectoris during myocardial ischemia.[32,34]

Cardiac reinnervation after OHT continues to be a subject of debate and controversy. Nerve fiber regrowth appears to follow a pattern of desynchrony and heterogenicity among post-OHT patients, and has been described to occur among 40%–70% of recipients.[32] Young donor age, young donor recipient, and non-ischemic cardiomyopathy as the reason for the OHT, have been described as factors associated to cardiac reinnervation, and particularly diabetes have been linked to be unfavorable for reinnervation.[35,36] Sympathetic and parasympathetic reinnervation occur at different stages after OHT, with most authors describing the former to develop 5–6 months and the latter 1 to 3 years after OHT respectively, although these times vary from one patient to another, and in some patients may never occur at all.[32]

Cardiac reinnervation re-introduces neurogenic control over the sino-atrial node and the ventricular contractility, as well as improved exercise performance of the graft—as norepinephrine is released from regenerated sympathetic nerve terminals. Intrinsic resting heart rate of the graft upon reinnervation becomes "partially normalized"; however, this regularization is heterogeneous and variable among recipients.[32,37,38]

PHARMACOLOGY OF THE TRANSPLANTED HEART

Immunosuppressive agents and interaction with anesthetic drugs

Prophylactic immunosuppressant therapy represents the basis for prevention of rejection, and the chief component in overall graft survival. The fine line between adequate immunosuppression and avoidance of infection is one of the upmost important factors responsible for overall survival after OHT.[5] Around 40% of heart transplant recipients develop an episode of acute rejection during the first year, on the other hand, the presence of infection is a predictor of poor outcome in the early post-OHT period, especially lung and central nervous system infections.[39,40]

Data from the 2016 International Society for Heart and Lung Transplantation (ISHLT) registry reported that infection was the cause of death in 32% of cases within 1-month to 1-year after OHT.[41] Similarly, the ISHLT registry described malignancy as the cause of death in 24% of all mortalities 10–15 years after OHT, coinciding with the findings of Marzoa *et al*. in which malignancy was the most common indication of surgery after OHT.[6,41]

Most patients are maintained in a drug regimen including a combination of *corticosteroids* used to suppress helper T-cell proliferation, *calcineurin inhibitors* (cyclosporine, tacrolimus), to suppress the production of Interleukin-2, and *antiproliferative agents* (Mycophenolate Mofetil, Azathioprine) to limit B-cell and T-cell proliferation.[3,26] Other agents such as the *Mammalian Target of Rapamycin (m-TOR) inhibitors* (Sirolimus, Everolimus), associated to inhibit T- and B-cell proliferation, have been mainly employed in OHT recipients as therapy to treat and delay coronary allograft vasculopathy or to decrease the nephrotoxicity associated to calcineurin inhibitors.[41] Further adverse effects from immunosuppressive therapies as well as pertinent perioperative drug-drug interactions are summarized in Table 4.

Cardiovascular drugs and its effect on the transplanted heart

As a general rule, indirectly acting drugs mediating its effects via the autonomic nervous system are usually futile and direct-acting myocardial drugs are effective as intrinsic alpha and beta receptors in the newly grafted heart are generally intact.[5] Outlined in Table 5 are the effects of the most commonly employed perioperative drugs in transplanted hearts. Drugs working in different phases of the cardiac tropism are also effective based on the desired effect: verapamil, quinidine, amiodarone, and procainamide are beneficial slowing the atrio-ventricular conduction.[26,42] Digoxin has been associated with negative chronotropic faculties in transplanted hearts, although it may enhance inotropy.[3] Lidocaine has been associated to a depressed inotropic effect.[5] Other drugs such as pancuronium does not have vagolytic effects in transplanted hearts and neostigmine have been associated to dose-response bradycardia episodes, and few cases have reported to be related to heart blocks and asystole.[3,5,39]

PERIOPERATIVE CONSIDERATIONS

Preoperative assessment

A thorough preoperative history and physical examination should be performed to determine current graft performance based on patient's activity level and exercise tolerance. The possibility of any type of rejection and active infection should be discarded before surgery and this significantly impacts morbidity and mortality after surgery. Functionality of other major organs should also be addressed, particularly those that may be affected by immunosuppressive therapy or due to dysfunction of the graft.[5] The 2016 ISHLT registry

Table 4: Common Immunosuppressive Therapies after Orthotopic Heart Transplantation

Drug	Common Adverse Effect	Drug-drug Interaction
Corticosteroids		
Prednisone, Methylprednisolone, etc.	Hyperglycemia, Diabetes Mellitus, Hyperlipidemia, Peptic Ulcer Disease, Pancreatitis, Hypertension, Adrenal Suppression	Amphotericin B (hypokalemia), Fluoroquinolones (risk of tendon rupture), Depolarizing Neuromuscular Blockers (prolonged neuromuscular blockade), Non-depolarizing Neuromuscular Blockade (prolonged neuromuscular blockade, myopathy)
Calcineurin Inhibitors		
Cyclosporine	Hypertension, Gingival Hyperplasia, Neurotoxicity, Nephrotoxicity, Diabetes Mellitus	Benzodiazepines, Opioids (decrease clearance, increase bioavailability, higher risk for toxicity), Macrolides, Fluoroquinolones (increase plasma Cyclosporine), Imipenem (neurotoxicity)
Tacrolimus	Hypertension, Diabetes Mellitus, Dyslipidemia, Neurotoxicity, Nephrotoxicity	Antifungals (QT-prolongation), Fluoroquinolones (QT-prolongation), Ganciclovir (nephrotoxicity), Loop Diuretics (acute renal insufficiency), Ondansetron (QT-prolongation), Sevoflurane (QT-prolongation), Diltiazem, Verapamil, Amiodarone (increase tacrolimus levels)
Antiproliferative Agents		
Mycophenolate Mofetil	Hypertension, Hyperlipidemia, Diabetes Mellitus, Pancytopenia, Electrolyte Imbalances	Omeprazole (increase clearance of mycophenolate), Acyclovir (increase acyclovir concentrations), Metronidazole (decreased mycophenolate concentrations)
Azathioprine	Myelosuppresion, Hepatotoxicity, Neoplasia, Pancreatitis	Lisinopril (increased risk of anemia/leukopenia), Warfarin (decrease anticoagulant effect), Trimethoprim-Sulfamethoxazole (increase bone marrow suppression)
Mammalian Target of Rapamycin (mTOR) Inhibitors		
Everolimus	Impaired wound healing, Hypertension, Peripheral edema	Erythromycin, Voriconazole (increased toxicity to Everolimus)
Sirolimus	Impaired wound healing, Nephrotoxicity, Anemia, Thrombocytopenia	Lisinopril, Captopril (increased risk of angioedema), Erythromycin, Voriconazole (increased risk of Sirolimus toxicity)

Table 5: Cardiovascular Effects in Heart Transplant Recipients of most commonly employed drugs in the perioperative period

Action	Drug	Effect on Heart Rate	Effect on Systemic Blood Pressure
Indirect	Ephedrine	Increase	Increase
	Atropine	None	None
	Glycopyrrolate	None	None
	Opioids	None	Decrease
	Glucagon	Increase	None
	Neostigmine	None	Decrease
Direct	Epinephrine	Increase	Increase
	Phenylephrine	None	Increase
	Esmolol	None	Decrease
	Metoprolol	None	Decrease
	Propranolol	Decrease	Decrease
	Isoproterenol	Increase	Decrease
	Dobutamine	Increase	Decrease
	Dopamine	Increase	None
	Norepinephrine	Increase	Increase

describes hypertension, hyperlipidemia, renal dysfunction, diabetes and cardiac allograft vasculopathy (CAV) as the most common morbidities present after OHT, with graft failure as the leading cause of death (31%–42%) in the early transplant period (defined as the first 12 months after OHT) and renal dysfunction, CAV and malignancy as the main causes of death in the late transplant period (beyond 12 months after OHT).[3,7]

Preoperative electrocardiography (ECG) is essential, as well as continuous monitoring of the electrical activity of the heart. Review of the most recent transplant team notes, endomyocardial biopsy results, angiography and echocardiographic reports, as well as recent pacemaker interrogation (if applicable) should be performed.[5,10,26] Given the side effects consequent of the immunosuppressant medications used in post-OHT patients, a preoperative laboratory evaluation should also be included particularly to determine current renal function, electrolytes, coagulation status and complete blood count to rule out bone marrow suppression.[26] Adequate preload should be assured before performing any neuraxial technique, and coagulation profile and platelet count should be checked.[5]

The role of Brain Natriuretic Peptide (BNP) as a predictive factor for allograft rejection continues to be controversial, with several authors advocating for significant positive correlation between BNP levels and high right atrial and pulmonary artery pressures (as indirect marker of cardiac allograft rejection), and others declining this relationship in further studies.[43]

Continuation of immunosuppressive therapy must be sought at all possible, and if the gastrointestinal tract is not available, adequate conversion from oral to intravenous doses should be made. Therapeutic serum levels of certain immunosuppressant agents (e.g. cyclosporine and tacrolimus) should be measured and closely monitored throughout the perioperative period. Perioperative stress dose of steroid should be considered in patients who are steroid-dependent

and perioperative glucose levels should be checked and appropriately corrected.[3,5]

Intraoperative care

Standard monitoring as recommended by the American Society of Anesthesiologists is typically sufficient in most cases, although the decision of further invasive monitoring in the form of arterial lines, central venous access, transesophageal echocardiography and so forth, should be tailored depending on the case. Different anesthetic techniques have been successfully employed in post-OHT patients. Aseptic technique must be employed during instrumentation of the airway, vascular access or any regional procedure, and antibiotic coverage is recommended during the perioperative period.[1,5,44]

Slow induction and titration of anesthetic drugs as well as adequate preload is warranted to avoid intraoperative hypotension as these patients cannot mount an adequate reflex sympathetic tachycardia response and therefore rely on the graft intrinsic Frank-Starling mechanism in order to increase the stroke volume and maintain the cardiac output.[1,3] Vasoactive medications for the management of intraoperative hypotension should be careful chosen since only direct-acting myocardial drugs are effective [Table 5]. If large blood losses or acute hypotensive episodes are anticipated, central venous catheterization or the use of transesophageal echocardiography is recommended.[3] Monitoring of tachycardia as a surrogate marker for pain is not valuable in post-OHT patients; therefore, blood pressure should be the main indicator of titration of the depth of anesthesia.[5]

Oral intubation should be preferred over nasal due to the high risk of pulmonary infection from nasal flora. Patients on Cyclosporine may be at risk of gingival hyperplasia, therefore careful manipulation of the airway is warranted in these patients to avoid bleeding during airway instrumentation.[3,5,26] Also, Cyclosporine and Tacrolimus have been related to decrease the seizure threshold, thus hyperventilation should be avoided.[26]

Management of tachyarrhythmias may be challenging during the perioperative period. Carotid massage and Valsalva maneuvers are not effective in these patients due to lack of parasympathetic innervation. Beta-blockers are generally avoided, though propranolol have been described for the management of tachyarrhythmias after OHT, as well as amiodarone and verapamil.[5,26,45] Similarly, digoxin ability to slow atrio-ventricular conduction is ineffective in these patients. Adenosine and neostigmine have been also employed, but it has been associated to prolonged heart blocks and asystole.[3,46]

Neuromuscular blocker devoid of liver and kidney elimination such as cisatracurium is recommended although a combination of rocuronium and sugammadex have been successfully employed as an effort to avoid anticholinesterase drugs (neostigmine, pyridostigmine) and anticholinergic drugs (atropine, glycopyrrolate) which may lead to a variety of responses in post-OHT patients.[47,48]

Postoperative care

In general, most literature agree that postoperative care should be similar to non-transplanted patients with certain special considerations: maintain adequate preload and use blood pressure data as oppose to heart rate as an indicator for adequate volume status and pain control, assure adequate infection prophylaxis, re-initiation of immunosuppressant therapy whenever feasible as well as chemical deep venous thrombosis prophylaxis.[26]

SUMMARY

OHT is linked not just to survival increase but also improved quality of life. Improved surgical technique, immunosuppressant therapies and perioperative care have led to a significant amount of post-OHT patients present for non-cardiac procedures, therefore becomes paramount for the general anesthesiologist to have a thorough understanding of graft's physiology and pharmacology when taking care of these patients perioperatively. Ideally, coordination with the heart transplant team should be done preoperatively to rule out graft rejection, current level of immunosuppression and associated side effects such as hypertension, diabetes, chronic kidney injury and so forth. The risk for drug-drug interaction is high, particularly during the perioperative period. Proper preoperative risk stratification should be performed and the decision regarding the anesthetic technique to employ and the use of invasive vascular access and monitoring should be individualized.

Financial support and sponsorship

Support was provided solely from institutional and/or departmental sources.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Swami AC, Kumar A, Rupal S, Lata S. Anaesthesia for non-cardiac surgery in a cardiac transplant recipient. Indian J Anaesth 2011;55:405-7.

2. Cheng DC, Ong DD. Anaesthesia for non-cardiac surgery in heart-transplanted patients. Can J Anaesth 1993;40:981-6.
3. Jurgens PT, Aquilante CL, Page RL 2nd, Ambardekar AV. Perioperative management of cardiac transplant recipients undergoing noncardiac surgery: Unique challenges created by advancements in care. Semin Cardiothorac Vasc Anesth 2017;21:235-44.
4. Mancini D, Colombo PC. Left ventricular assist devices: A rapidly evolving alternative to transplant. J Am Coll Cardiol 2015;65:2542-55.
5. Ashary N, Kaye AD, Hegazi AR, M Frost EA. Anesthestic considerations in the patient with a heart transplant. Heart Dis (Hagerstown, Md) 2002;4:191-8.
6. Marzoa R, Crespo-Leiro MG, Paniagua MJ, Bendayan I, Rios R, Franco R, *et al*. Late noncardiac surgery in heart transplant patients. Transplant Proc 2007;39:2382-4.
7. Lund LH, Edwards LB, Dipchand AI, Goldfarb S, Kucheryavaya AY, Levvey BJ, *et al*. The Registry of the international society for heart and lung transplantation: Thirty-third adult heart transplantation report-2016; Focus theme: Primary diagnostic indications for transplant. J Heart Lung Transplant 2016;35:1158-69.
8. McCartney SL, Patel C, Del Rio JM. Long-term outcomes and management of the heart transplant recipient. Best Pract Res Clin Anaesthesiol 2017;31:237-48.
9. Velanovich V, Ezzat W, Horn C, Bernabei A. Surgery in heart and lung transplant patients. Am J Surg 2004;187:501-4.
10. Lyons JB, Chambers FA, MacSullivan R, Moriarty DC. Anaesthesia for non-cardiac surgery in the post-cardiac transplant patient. Ir J Med Sci 1995;164:132-5.
11. Mueller XM, Tevaearai HT, Stumpe F, Hurni M, Ruchat P, Seydoux C, *et al*. Extramediastinal surgical problems in heart transplant recipients. J Am Coll Surg 1999;189:380-8.
12. Bhatia DS, Bowen JC, Money SR, Van Meter CH Jr., McFadden PM, Kot JB, *et al*. The incidence, morbidity, and mortality of surgical procedures after orthotopic heart transplantation. Ann Surg 1997;225:686-93; discussion 693-84.
13. Melendez JA, Delphin E, Lamb J, Rose E. Noncardiac surgery in heart transplant recipients in the cyclosporine era. J Cardiothorac Vasc Anesth 1991;5:218-20.
14. Yee J, Petsikas D, Ricci MA, Guerraty A. General surgical procedures after heart transplantation. Can J Surg 1990;33:185-8.
15. Dell'Aquila AM, Mastrobuoni S, Bastarrika G, Praschker BL, Aguero PA, Castano S, *et al*. Bicaval versus standard technique in orthotopic heart transplant: Assessment of atrial performance at magnetic resonance and transthoracic echocardiography. Interact Cardiovasc Thorac Surg 2012;14:457-62.
16. Toscano G, Bottio T, Gambino A, Bagozzi L, Guariento A, Bortolussi G, *et al*. Orthotopic heart transplantation: The bicaval technique. Multim Man Cardiothorac Surg 2015;2015. doi: 10.1093/mmcts/mmv035.
17. Jacob S, Sellke F. Is bicaval orthotopic heart transplantation superior to the biatrial technique? Interact Cardiovasc Thorac Surg 2009;9:333-42.
18. Morgan JA, Edwards NM. Orthotopic cardiac transplantation: Comparison of outcome using biatrial, bicaval, and total techniques. J Card Surg 2005;20:102-6.
19. Rivinius R, Helmschrott M, Ruhparwar A, Erbel C, Gleissner CA, Darche FF, *et al*. The influence of surgical technique on early posttransplant atrial fibrillation-comparison of biatrial, bicaval, and total orthotopic heart transplantation. Ther Clin Risk Manag 2017;13:287-97.
20. Aziz T, Burgess M, Khafagy R, Wynn Hann A, Campbell C, Rahman A, *et al*. Bicaval and standard techniques in orthotopic heart transplantation: Medium-term experience in cardiac performance and survival. J Thorac Cardiovasc Surg 1999;118:115-22.
21. Dreyfus G, Jebara V, Mihaileanu S, Carpentier AF. Total orthotopic heart transplantation: An alternative to the standard technique. Ann Thorac Surg 1991;52:1181-4.
22. Riberi A, Ambrosi P, Habib G, Kreitmann B, Yao JG, Gaudart J, *et al*. Systemic embolism: A serious complication after cardiac transplantation avoidable by bicaval technique. Eur J Cardiothorac Surg 2001;19:307-11; discussion 311-302.
23. Schnoor M, Schafer T, Luhmann D, Sievers HH. Bicaval versus standard technique in orthotopic heart transplantation: A systematic review and meta-analysis. J Thorac Cardiovasc Surg 2007;134:1322-31.
24. Laske A, Carrel T, Niederhauser U, Pasic M, von Segesser LK, Jenni R, *et al*. Modified operation technique for orthotopic heart transplantation. Eur J Cardiothorac Surg 1995;9:120-6.
25. Milano CA, Shah AS, Van Trigt P, Jaggers J, Davis RD, Glower DD, *et al*. Evaluation of early postoperative results after bicaval versus standard cardiac transplantation and review of the literature. Am Heart J 2000;140:717-21.
26. Blasco LM, Parameshwar J, Vuylsteke A. Anaesthesia for noncardiac surgery in the heart transplant recipient. Curr Opin Anaesthesiol 2009;22:109-13.
27. Scott CD, Dark JH, McComb JM. Arrhythmias after cardiac transplantation. Am J Cardiol 1992;70:1061-3.
28. Meyer JA. Werner Forssmann and catheterization of the heart, 1929. Ann Thorac Surg 1990;49:497-9.
29. Verani MS, Nishimura S, Mahmarian JJ, Hays JT, Young JB. Cardiac function after orthotopic heart transplantation: Response to postural changes, exercise, and beta-adrenergic blockade. J Heart Lung Transplant 1994;13:181-93.
30. Bovard JM, De Souza AM, Harris KC, Human DG, Hosking MC, Potts JE, *et al*. Physiological responses to exercise in pediatric heart transplant recipients. Med Sci Sports Exerc 2019;51:850-7.
31. StGoar FG, Gibbons R, Schnittger I, Valantine HA, Popp RL. Left ventricular diastolic function. Doppler echocardiographic changes soon after cardiac transplantation. Circulation 1990;82:872-8.
32. Awad M, Czer LS, Hou M, Golshani SS, Goltche M, De Robertis M, *et al*. Early denervation and later reinnervation of the heart following cardiac transplantation: A review. J Am Heart Assoc 2016;5:e004070.
33. Wilson RF, Christensen BV, Olivari MT, Simon A, White CW, Laxson DD. Evidence for structural sympathetic reinnervation after orthotopic cardiac transplantation in humans. Circulation 1991;83:1210-20.
34. Hunt SA. Current status of cardiac transplantation. JAMA 1998;280:1692-8.
35. Bengel FM, Ueberfuhr P, Hesse T, Schiepel N, Ziegler SI, Scholz S, *et al*. Clinical determinants of ventricular sympathetic reinnervation after orthotopic heart transplantation. Circulation 2002;106:831-5.
36. Beitzke D, Wielandner A, Wollenweber T, Vraka C, Pichler V, Uyanik-Uenal K, *et al*. Assessment of sympathetic reinnervation after cardiac transplantation using hybrid cardiac PET/MRI: A pilot study. J Magn Reson Imaging 2019;50:1326-35.
37. Halpert I, Goldberg AD, Levine AB, Levine TB, Kornberg R, Kelly C, *et al*. Reinnervation of the transplanted human heart as evidenced from heart rate variability studies. Am J Cardiol 1996;77:180-3.
38. Buendia Fuentes F, Martinez-Dolz L, Almenar Bonet L, Sanchez-Lazaro I, Navarro Manchon J, Sanchez-Gomez JM, *et al*. Normalization of the heart rate response to exercise 6 months after cardiac transplantation. Transplant Proc 2010;42:3186-8.
39. Aguero J, Almenar L, Martinez-Dolz L, Moro JA, Rueda J, Raso R, *et al*. Influence of immunosuppressive regimens on short-term morbidity and mortality in heart transplantation. Clin Transplant 2008;22:98-106.
40. van de Beek D, Kremers WK, Del Pozo JL, Daly RC, Edwards BS, McGregor CG, *et al*. Effect of infectious diseases on outcome after heart transplant. Mayo Clin Proc 2008;83:304-8.
41. Soderlund C, Radegran G. Immunosuppressive therapies after heart transplantation--The balance between under- and over-immunosuppression. Transplant Rev (Orlando, Fla) 2015;29:181-9.
42. Stein KL, Darby JM, Grenvik A. Intensive care of the cardiac transplant recipient. J Cardiothorac Anesth 1988;2:543-53.
43. Talha S, Charloux A, Piquard F, Geny B. Brain natriuretic peptide and right heart dysfunction after heart transplantation. Clin Transplant 2017;31. doi: 10.1111/ctr. 12969.

44. Choudhury M. Post-cardiac transplant recipient: Implications for anaesthesia. Indian J Anaesth 2017;61:768-74.
45. Cannom DS, Rider AK, Stinson EB, Harrison DC. Electrophysiologic studies in the denervated transplanted human heart. II. Response to norepinephrine, isoproterenol and propranolol. Am J Cardiol 1975;36:859-66.
46. Cachemaille M, Olofsson M, Livio F, Pascale P, Zingg T, Boegli Y. Recurrent asystole after neostigmine in a heart transplant recipient with end-stage renal disease. J Cardiothorac Vasc Anesth 2017;31:653-6.
47. Tezcan B, Saylan A, Bolukbasi D, Koculu R, Karadeniz U. Use of sugammadex in a heart transplant recipient: Review of the unique physiology of the transplanted heart. J Cardiothorac Vasc Anesth 2016;30:462-5.
48. Gomez-Rios MA, Lopez LR. Use of combination of rocuronium and sugammadex in heart transplant recipients. Anaesth Intensive care 2012;40:903-4.