Anesthetic Considerations for an Adult Heart Transplant Recipient Undergoing Noncardiac Surgery: A Case Report

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Approximately 3,500 Americans undergo heart transplantation each year. A portion of this patient population will possibly present later for an elective noncardiac surgery. Anesthesia professionals can be tasked to assess and provide the anesthesia management for heart transplant recipients undergoing a noncardiac surgical procedure.

A 57-year-old man with a complicated cardiac history before undergoing heart transplantation was scheduled to undergo a right inguinal hernia repair. The patient underwent general anesthesia and had an uneventful course of surgery and recovery. Management of the patient with a heart transplant includes consideration of the altered physiology of a denervated heart; the perioperative anesthetic considerations specific to this patient population; and the risks of rejection, infection, and pharmacologic interactions brought about by immunosuppression. The purposes of this case report were to discuss the indications for the perioperative care of heart transplant recipients undergoing noncardiac procedures, and to discuss the evidence-based literature to provide delivery of safe and effective patient care.

Keywords: Anesthesia, denervated heart, noncardiac surgery, postheart transplant.

Decompensated heart failure or heart failure refractory to medical therapy, end-stage ischemic heart disease, and idiopathic dilated cardiomyopathy are common diagnoses of patients in need of heart transplantation (Figure).[1,2] After successful cadaver heart transplantation, the clinical goal is the recipient's return to optimal functional capacity resulting from the improvements in cardiac performance. Advances in patient selection criteria, enhanced perioperative monitoring, and development of highly efficacious pharmacologic agents, such as immunosuppressants, offer the transplant recipients an opportunity for a high quality of life.[3] As a result, these patients will possibly present for routine surgical procedures. In these cases, the surgical and anesthesia teams must base their coordinated efforts on knowledge of the physiology of the denervated heart and the necessary pharmacologic interventions.

The absence of sensory, sympathetic, and parasympathetic innervations to the transplanted heart occurs following heart transplantation.[3-5] These alterations to the normal function of the heart should be addressed by the anesthetist with careful consideration to the physiological effect of denervation, the unique anesthetic implications of a transplanted heart, and potential patient risks such as rejection and infection brought about by immunosuppression.

This case report reviews the anesthetic management of a heart transplant recipient undergoing a right open inguinal hernia repair.

Case Summary

A 178-cm, 80-kg, 57-year-old man, the recipient of a cadaveric heart transplant 4 months earlier, presented with a right inguinal hernia for an elective hernia repair. The patient's past medical history included nonischemic dilated cardiomyopathy, hypertension, diabetes (controlled by diet), gastroesophageal reflux disease (GERD), depression, and skin cancer. The patient's additional surgical history included an implantable dual-chamber pacemaker placement and laparoscopic cholecystectomy. All of his past surgical procedures were performed under general anesthesia, and no complications were noted. The pacemaker was inserted because of a syncopal episode secondary to bradycardia 15 days after the heart transplantation. Medications included mycophenolate mofetil, tacrolimus, amlodipine, prednisone, pravastatin sodium, sulfamethoxazole-trimethoprim, valganciclovir, esomeprazole, venlafaxine hydrochloride, vitamin C, calcium, and docusate sodium. The patient took mycophenolate mofetil, tacrolimus, and amlodipine on the morning of surgery.

The physical examination of the airway showed normal findings. Laboratory findings that were within reference ranges included white blood cells, $6.3 \times 10^3/\mu L$; hemoglobin, 12.2 g/dL; hematocrit, 37.1%; platelets, 192

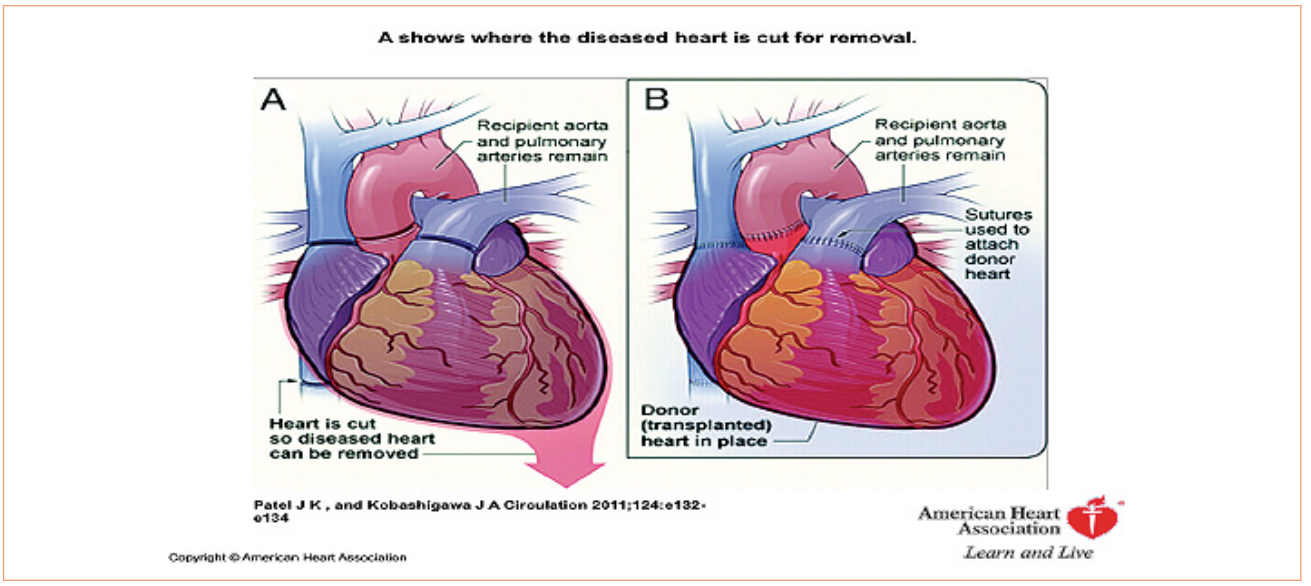

Figure. Image of Transplanted Heart
Note: **A** identifies the surgical dissection of the diseased heart.
B identifies the placement of the transplanted healthy heart and site of suture lines at the aorta and pulmonary artery.
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× 10^3 /µL; blood chemistry panel (sodium, 140 mmol/L; potassium, 3.9 mmol/L; creatinine, 0.53 mg/dL; glucose, 118 mg/dL); and coagulation studies (international normalized ratio, 1.1; prothrombin time, 14.1 seconds; partial thromboplastin time, 32.7 seconds). The transthoracic echocardiogram (TTE) obtained 1 month before the hernia procedure demonstrated a normal left ventricular size and function with an ejection fraction (EF) of 64%. Preoperative vital signs were a heart rate (HR) of 81/min and blood pressure (BP) of 112/59 mm Hg. The electrocardiogram (ECG) showed paced rhythm. The plan was to proceed with general anesthesia.

In the preoperative holding area, the patient's pacemaker was interrogated (setting was on DDD). The patient was given intravenous (IV) hydrocortisone, 100 mg, because of a possible decrease in adrenocorticotropic hormone and was premedicated with midazolam, 2 mg IV, to allay anxiety.

On the patient's arrival in the operating room, all standard monitors were applied, including a pulse oximeter, noninvasive BP monitoring, ECG monitoring in leads II and V, capnography, and nerve stimulator. The patient was preoxygenated for 5 minutes and received fentanyl, 50 µg IV. For the rapid-sequence induction, cricoid pressure was applied and propofol 200 mg IV was titrated followed by succinylcholine, 90 mg IV. The direct laryngoscopy was atraumatic, and the vocal cords showed a grade 1 view. The endotracheal tube was inserted successfully, with placement confirmation by positive end-tidal carbon dioxide and bilateral breath sounds. A single 8-mg dose of cisatracurium was administered IV before positioning the patient. Sevoflurane, 1.3% to 1.9%, was used as the anesthetic maintenance agent with 50% oxygen and 50% air. The patient's heart rhythm remained paced throughout the procedure, and minimal cautery was used by the surgeons.

Ondansetron, 4 mg, was administered IV 20 minutes before surgery completion. The neuromuscular blockade was antagonized using neostigmine, 3 mg IV, and glycopyrrolate, 0.6 mg IV. The train-of-four monitor revealed 4/4 twitches with a sustained tetany for 5 seconds. After pharyngeal suctioning and extubation criteria were met, the endotracheal tube was removed from the trachea. The patient was admitted to the postanesthesia care unit (PACU) and had an uneventful postoperative recovery. The serum glucose level in the PACU was 131 mg/dL. Pacemaker interrogation after the procedure did not show any alterations in the original setting. No anesthesia complications were noted, and he was discharged the next day.

Discussion

Knowledge of the physiological changes in the transplanted heart is essential to coordinate a strategy for the safe and effective management of these patients. Cardiac hemodynamics are greatly reconditioned following heart transplantation.[6,7] As an example of this patient's improved cardiac function, the TTE revealed an EF of 64% with no valvular abnormality. This is an improvement from his baseline TTE values before the heart transplant to include an EF of 15% to 20% with severe mitral insufficiency and aortic regurgitation. Although transplanted patients can present with more optimal myocardial function, anesthetists should carefully consider the effects of denervation, the anesthetic considerations (ie, preop-

Category	Normal heart	Transplanted heart
Innervation	Presence of sensory, sympathetic, and parasympathetic innervations	No sensory, sympathetic, and parasympathetic innervations
Resting HR	60-100/min	90-110/min (due to loss of vagal tone)
ECG	Normal sinus rhythm	May present with 2 P waves, common occurrence of atrial flutter or fibrillation
Response to hypovolemia	Increase in CO via neurohormonal stimulation (increase in HR and contractility)	CO is highly dependent on venous return (preload dependent)

Table 1. Physiological Comparison of Normal Heart and Transplanted Heart
Abbreviations: CO, cardiac output; ECG, electrocardiogram; HR, heart rate.

erative, intraoperative, and postoperative anesthetic management), the impact of immunosuppressant therapy, and subsequent patient immunosuppression.

• ***The Denervated Heart***. As a consequence of denervation, the transplanted heart has no sensory, sympathetic, and parasympathetic innervations.[3,4] Because the parasympathetic innervation that normally lowers the HR is not present, a higher resting HR for a heart transplant recipient is expected to be 90/min to 110/min.[4] Fallen et al[8] have shown that the mean HR in patients following human heart transplantation was increased compared with nontransplant cardiac patients (95.3/min vs 65.5/min).

During hypovolemia or hemorrhage, the transplanted heart responds by increasing stroke volume caused by circulating catecholamines. An increase in cardiac output is consequently dependent on the venous return, and this is the primary reason why transplanted heart patients are said to be "preload dependent".[3,9] This phenomenon is different in a normal heart, whereby the increase in cardiac output is accomplished by neurohormonal stimulation. When there is a decrease in blood volume, the normal heart will increase the cardiac output through an increase in HR and cardiac contractility.

Most posttransplant patients have an ECG demonstrating 2 P waves: 1 representing the recipient's own SA node and the other representing the donor's SA node. Although the innate pacemaker remains undamaged from the original heart, its electrical activity cannot be conducted through the suture line. As a result, the patient's own SA node has no impact on the chronotropic activity of the transplanted heart. This patient's ECG showed AV-paced rhythm throughout the case and did not exhibit 2 P waves. Table 1 shows the physiological comparison of the normal heart and the transplanted heart.

• ***Preoperative Management.*** The preoperative evaluation is essential to determine the safest anesthetic approach to the post-heart transplant patient. Anesthesia professionals should focus the evaluation on the current function of the heart through information on the level of exercise tolerance, evaluation of the TTE, and stress test findings, and/or they should request a cardiology consultation.[3] In this case, the TTE done 1 month before the hernia surgery showed good myocardial function without wall motion abnormality. Cardiac allograft vasculopathy was excluded by a normal myocardial biopsy specimen obtained 3 months after transplant. According to Ng and Cassorla,[10] vasculopathy is common in patients more than 1 year after transplant and is the most frequent cause of repeated transplantation or death after 1 year. The patient in this case was at risk of transplanted organ dysfunction. He was assessed for the presence of rejection and infection as possible complications of immunosuppression (Table 2). The highest frequency of rejection usually occurs within the first 3 months after transplant.[11] Because of this, the surgery was delayed for 4 months even though the hernia diagnosis was made 1 month after transplantation surgery. An interrogation of the pacemaker was also done preoperatively to determine the type of pacemaker and ensure that it was functioning properly. The pacemaker was placed 1 month after the heart transplantation because of an incident of bradycardia with syncope.

Shortness of breath
Fever
Anuria/oliguria
Fatigue
Fluid retention leading to weight gain
Cardiac allograft vasculopathy

Table 2. Signs of Organ Rejection[5,9]

Treatment with immunosuppressant medications (mycophenolate mofetil and tacrolimus) was continued as scheduled before the surgical procedure to maintain an optimum blood level and avoid possible organ rejection. Because heart transplant patients are often receiving corticosteroid therapy, it is important to provide additional glucocorticoids to those patients presenting on a long-term regimen of corticosteroids (5 mg/d of prednisone or an equivalent).[12] In this case, the patient had been receiving oral prednisone (10 mg/d), and hydrocortisone (100 mg) was administered IV preoperatively.

A variety of anesthetic techniques have been successfully used in posttransplant patients such as general anesthesia, regional anesthesia, and monitored anesthetic care. The need for muscle relaxation intraoperatively and

1. Assess current function of the transplanted heart: ECG, stress test, TTE, cardiology consult, recent cardiac catheterization, and myocardial biopsy
2. Look for signs of rejection and infection
3. Review important laboratory findings (hematology results, chemistry panel, coagulation studies)
4. Examine other organ involvement due to long-term use of immunosuppressant medications (using BUN, creatinine, AST, ALT, PT, INR)
5. Ensure proper function of pacemaker or implanted defibrillator
6. Do not stop immunosuppressive medications
7. Administer corticosteroid when applicable before induction
8. Standard premedication may be used unless contraindicated

Table 3. Preoperative Considerations

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, serum urea nitrogen; ECG, electrocardiogram; INR, international normalized ratio; PT, prothrombin time; TTE, transthoracic echocardiogram.

1. General, regional, or monitored anesthesia care may be performed[5]
2. Standard monitoring (dependent on the type of surgery, anesthesia approach, and equipment available)[9]
3. High-risk operation may require invasive monitoring (observe aseptic technique)
4. Laryngeal mask airway is not contraindicated
5. Slow induction is preferred; maintain preload (hypotensive episode may occur because of cardiac depressive effects of anesthesia)
6. Drugs with direct vasoactive activity or chronotropic effects are required
7. Morphine may have a relative contraindication for renal impairment due to the active metabolites (M3G and M6G)
8. Exercise caution with the use of NSAIDs (possible nephrotoxicity, GI bleed, and gastric dysfunction)
9. Initiate DVT prophylaxis such as sequential compression boots (increased risk of thromboembolism)[17]
10. Consider risk of airway obstruction due to posttransplant lymphoproliferative disease[18]
11. Be aware of infectious risk
12. Consider side effects of immunosuppressive regimen
13. Standard extubation criteria apply

Table 4. Intraoperative Considerations

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; GI, gastrointestinal; DVT, deep vein thrombosis; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide.

the potential for hypotension during regional anesthesia made general anesthesia the preferred technique for this patient. On review of the literature, there is no specific technique that demonstrates superiority over another in proceeding with cases similar to that of the patient. Table 3 summarizes the preoperative management of the patient with a transplanted heart.

• ***Intraoperative Management.*** The goal of the intraoperative management of patients with a heart transplant undergoing noncardiac surgery is avoidance of substantial hypotension, vasodilation, and an acute decrease in preload because of the importance of end-diastolic volume to maintain the cardiac output.[4,9] The use of standard monitoring is indicated and may vary depending on the type of surgery, anesthesia technique, and the patient's condition. Invasive CVP and arterial monitoring were not used in this case because of the patient's preoperative stability, minimal surgical risk, and the low possibility of massive fluid shifts occurring during the inguinal hernia repair. Tracheal intubation and laryngoscopy may not produce a sympathetic response because of the loss of cardiac baroreceptor reflex.[13,14] In this case, the patient did not demonstrate any hemodynamic changes before and immediately following the intubation. The BP remained stable at 110/60 mm Hg, and the HR was paced at 80/min. Because of the patient's history of GERD, a rapid-sequence induction was performed. A slow induction to prevent a hypotensive episode is preferred.

The choice of anesthetic agents used in this case was based on the renal and hepatic functions of the patient. Fentanyl was chosen over morphine because despite normal preoperative blood urea nitrogen and creatinine levels, the patient's long-term use of immunosuppressants could potentially cause renal insufficiency, which could lead to the accumulation of unfavorable metabolites such as morphine-3-glucuronide and morphine-6-glucuronide if morphine is used.[3] For muscle relaxation, cisatracurium was administered because of its organ-independent metabolic profile via Hoffman elimination. The anticholinesterase medications used to antagonize muscle relaxation such as edrophonium, pyridostigmine, and neostigmine do not demonstrate the normal muscarinic cholinergic response (ie, bradycardia).[3,5] However, a case study by Bjerke and Mangione[15] reported an incident of asystole after giving neostigmine in a heart transplant recipient. It is imperative to prepare for a profound cardiac response after administering anticholinesterase medications, despite surgical denervation.[15] Also, giving atropine or glycopyrrolate during bradycardia will not increase the HR because of denervation.[3,5] An experimental study by Bernheim et al[16] revealed a paradoxical response to atropine with development of atrioventricular block after heart transplantation. This patient was given neostigmine as the reversal agent, followed by glycopyrrolate, at the end of the case. Bradycardia was not observed because the patient was being paced throughout the surgery. However, if bradycardia had ensued, direct-acting vasoactive medications (epinephrine and isoproterenol) are more effective than indirect-acting vasoactive drugs such as ephedrine

Patient's drug regimen	Mechanism of action	Class	Side effects that have direct anesthetic impact	Black box warning
Tacrolimus (Prograf)	Inhibits T- lymphocyte activation Forms complex that inhibits calcineurin phosphatase Inhibits interleukin-2 gene expression in T helper cell	Immune suppressant, calcineurin inhibitor	Hypertension Diabetes Neurotoxicity Renal insufficiency	Increased susceptibility to infection Development of malignancies due to immunosuppression
Mycophenolate mofetil (CellCept)	Inhibits inosine monophosphate dehydrogenase Cytostatic effect on T- and B-cell lymphocytes	Immune suppressant	Anemia Leukopenia Thrombocytopenia	Increased susceptibility to infection Development of malignancies due to immunosuppression
Prednisone	Anti- inflammatory effects on organ systems	Adrenal glucocorticoid, endocrine-metabolic agent	Hypertension Diabetes Neurotoxicity	None

Table 5. Review of Immunosuppressant Therapy

because of the absence of catecholamine stores in myocardial neurons.[5,9] Low-dose epinephrine is also beneficial in hypotensive emergencies, and its availability is critical in the heart transplant patient. Also, because this patient was highly dependent on preload, a normal fluid maintenance was carefully carried out during the intraoperative period. This patient's hemodynamics remained stable throughout the case, and no direct-acting vasoactive medications were required. Table 4 summarizes the intraoperative anesthetic management of a patient with a transplanted heart.[5,9,17,18]

• ***Postoperative Management.*** The postoperative management of the cardiac transplant patient is not the same as the nontransplanted patient. In addition to routine postoperative care, an increased attention to the patient's vascular preload, renal function, and possibility of infection is recommended.[5] Knight and Morris[19] suggested that treatment with immunosuppressant drugs such as tacrolimus must be continued postoperatively, and blood levels are to be monitored. This patient was hemodynamically stable in the PACU. The IV fluids were maintained, urine output was adequate, and the tacrolimus level returned to normal at 12.5 ng/mL (reference range, 10-20 ng/mL). Overall, no anesthesia complications were noted.

• ***Immunosuppressant Therapy***. Immunosuppressive drugs are a standard regimen for the patient following heart transplantation to prevent rejection. Common drugs used are glucocorticoids, calcineurin inhibitors, and immune suppressant agents.[20] These medications function to prevent an immune response such as acute and chronic rejection and to minimize drug-induced toxicity such as neurotoxicity and nephrotoxicity.[21(p2178)] This patient had been receiving long-term treatment with prednisone, tacrolimus, and mycophenolate mofetil, causing him to be highly susceptible to the many potential side effects of these immunosuppressive drugs, which could have an impact on anesthesia management (Table 5). Nephrotoxicity can alter drug elimination, which necessitates the prevention of using medications that produce active metabolites such as morphine, meperidine, and nondepolarizing muscle relaxants. Cytochrome P-450 (CYP-450) enzymes metabolize tacrolimus. As a result, any anesthetic that inhibits or induces CYP-450 may affect the plasma concentration of tacrolimus. Barbiturates are known to induce CYP-450, thereby decreasing the blood level of tacrolimus. Propofol inhibits CYP-450, although it is unclear whether there is any clinical consequence.[21(p511)] The Food and Drug Administration reported an interaction between tacrolimus and propofol. The results suggested an incidence of respiratory failure in approximately one-third of patients with the concomitant administration of tacrolimus and propofol.[22] These data regarding respiratory depression can affect a patient's return to spontaneous breathing before extubation. No signs of impaired respirations were noted in this patient at the end of the case, extubation criteria were met, and the patient's postoperative course was uneventful.

Cyclosporine, another immunosuppressant with similar activity to tacrolimus, has been shown to interact with barbiturates, fentanyl, and isoflurane in animal studies.[23-26] In addition, some case reports[27,28] have shown an enhanced neuromuscular blockade with cyclosporine. Although further trials in humans are needed, these studies suggest careful consideration of the anesthetic agents administered to patients receiving

immunosuppressant therapy after heart transplantation. In this case, no altered effect of the anesthetic agents or neuromuscular blockade was noted.

Another impact of long-term immunosuppression is the likelihood of sepsis. Patients receiving immunosuppressant therapy do not manifest fever and leukocytosis as early symptoms of sepsis.[3] In heart transplant recipients, sepsis can advance quickly and must be promptly identified to properly treat.[6] According to Montoya et al,[29] infectious complications were a major cause of morbidity and mortality, second to rejection, based on 620 consecutive heart transplant patients. In this retrospective review, 1,073 infectious episodes were documented. The causative agents were bacteria (43.6%), viruses (41.7%), fungi (10.2%), P*neumocystis carinii* (4%), and protozoa (0.6%).[29] The patient in this case was carefully evaluated for any signs of sepsis throughout the perioperative course such as elevated temperature, elevated white blood cell count, and presence of chills or rigor. Strict universal precautions were practiced throughout the case.

Hypertension is one of the frequent side effects of immunosuppressant therapy. The patient in this case has a history of hypertension treated with amlodipine. Patients receiving calcium channel blocker medication (ie, amlodipine) as in this case are advised to continue their regimen before surgery to prevent hemodynamic instability.[30] This patient took his routine amlodipine dose on the morning of surgery. No hemodynamic alterations were noted.

In summary, following heart transplantation, the patient will perhaps have an adequate cardiac function similar to this case report. However, due to the alterations in the physiology of the transplanted heart, major consequences related to the denervation of the heart can occur perioperatively. Anesthesia professionals must have a sound knowledge regarding the newly established functions of a transplanted heart, its specific perioperative anesthesia considerations, and the pharmacologic effects of immunosuppressive medications. Furthermore, an understanding of the importance of preload dependence; proper administration of direct vasoactive drugs if needed; and awareness of infectious risk, potential for rejection, and possible side effects of an immunosuppressive regimen are essential to prevent perioperative complications.

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