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Perioperative care of heart transplant recipients undergoing non-cardiac surgery

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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][2][3][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][6][7][8] Due to increase awareness for organ donation 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, intricate 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

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Full Text
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. 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. 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. 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.

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]. 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%).

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% [Table 2].

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. 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. 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.

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. 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. The major disadvantage related to this technique has been longer cold ischemic, operative time, and cardiopulmonary bypass use.

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 pulmonary vein cuffs which are anastomosed with the donor left atrium. 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.

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. 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**.

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 cm² vs. 20+/- 3 cm²; P = 0.01). 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 bivacal group (P = 0.001), as well as higher left and right atrial end-diastolic and end-systolic volumes in the former group. Likewise, Aziz et al., in a retrospective analysis revealed that patients who underwent the bivacal technique had lower right atrial pressures (4.3+/- 4.0 mmHg vs. 10.9+/- 4.8 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][24][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][20] Similarly, the presence of tachycardia as an ominous sign of underlying physiologic distress (e.g. pain, hypovolemia, etc.), may be blunted as well 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.[5][3][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 heterogeneity 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 immunosuppression 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]
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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 (Mycothenolate Mofetil, Azathioprine) to limit B-cell and T-cell proliferation.[5][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] [Table 5]

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.[3] The 2016 ISHLT registry 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.[3][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.

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Conflicts of interest

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