A 41-Year old man with a history of idiopathic dilated cardiomyopathy is admitted to the cardiac care unit in a quaternary cardiac center for potential heart transplantation assessment. He has known systolic dysfunction, with an ejection fraction of less than 25/0 on transthoracic echocardiogram. Recurrent ventricular arrhythmias necessitated insertion of an implantable cardioverter defibrillator (ICD). Right heart catheterization revealed a pulmonary vascular resistance of 4 Wood units. Recently, his symptoms have been worsening and progressed to New York Heart Association (NYHA) class IV. During this hospital admission his clinical status continued to deteriorate necessitating the initiation of inotropic support and the insertion of an intraaortic balloon pump (IABP). He is subsequently placed on the transplant list, with high priority. However, due to further deterioration, consideration is being given to the insertion of a left ventricular assist device (LVAD) to maintain adequate end-organ perfusion while waiting for a donor heart to become available.

What are the criteria and contraindications for recipient selection?

It should be noted that indications/contraindications can be flexible and can vary from center to center. Criteria include the following:

- End-stage heart disease (New York Heart Association [NYHA] class III to IV) not responsive to medical management
- Physiologic age less than 65. However, in 2004, 8.3% of heart recipients were more or equal to 65 years of age.
- Maximal oxygen uptake less or equal to 14 mL/kg/minute (V02max) on a metabolic stress test. However, patients with V02max of 14 to 18 mL/kg/minute are more controversial. If these patients have other criteria that increase their potential mortality (very low ejection fraction, arrhythmia, hyponatremia), they may have greater consideration.

Contraindications
Absolute

a. Neoplasm, with the exception of skin
b. Acquired immunodeficiency syndrome (AIDS)
c. Multi-system lupus erythematosus or sarcoid
d. Fixed pulmonary hypertension: pulmonary vascular resistance greater than 400 dyne/second/cm$^5$ (5 Wood units)
e. Any systemic illness that would limit survival despite transplant

Relative

a. Age over 65
b. Peripheral vascular disease, carotid stenosis (depending on severity)
c. Human immunodeficiency virus (HIV), hepatitis B
d. Severe pulmonary disease
e. Diabetes with end-organ damage
   o Neuropathy, nephropathy, retinopathy
f. Psychosocial impairments
   o Drug or alcohol addiction, smoking, mental defect, history of noncompliance


**What are the criteria for donor heart selection?**

The limiting factor in heart transplantation is the shortage of donor organs. In the United States there are approximately 40,000 potential recipients from infancy to age 65, with approximately 2,500 donor hearts per year. Following establishment of brain death, organ harvest may be considered for the purpose of donation. The donor should not have sustained prolonged cardiac arrest, severe chest trauma,
intracardiac injections, septicemia, or excessive inotropic support. In all cases, a careful clinical examination of the potential donor is undertaken to rule out coronary artery atherosclerosis and contractile dysfunction-investigations may include angiography and echocardiography. The use of coronary angiography would be dictated by patient age, sex, and risk factors. Generally a contrast ventriculogram is avoided to reduce the risk of nephrotoxicity. Transplantation can proceed with mild left ventricular hypertrophy (LVH), however, wall thickness greater than 13 mm or electrocardiogram (ECG) criteria for LVH would make transplantation unadvisable. Generally severe congenital or valvular abnormalities would preclude donation, with the exception of abnormalities in which "bench" repair can be undertaken before transplant. ABO compatibility is important, as mismatch may result in hyperacute rejection. The donor body weight should be within 20% of that of the recipient. However, in the case of a small donor matching with body mass index (BMI) or height is more accurate than using weight. Preferably donor heart ischemic time should be less than 4 hours. Prolonged ischemic time may contribute to early allograft failure; however, techniques to allow improved tolerance of ischemia may be on the horizon. The use of non-heart-beating donors (NHBD) has been used successfully for nonthoracic organ transplantation. There is evidence that this approach may also be applicable to heart transplantation. However, at present there are a number of ethical, technical, and logistic hurdles regarding the use of NHBD for heart transplantation.


**What are the risk factors associated with posttransplant mortality?**
Overall survival at 1 year is 83%. Having congenital heart disease as the indication for transplant is a powerful predictor of postoperative 1-year mortality. In addition, the requirement of extracorporeal circulatory support, dialysis, preoperative mechanical ventilation, coronary artery disease (CAD) as the indication for transplant and being hospitalized immediately before transplant all are risk factors for 1-year mortality. Mortality during the first year is 1.4 times the next 4 years combined, so risk factors associated with 1-year mortality are powerful predictors of 5-year mortality. For those that have survived after 1 year, previous transplant, stroke before transplant, allograft vasculopathy during first year posttransplant, treatment for rejection in year 1, treatment of infection before discharge, human leukocyte antigen (HLA) mismatches, recipient age, donor age and recipient weight are risk factors for 5-year mortality. The most common causes of death are the following:

- Within 30 days posttransplant
  - Graft failure, multiorgan failure, non-cytomegalovirus (CMV) infection
- From 31 to 365 days posttransplant
  - Non-CMV infection, graft failure, acute rejection
- After 5 years
  - Allograft vasculopathy, late graft failures, malignancies, non-CMV infections


**When is combined heart/lung transplant indicated? What are the important differences?**

Congenital cardiac disease is the most common indication for combined heart/lung transplant. Other indications include primary pulmonary hypertension, cystic fibrosis, antitrypsin deficiency and other forms of lung disease, such as emphysema and idiopathic pulmonary fibrosis. The procedure is performed through a transverse thoracotomy incision and the donor heart/lungs are transplanted en bloc. Important postoperative problems include bleeding and reperfusion lung injury that may require nitric oxide (NO) or occasionally extracorporeal membrane oxygenation (ECMO). Survival
following heartlung transplant is 63%, 43%, and 28% at 1, 5, and 10 years respectively.


What are the medical and surgical alternatives to cardiac transplantation?

An ongoing worldwide shortage of donor hearts has meant increased pressure to medically manage patients with end-stage cardiac failure. As heart failure progresses patients may respond to a variety of medications. Angiotensin converting enzyme (ACE) inhibitors have been shown to improve symptoms and decrease mortality in patients with heart failure. Patients with severe forms of heart failure may also benefit from a low-dose aldosterone antagonist (spironolactone), with attention paid to potential hyperkalemia. β-Blockade with carvedilol, sustained release metoprolol or bisoprolol has been shown to reduce the risk of death. In addition, patients with advanced heart failure may reduce their risk of sudden cardiac death by the insertion of an implantable cardioverter defibrillator (ICD). Furthermore, ICD implantation can be combined with cardiac resynchronization therapy (biventricular pacing), which has been shown to improve functional class and survival in advanced heart failure, once patients have also achieved optimal medical management. Increasingly, ventricular assist device (VAD) implantation or semiimplantable pericorporeal devices are also finding a role in the management of these patients.


What are the considerations in anesthetizing patients for left ventricular device (LVAD) insertion
Significant cardiac abnormalities, for example, aortic insufficiency, patent foramen ovale, should be identified preoperatively and, if necessary, addressed at the time of surgery. Bleeding is a major problem in the perioperative management of these patients and adequate amounts of blood and blood products should be available. Many centers routinely give antifibrinolytics before LVAD implantation. Transesophageal echocardiography (TEE) is mandatory for LVAD insertion to assess for patent foramen ovale, to ensure aortic valve competence, assess adequate left ventricular decompression and to monitor right ventricular function. Inadequate rightsided heart function is a potential complication after LVAD insertion and can be treated with phosphodiesterase inhibitors and inhaled nitric oxide. Vasopressin and/or norepinephrine may be required to maintain adequate systemic vascular resistance postcardiopulmonary bypass.


Three weeks after insertion of a left ventricular assist device (LVAD), a donor heart becomes available.

**How would you assess this patient preoperatively?**

Prospective transplant candidates have usually been fully preoperatively evaluated by a multidisciplinary team including cardiology, pulmonology, and surgery, as well as anesthesia. In case of subsequent deterioration, however, the anesthesiologist should review the recipient's current cardiac status including medications and level of mechanical support, with particular attention to hemodynamic parameters and reversibility of elevated pulmonary vascular resistance (PVR). Pertinent anesthetic history, concomitant diseases and fasting status must also be ascertained. Baseline electrolytes, urea, creatinine, blood glucose, international normalized ratio (INR)/prothrombin time (PIT), complete blood count should be
obtained. In addition, specific preoperative investigations need to be reviewed such as pulmonary function tests, electrocardiogram (ECG) and chest radiograph. There are typically two types of patients presenting for heart transplantation. The first type of patient is "relatively compensated, requiring possible intravenous inotropic support or may even be ambulatory in a nonhospital setting. The second type is moribund and decompensated, requiring mechanical ventilation and/or mechanical circulatory support. At the time of transplant 47.9% of patients are on intravenous inotropes, 20.6% have a left ventricular assist device, 5.7% have an intraaortic balloon pump (IABP), and 2.5% are mechanically ventilated. Only 0.4% requires extracorporeal membrane oxygenation (ECMO) before transplant.

Recipients who have undergone prior cardiac surgery need to be identified as this will increase the surgical time to achieve cardiopulmonary bypass (CPB) due to adhesions and bleeding. Many centers will treat these patients with antifibrinolytics to attenuate the risks of bleeding. Large bone intravenous access must be secured and cross-matched blood should be readily available in the operating room before the commencement of surgery.


**What is the role of transesophageal echocardiography (TEE)?**

In addition to its potential role in assessment of the donor heart before harvesting, TEE may also be of benefit in the immediate posttransplant period. The echocardiographer can provide feedback to the surgeon and the anesthesiologist regarding overall function of the transplanted heart. In particular, wall motion abnormalities, end diastolic volume and valvular function can be assessed. Of particular interest are right ventricular (RV) function and an assessment of pulmonary artery pressures. TEE may also be useful in the assessment of surgical anastomosis, by an echocardiographer with advanced training. Specifically, the main pulmonary artery anastomosis should be evaluated for stenosis. The long axis view of the left atrium is composed of recipient and donor tissue and may appear large. If
excessive tissue is present, acquired cortriatriatum may develop due to an unfolding of redundant tissue.


What are the mechanisms of right heart failure?

Right-sided heart failure is an important cause of posttransplant morbidity and 'mortality. It has a diverse number of causes related to both increases in flow and resistance across the pulmonary vascular bed. One prime cause is long standing elevation in left ventricular pressure leading to an increase in pulmonary pressure and vasoconstriction. This pulmonary vasoconstriction may become fixed over time, compromising right ventricular (RV) function after transplant. However, a normal preoperative pulmonary vascular resistance (PVR) does not rule out the potential for RV failure posttransplant. Poor organ preservation and cardiopulmonary bypass (CPB) can also have deleterious effects of graft ventricular function.


How would you treat right heart failure following heart transplantation?

Right ventricular (RV) failure can lead to dilation, ischemia and poor contractility. This can result in a shift of the ventricular septum to the left, with a reduction in left ventricular filling and reduced cardiac
output (CO). Basic therapeutic goals are to maintain adequate coronary perfusion, optimize oxygen delivery, prevent further distention of the right ventricle by judicious use of fluids, minimizing myocardial oxygen consumption and reduce pulmonary vascular resistance (PVR) to decrease RV afterload. Phosphodiesterase inhibitors, such as milrinone, which have systemic and pulmonary vasodilatory effects in addition to positive inotropy, are particularly useful. Prostacyclin (PGI2), prostaglandin E1, isoproterenol (1 to 5 mg/minute), dobutamine and nitrates have also been used with success to treat transient increases in PVR. However, vasodilator use can often be accompanied by arterial hypotension, requiring the administration of vasopressors to maintain adequate coronary perfusion. Inhaled nitric oxide (NO) is also widely used as a selective pulmonary vasodilator, in severe pulmonary hypertension and RV failure. It should be remembered that simple management goals of avoiding hypoxia, hypercarbia, and excessive positive end-expiratory pressure (PEEP) will help avoid elevated PVR. In severe cases of refractory RV failure posttransplant, right ventricular assist device (RVAD) has been successfully used. Extracorporeal membrane oxygenation (ECMO) is also a potential option in refractory cases.


**How does inhaled nitric oxide (NO) work as a selective pulmonary vasodilator?**

The advantage of inhaled NO as a pulmonary vasodilator lies mainly in the fact that its smooth muscle relaxant effect is limited to the pulmonary vasculature—the half-life in vivo of inhaled NO is only a few seconds. Therefore it has little effect on the systemic circulation, unlike intravenous vasodilators such as nitroprusside, nitroglycerin, prostaglandins and calcium channel blockers. Furthermore, inhaled NO selectively causes vasodilation in ventilated lung units, therefore decreasing V/Q mismatch and shunt. Inhaled NO (1 to 20 ppm) can result in significant decreases in pulmonary artery pressure, pulmonary vascular resistance (PVR), and central venous pressure (CVP), while increasing mean arterial pressure (MAP), cardiac output (CO), and arterial oxygenation (Pao2). In addition, a transesophageal
echocardiography (TEE) documented alteration of the ventricular septal shift with a significant reduction in right ventricular (RV) chamber and tricuspid valvular annulus size can be seen.


Konstadt S. Nitric oxide: has it progressed from molecule of the year to wonder drug of the decade? J Cardiothorac Casc Anesth 1995;9(6):625-626

**What is the pathophysiology of the denervated heart?**

Following cardiac transplantation, the cardiac plexus is interrupted and the heart is denervated. The recipient atrium remains innervated but hemodynamically unimportant, whereas the donor atrium is denervated and is responsible for the electrophysiological responses of the transplanted heart. The electrocardiogram (ECG) often contains two P waves.

The denervated heart retains its intrinsic control mechanisms which include the Frank-Starling mechanism and intact α- and β-adrenoreceptor responses to circulating catecholamines. This denervated heart lacks the ability to respond acutely to hypovolemia or hypotension with reflex tachycardia, but responds to stress primarily by an increase in stroke volume. This reflects dependence of the sinus node on direct stimulation by endogenously released catecholamines and the absence of control through neural mechanisms. This is why heart transplanted patients are said to be "preload dependent". Interesting, however, some studies have demonstrated reinnervation within a year after transplantation. This has lead to symptoms of angina pectoris when ischemia develops in the transplanted heart.


Kobashigawa JA. Postoperative management following heart transplantation. Transplant Proc 1993;31:2038-2046
The patient recovers successfully following heart transplant. However, 2 years postoperatively he fractures his left radius after a fall. He presents for open reduction and internal fixation of the fracture.

**How would you monitor this patient?**

This patient should have similar monitoring requirements for non-transplant patients undergoing similar procedures. Patients who require invasive monitoring do so in keeping with a particular procedure, for example, arterial line for thoracotomy and open lung biopsy, central venous pressure (CVP) monitor for small bowel resection, or because the patient is unstable preoperatively. Smooth and safe anesthesia is contingent upon careful preoperative assessment that may reduce the need for invasive monitoring with all its attendant risks. Adequate preload must be attained preoperatively and intravascular volume status maintained intraoperatively because these patients are "preload dependent." Monitors in the case mentioned earlier would include, an electrocardiogram (ECG), noninvasive blood pressure cuff, capnometer, oxygen saturation probe and if general anesthetic was delivered a temperature probe and neuromuscular stimulator would be applied.


**What is the significant implication of the denervated heart?**

The denervated heart retains its intrinsic control mechanisms which include: Frank-Starling mechanism, impulse formation and conductivity and responsiveness to circulating catecholamines in the from of increased heart rate and contractility. But the normal respiratory variations or response to carotid sinus massage and Valsalva maneuvers are absent. At rest the heart rate reflects the intrinsic rate of depolarization at the donor sinoatrial node, and in the absence of any vagal tone, is faster than normal at approximately 90 to 100 beats per minute. The heart rate shows minimal response to
drugs such as muscle relaxants (pancuronium), anticholinergics (atropine, glycopyrrolate and scopolamine), cholinesterase inhibitors (neostigmine, edrophonium, pyridostigmine, physostigmine), digoxin, nifedipine, phenylephrine, or nitroprusside, but will respond to isoproterenol, ephedrine, dopamine, and glucagon. Cardiac dysrhythmias may occur in heart-transplanted patients. First-degree atrioventricular (AV) block is common. Dual AV nodal pathways are frequently observed, but reentry dysrhythmias are rare. Bradyarrhythmic therapy in these patients should be a direct β-adrenergic stimulating agent (epinephrine, isoproterenol). Glucagon is also useful as a positive chronotrope and inotrope. Medications used to treat tachyarrhythmias (calcium channel blockers, β-blockers) need to be used with caution due to their negative inotropic effects.
