Anesthetic considerations for the postcardiac transplant patient

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The first human heart transplant was performed in 1967. The low survival rates of the early transplant patients revealed that the surgical procedure was only a small part of successfully managing these patients. Patient outcome depended upon the interrelationship of surgery, immunology, pharmacology, epidemiology and oncology. A comprehensive understanding of the transplanted heart is essential to effectively plan the anesthetic management of posttransplant patients requiring any type of surgery. The transplant recipient has a healthy heart which utilizes different mechanisms to meet the body's requirements. The autonomic regulatory mechanisms are not available to prevent wide swings in the patient's hemodynamic state, and the stress response is slower than normally expected. Since cardiac parameters are significantly altered, patients may demonstrate decreases in systemic blood pressure and cardiac filling pressures. Compensatory maneuvers are delayed and reductions in cardiac output lead to lessened cerebral perfusion. Anesthetists must allow time for the denervated heart to compensate for these changes.

Pharmacologic intervention should consist of drugs with direct action on the myocardium and vasculature. Posttransplant patients are immunosuppressed and maintenance of a delicate balance is essential for survival. Protocols for immunosuppressive therapy must be individualized to achieve optimal effects. Cyclosporine plays a major role in immune system depression. Anesthetic management must compensate for alterations in hepatic and renal function, vascular integrity and cardiac function.

Strict adherence to aseptic technique helps reduce infections related to anesthesia management.

Key words: Anesthesia for immunosuppressive patients, anesthesia for postcardiac transplants, cardiac transplantation, denervated heart, postcardiac transplantation.

Historical perspectives

The history of cardiac transplantation dates back to the beginning of the twentieth century. In 1905, Carrell and Guthrie performed reliable vascular anastomoses, paving the way for organ grafting. Their early experiments demonstrated surgical feasibility of cardiac transplantation involving puppy hearts connected to the internal jugular veins and carotid arteries in adult dogs. Fifty years passed before the next major experimental breakthrough presented evidence that would eventually lead to human cardiac transplantation. Canine laboratory experiments were conducted by Lower and Shumway in the early 1960s. Their experimental work led to the design of a successful surgical technique, methods for cardiac preservation during coronary flow interruption, satisfactory posttransplantation function of an orthotopically placed denervated heart and approaches to controlling acute and chronic graft rejection. Their studies demonstrated that the transplanted denervated heart was capable of supporting normal activities.

The first human heart transplant was performed on December 3, 1967 by Dr. Christian Barnard in South Africa. Although the recipient died 18 days later from pneumonia, this was a major breakthrough in human transplantation. Low survival rates soon revealed that the surgical procedure was only a small part of successfully managing
these patients. The need for multidisciplinary relationships became apparent in the 1970s. Contemporary transplantation integrates medicine, surgery, immunology, pharmacology, epidemiology and oncology. The average cost for a heart transplant in 1988 was $57,000 to $110,000 according to the Health Resources Services Administration.3 (See Table I.)

### Table I

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<th>Year</th>
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In 1988, a total of 1,646 heart transplants were performed in the United States. At the authors' institution, the University of Pittsburgh Medical Center—Presbyterian-University Hospital, 50 heart transplants were performed in 1989. Presently, the one-year expected survival rate of the cardiac transplant recipient is greater than 80% with a five-year survival approaching 60%. More than 85% of the one-year survivors are rehabilitated to a satisfactory quality of life.4 With increasing survival rates, it is certain that anesthesia providers will encounter these patients for noncardiac related surgical procedures.

### Physiology of the denervated heart

A comprehensive physiological understanding of the transplanted heart is mandatory to plan the appropriate anesthetic management for this patient population.

The operative technique for cardiac transplantation described by Lower and Shumway in 1959 has remained standard over the past several decades with only slight modifications. They performed the surgical procedure by retaining a small portion of the recipient's left and right atria including the sinoatrial node tissue.5 The donor heart is excised also avoiding injury to the sinoatrial node and its blood supply.6 By excising the donor and recipient hearts at midatrial level, only a single continuous suture line is required for anastomosis.7 No electrical conduction will penetrate the suture line; therefore, the recipient's sinoatrial node does not initiate electrical stimulation in the transplanted heart. This function is now solely controlled by the donor sinus node. The clinician must recognize the donor heart now operates on the automaticity of the cardiac fibers themselves without any autonomic innervation. This has great implications for pharmacological intervention.

### Electrocardiographic interpretation of the denervated heart

All known dysrhythmias have been demonstrated and documented in the cardiac transplant recipient.6 Junctional rhythms are common immediately after cardiopulmonary bypass secondary to acute denervation, edema, surgical trauma and the possible direct cardiac depressant effect of most anesthetic agents.

The electrocardiogram may demonstrate two P waves since the sinoatrial nodes from both the donor and the recipient hearts are intact and functioning independently.

The atrioventricular conduction system is unaltered by the surgical procedure. A delay in sinoatrial-atrioventricular conduction in the early postoperative period may be a result of surgical damage or in the later postoperative period from rejection or arteriosclerosis. The presence of a new dysrhythmia must be considered rejection until proven otherwise.

### Dynamics of the denervated heart

Anesthesia providers must consider the functional dynamics of the transplanted heart and how it maintains a normal state of homeostasis. Cardiac transplantation recipients no longer have a sick heart. They have a healthy heart which utilizes different mechanisms to meet the body's requirements.

Preload augmentation and increased inotropy maintain normal hemodynamics in the cardiac transplant recipient. The initial changes in the myocardial contractile state follow preload augmentation from an increased venous return secondary to muscular activity. Further elevation of cardiac output occurs several minutes after being exposed to a stressful stimuli. There is a rise in the plasma catecholamine level resulting in increased inotropy and an elevation in both heart rate and cardiac output.

Curling concluded that the denervated heart exhibited a normal Frank-Starling effect. An increase in heart rate and contractility in response to stress is delayed until circulating catecholamine levels rise. Therefore, an initial increase in cardiac output is dependent upon an increase in venous return. Curling found intact alpha- and beta-adrenergic receptor activity without evidence of denervation hypersensitivity. Coronary artery flow...
of the denervated heart shows loss of basal alpha-adrenergic tone with a beneficial increase in the resting coronary flow. The coronary arteries remain responsive to adrenergic drugs and coronary spasm has been demonstrated in these patients.\textsuperscript{8} Kaplan reviewed sinoatrial node activity and found that donor-sinus response to exercise is markedly blunted. There is no donor-sinus response to hand-grip, Valsalva maneuver, cartoid sinus massage, atropine, tyramine and amyl nitrate. Kaplan also noted that posttransplant patients do not experience cardiac pain.\textsuperscript{1} It is crucial to realize that autonomic nervous system regulatory mechanisms are not available in preventing wide swings in this patient's hemodynamic state. Consequently, the stress response seen in this patient population will be slower than ordinarily expected. Upon initiation of exercise, the donor sinus node rate increases gradually, obtaining maximal levels toward the end of 10 minutes of a continuous steady stress effort.\textsuperscript{5} The deceleration phase after cessation of the stressor is also a gradual process. These patients often have increased filling pressures in order to compensate for the cardiac denervation.\textsuperscript{1} The altered response of the cardiovascular system must be considered for safe anesthetic management.

Many anesthetic agents are associated with altering cardiovascular properties, e.g., decreasing systemic vascular resistance, increasing venous capacitance and direct myocardial depressant effect. These reactions could lead to a drop in systemic blood pressure and reduction in cardiac filling pressures. The denervated heart is left without a rapid compensatory maneuver to increase heart rate unlike the normal heart utilizing the baroreceptor reflexes and sympathetic stimulation. A drastic reduction in cardiac output could result in minimal cerebral tissue perfusion. Careful, indepth planning is vital in choosing anesthetic techniques to optimally preserve cardiac output. Allowing adequate time for the denervated heart to compensate for these changes is critical.

**Cardiovascular drug effects on the denervated heart**

It may be necessary to administer pharmacologic assistance to the cardiovascular system in order to maintain a state of hemodynamic stability. Before rendering these supportive measures, the response of the denervated heart to cardiovascular drugs must be considered.

The anesthetist must choose drugs with direct action on the myocardium and/or the vasculature. Those drugs producing indirect actions on the myocardium will be ineffective or may result in unpredictable outcomes.\textsuperscript{7} An example of unpredictability is seen when hydralazine is administered to treat hypertension. Hydralazine will often produce a tachycardia as systemic vascular resistance falls, thus blunting its hypotensive effect to a certain degree.\textsuperscript{7} This reflex tachycardia will not be seen in the denervated myocardium, and the hypotensive effect of hydralazine may be greatly amplified.

Both labetalol and ephedrine can be incorporated effectively in the anesthetic regimen to treat an increase or decrease in blood pressure. The unique properties of labetalol as an antihypertensive agent exhibit both selective alpha-1 and nonselective beta-adrenergic blocking activities.\textsuperscript{9} The ratio of alpha to beta blockade is estimated at a ratio of 1 to 7 after intravenous administration, thus demonstrating a more potent effect on the beta blockade mechanism. The alpha and beta receptors are not hindered or altered by cardiac transplantation. Labetalol administration results in reduction of total peripheral resistance and plasma renin activity with little change in heart rate and cardiac output. Ephedrine may be useful when pharmacologic treatment is necessary for hypotension. Ephedrine stimulates both alpha and beta receptors. Its cardiovascular effects are similar to those of epinephrine, but action may persist up to 10 times longer. Clinical results of ephedrine administration are an increase in systolic and diastolic blood pressure, an increase in pulse pressure and vasoconstriction of the peripheral vasculature. Vasoconstriction augments venous return resulting in an increase in cardiac output and direct enhancement of myocardial contractility.\textsuperscript{8}

Common to all literature reviewed was that atropine, being a parasympathetically mediated drug, will have no effect in this patient population in treating bradycardia. The drug of choice for the management of bradycardia in the denervated heart is isoproterenol. Isoproterenol concentrates most of its action nonspecifically on beta receptors with little effect on alpha receptors. Its effects on the cardiovascular system include a decrease in peripheral vascular resistance with a fall in diastolic blood pressure, positive inotropic and chronotropic actions resulting in an increased cardiac output, increased heart rate and an increase in systolic blood pressure which may occur due to elevation of cardiac output.\textsuperscript{9}

In the management of tachycardia, the denervated heart will respond normally to propranolol, calcium channel blockers and any agents that act to decrease the circulating supply of endogenous catecholamines. Digoxin has been shown to have no immediate effect on heart rate or atrioventricular nodal conduction when administered acutely. However, when administered orally, long-term digoxin
causes a decrease in atrioventricular nodal conduction as in the normal innervated heart.

**Coronary artery disease and the denervated heart**

Studies at Stanford University revealed the tendency of cardiac recipients to develop an accelerated form of atherosclerosis involving the allograft coronary arteries. More than 75% of patients transplanted between 1968-1970 developed coronary arterial stenoses within one year postoperatively. The percentage was substantially reduced once measures were instituted to maintain a low fat/low cholesterol diet, initiate a regular exercise program and the use of long-term anticoagulation therapy. The outpatient management procedures of Stanford University School of Medicine, Stanford, California, require all patients to return at yearly intervals for comprehensive cardiologic studies which include catheterization, coronary arteriography and endomyocardial biopsy. Coronary bypass grafting, as a therapeutic choice of treatment in these patients, is impossible. As previously mentioned, the postcardiac transplant patient is more susceptible to atherosclerotic lesion formation but will not experience cardiac pain with anginal or ischemic changes due to the denervation of the heart.

If coronary artery disease (CAD) is suspected, other areas of cardiac function should be evaluated. Physical examinations should include protocol currently followed by cardiac specialists. Patients should be questioned about exercise limits, syncopal episodes and palpitations. The electrocardiogram (ECG) must be reviewed for any significant changes in rate/rhythm, presence and location of ischemia or infarct, and any arrhythmia. Further information and laboratory test results may be obtained through collaboration with a consulted cardiologist.

If findings support a positive diagnosis of CAD, the anesthetic management must be altered to allow compensation. Anesthetic management involves recognizing the importance of the balance between myocardial oxygen supply and demand in the presence of coronary artery disease. All factors increasing myocardial oxygen demand and those decreasing myocardial oxygen supply must be avoided.

In conjunction with the minimal monitoring equipment standard for general anesthesia, further invasive monitoring may be necessary for close evaluation of the patient's hemodynamic status, i.e., arterial catheter, central venous pressure catheter or a thermodilution pulmonary artery catheter, and urinary bladder catheter. The use of such invasive equipment must be weighed against the potential increased risk of infection related to their insertion. The decision is based on the patient's health condition and surgical procedure being performed.

**Immunosuppression and the anesthetic considerations**

Infection continues to be the major causative factor in posttransplantation morbidity and mortality. This patient population is at greater risk for serious complications from infection due to the immunosuppressed condition of their systems. Maintenance of a delicate balance of immunosuppression is one of the major determinants of survival following heart transplantation. An over-abundance of any one of the immunosuppressive drugs may lead to the complications of drug toxicity or infection, while less conservative therapy may result in rejection. Protocols are frequently altered and individualized to achieve optimal effects. Literature review found no data supporting the complete elimination of the immunosuppressant regimen without results of rejection and death.

The key to immunosuppressive therapy appears to be the ability to diagnose acute rejection episodes. Signs and symptoms of acute rejection include a decrease in the QRS voltage on the standard ECG, the development of atrial/ventricular arrhythmias and infiltration of myocardium by lymphocytes as seen on a biopsy report. Any of these findings provide rationale for delay or cancellation of the surgical procedure until further investigational measures are completed.

The immunosuppressive regimen for transplant patients currently focuses on the administration of the fungal metabolite, cyclosporine. Its utilization in cardiac transplant recipients began in 1981, and improvement in patient survival rates has been documented worldwide. Cyclosporine has primarily aided cardiac transplantation by decreasing the severity of rejection episodes. Approximately one to two rejection episodes occur in each patient following transplantation. However, the rejection episodes do not render the same level of severity as those preceding the cyclosporine era.

Cyclosporine is a cyclic polypeptide with high lipid solubility and poor absorption from the gastrointestinal tract. It is primarily metabolized by the cytochrome P450 liver microsomal enzyme system and excreted through the bile. Due to the unpredictable absorption, the patient's blood level should be closely followed by using radioimmune assay. Mechanism of action produced by cyclosporine reveals an inhibition of T-helper cell function with an increase in abundance of T-suppressor cells. The T-cells generally described are lymphocytes that are conditioned by the thymus and have acquired the ability to mediate delayed hypersensitivity and the rejection of foreign transplanted tissue. They play a major role by aiding the im-
mune system in defense against viral, fungal and certain bacterial insults.

Cyclosporine may or may not be administered intravenously (IV). When given IV, cyclosporine is a pressor and causes immediate vasoconstriction and hyperkalemia; it must be given slowly (2 mg/kg IV over one hour). Long-term toxicities include hepatic necrosis, chronic renal failure and hyperkalemia.1

The incidence of nephrotoxicity appears to be a dose-related and time-related result of cyclosporine therapy. Histologic changes in the kidneys present a loss of glomeruli with a significant decrease in glomerular filtration rate, reduced renal plasma flow and sclerosis within the kidney parenchyma. These findings result from chronic high-dose cyclosporine treatment and seem to have no correlation to alteration in cardiac output. If renal insufficiency is present, the anesthesia provider must consider strict fluid management, electrolyte imbalance, avoidance of anesthetic drugs relying solely on renal excretion and prolonged drug actions due to decreased elimination process.

Chronic arterial hypertension is commonly diagnosed in the cyclosporine-treated patient population and is often detected 2-3 months postoperatively. The mechanism is still not clearly understood but may be a secondary result of significant renal damage. Because of the uncertainty of origin, the hypertensive patient is often difficult to treat, requiring a combination of agents, such as vasodilators and false neurotransmitters. Some conditions have led to discontinuation of cyclosporine with institution of conventional immunosuppression with steroids.

Hepatotoxicity related to cyclosporine has been extensively studied in animals and reported in humans. The literature supports the need for serial liver function tests and possible adjustments in the cyclosporine regimen. If hepatotoxicity is present, the anesthesia provider must be prepared for alterations in anesthetic drug metabolism and excretion, coagulation complications and decreased drug protein binding.

As long-term survival rates continue to improve postcardiac transplantation, the oncogenic potential of the immunosuppressive agents becomes increasingly apparent. The present incidence of malignancy occurring in the postcardiac transplantation population is approximately 6%. Stanford University has found cardiomyopathy patients to exhibit immunologic abnormalities preoperatively, particularly in relation to suppressor cell function which may contribute to the apparent increased susceptibility for tumor development in these patients. The oncogenic potential of these patients does not significantly alter the anesthetic management, although it does emphasize the importance of minimizing the immunosuppressant therapy.

Three other immunosuppressant medications currently used with cyclosporine are azathioprine, methylprednisolone in the intravenous preparation with prednisone in the oral preparation and rabbit antithymocyte globulin.

Azathioprine is metabolized by the liver and acts as a false purine interrupting the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which is known to suppress antibody formation and exert an anti-inflammatory effect. Bone marrow toxicity resulting in leukopenia, thrombocytopenia and anemia has been demonstrated with the drug's chronic use, along with hepatic toxicity of hepatocellular and cholestatic types.

The steroid course involves methylprednisolone in intravenous preparation, which is later replaced with prednisone in oral tablets for long-term therapy. The side effects of steroids are numerous and include insulin antagonism, sodium retention and suppression of the hypothalamic pituitary adrenal axis making patients susceptible to Addisonian crisis in the event of sudden withdrawal. Also encountered may be Cushing's syndrome demonstrated by redistribution of body fat resulting in a moon face, buffalo hump, truncal obesity, supraclavicular fat pads, striae, thinning of the skin, ecchymoses, acneiform lesions, muscle wasting of the extremities, osteoporosis and necrosis.

The complications resulting from the steroid and azathioprine portion of the immunosuppressive therapy must be acknowledged. Considerations involve:

- Possible endotracheal intubation difficulties or airway management problems if Cushing's syndrome is present.
- Increased bleeding if coagulation studies are altered.
- Hypertension and difficulty with fluid/electrolyte balance if sodium retention or insulin antagonism exists.
- Hepatic and renal complications previously reviewed.

Currently, FK506 and other antirejection agents are being used experimentally at the University of Pittsburgh Medical Center. Early studies have shown them to be effective, but further research is required.

Aseptic technique is mandatory while managing this patient population. In particular, it is essential to avoid contamination of IV equipment by airway or enteric organisms. Good activity organization can prevent pathogens from being transferred by anesthesia personnel's manipulation of
patient, IV apparatus and airway equipment. Handwashing should be done before anesthesia care begins. Changing gloves after airway, nasogastric or excretion removal procedures may lower infection risks.

All procedures should be performed as aseptically as possible with proper disposal of contaminated equipment away from airway and IV preparation fields. Kaplan recommends all IV ports be capped or contain syringes to avoid contamination from fingers or resting surfaces. Drugs can more safely be administered through the luer connectors rather than the rubber ports located along the IV tubing sets.

Planning for infection control and exercising critical caution may be the most important factors to decrease infection complications.

**Outpatient management**

The average hospitalization period for the cardiac transplant recipient is approximately two months. The incidence of infection and rejection decreases substantially after the first two postoperative months, but continued close surveillance for these two potentially life-threatening complications must be strictly maintained.

Between the four to six month postoperative period, patients require biweekly evaluation. Outpatient clinical visits should include a thorough physical examination, chest x-ray, electrocardiogram and appropriate blood tests. Along with the x-ray results, regular sputum cultures are evaluated since most infectious complications are pulmonary in origin. Rapid and concise treatment is mandatory if results are positive with further investigation for the development of secondary complications. Endomyocardial biopsies with right-heart catheterizations are performed on a regular schedule to ensure early recognition and treatment of rejection.

**Summary**

Cardiac transplantation is no longer an experimental procedure. It is now accepted as a reliable therapeutic alternative for many individuals suffering from end-stage cardiac disease. Advances in the surgical technique, immunosuppression therapy and patient management have led to a greater prognosis and survival rate of these patients. As the number of patients receiving cardiac transplants expands, the anesthetic community becomes more likely to be confronted with one or more of these patients for a procedure other than open heart surgery. A comprehensive understanding of the transplanted heart is essential.

The transplant recipient has a healthy heart which utilizes different mechanisms to meet the body’s requirements. The autonomic regulatory mechanisms are not available to prevent wide swings in the patient’s hemodynamic state, and the stress response is slower than normally expected. Since cardiac parameters are significantly altered, patients may demonstrate decreases in systemic blood pressure and cardiac filling pressures. Compensatory maneuvers are delayed and reductions in cardiac output lead to lessened cerebral perfusion. Anesthetists must allow time for the denervated heart to compensate for these changes.

Pharmacologic intervention should consist of drugs with direct action on the myocardium and vasculature. Posttransplant patients are immunosuppressed and maintenance of a delicate balance is essential for survival. Protocols for immunosuppressive therapy must be individualized to achieve optimal effects. Cyclosporin plays a major role in immune system depression. Anesthetic management must compensate for alterations in hepatic and renal function, vascular integrity and cardiac function. Strict adherence to aseptic technique helps reduce infections related to anesthesia management.

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