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Cardiac transplantation

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Cardiac transplantation, first performed in 1966 by Christian Barnard in South Africa, remained relatively uncommon until the development of more effective antirejection drug regimens in the 1970s and 1980s, leading to an increase in the number of centers that performed the procedure. The Scientific Registry of Transplant Recipients reported that 2143 heart transplants were performed in the United States in the year ending June 30, 2003; more than 70% were carried out at centers performing fewer than 20 heart transplants per year [1]. There were 3841 patients on the waiting list for cardiac transplantation on June 30, 2003, highlighting the lack of sufficient donor hearts to meet the demand. The two most common forms of cardiac disease that lead to transplantation are ischemic cardiomyopathy and idiopathic dilated cardiomyopathy, which together comprise approximately 90% of cases. Less common forms of heart disease that have been treated with transplantation include viral cardiomyopathy, infiltrative cardiomyopathy, post partum cardiomyopathy, valvular heart disease, and congenital heart disease.

Results of heart transplantation

Treatment of patients with end-stage heart failure by heart transplantation is based on the assumption that their survival and quality of life after surgery are better than with conventional treatment. The prognosis of patients with congestive heart failure generally is poor, with the 5-year survival reported in one study [2] to be less than 30%. Nonetheless, significant advances have been made in the medical management of these patients over the past 10 years. As a result, the heart transplant waiting list mortality has decreased from 432 per

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1000 patient years in 1990 to 172 per 1000 patient years in 1999 [3]. At the same time, there has been an expansion in the selection criteria for donors to increase the number of organs available. These changes have shifted the selection of patients for heart transplantation toward higher acuity recipients while providing less ideal organs than in the past. Yet, despite these trends, the 1-year survival after heart transplantation improved from approximately 75% in the early 1980s to approximately 85% in the late 1990s [3]. The 10-year survival after heart transplantation at Stanford (Palo Alto, California) was reported recently at 40.6% [4]. The authors noted generally excellent functional status in these patients but found high incidences of medical problems including hypertension, malignancy, renal dysfunction, and graft coronary artery disease, which highlight the intensity and complexity of the medical management required by heart transplant recipients.

Recipient selection

Heart transplant recipient selection is based on an extensive multidisciplinary evaluation intended to assess the patients' disability and prognosis without transplantation and their ability to survive the procedure and comply with the required postoperative management. Most patients referred for evaluation have severely impaired left ventricular function, but occasionally patients with good systolic function also are referred for severe, intractable angina, unmanageable arrhythmias, or severe diastolic failure. Cardiac conditions amenable to other surgical procedures, such as valve repair and comorbid conditions that would exclude long-term survival after transplantation, should not be present. Heart transplant candidates are evaluated for significant pulmonary disease (including severe, irreversible pulmonary hypertension, which is considered a contraindication to heart transplantation), renal dysfunction, hepatic dysfunction, and active infectious disease before being listed for transplantation. Although there are no absolute age limitations, most centers do not consider candidates more than 65 years of age. A candidate selected for transplantation is placed on the list to wait for an appropriately sized and ABO type donor organ that matches the recipient. Patients awaiting heart transplantation are prioritized according to the level of medical support they require. Patients who can be managed successfully outside the hospital are the lowest priority. Intermediate priority is given to those requiring hospitalization and some continuous inotropic support. The highest priority is given to patients requiring high-dose inotropic support or mechanical support such as intra-aortic balloon counterpulsation or ventricular assist device.

Donor selection

Candidates who donate their hearts for transplantation must fulfill the criteria for brain death. They should have no known serious cardiac disease or refractory

ventricular arrhythmias. Usually candidates are less than 55 years of age, but older hearts are occasionally used because of the shortage of hearts available for transplantation. Assessment of a potential donor heart with echocardiography or angiography can be helpful, especially in older candidates. Donors should not have evidence of an active infectious process or malignancy and should not have had a prolonged cardiac arrest or required resuscitation. The final decision to accept a heart for transplantation is made at the time of harvesting after direct examination for previous myocardial infarction, trauma, and coronary calcifications.

Donor heart harvest

The medical condition or injury causing the brain death of the organ donor can result in significant metabolic and hemodynamic aberrations, making management of the organ harvest challenging for the anesthesiologist attending the procedure [5,6]. Invasive monitoring may be helpful in guiding fluid therapy and administering vasoactive drugs. In the early days of heart transplantation, the brain-dead donor was transported to the transplant center so that organ harvesting and preparation of the recipient could take place in adjacent operating rooms. Techniques for myocardial preservation now allow remote harvesting for up to 6 hours before reimplantation, greatly simplifying the logistics of heart transplantation. The heart is harvested through a median sternotomy. Just before excision, the donor is heparinized and then exsanguinated by opening the inferior vena cava inside the pericardial well. Once the heart stops ejecting, the ascending aorta is clamped and hyperkalemic cardioplegia solution is infused into the aortic root to produce asystole. The pulmonary veins, vena cava, pulmonary artery, and ascending aorta are divided, and the donor heart is removed and placed on ice in a sterile container to improve myocardial preservation. The heart is then transported to the recipient as quickly as possible. Usually, other organs such as the lungs, liver, and kidneys are taken after the heart.

Anesthetic preparations

Because the timing of heart transplants is determined by donor availability, the procedures occur on an emergency basis at all hours, and the preoperative evaluation and preparation of the recipient must be carried out expeditiously. There needs to be close communication between the team harvesting the donor heart and the team preparing the recipient. Ideally, to minimize the ischemic time, the recipient will be on cardiopulmonary bypass (CPB), with the recipient heart resected when the donor heart arrives; however, induction of anesthesia and making the incision in the recipient should not occur until the transplantation procedure is a full ‘‘go,’’ which does not usually occur until the harvesting team is in the operating room and has had an opportunity to actually examine the donor

heart to be certain it is suitable. Factors that need to be considered in timing the recipient operation include the distance and time it will take to transport the donor heart to the recipient and the time it will take to prepare the recipient (eg, whether the patient has had previous heart surgery and will take more time to open).

When evaluating the recipient, key points include the patient's feeding status (may need rapid sequence induction if full stomach), the current level of support needed for the cardiovascular system (drugs taken, infusions running, mechanical assist devices), and the presence and current status of implanted devices such as pacemakers or defibrillators. Recent deteriorations in cardiac function requiring escalating levels of support should be noted. Many patients with end-stage heart disease are undergoing anticoagulation with warfarin. If a recent international normalized ratio is elevated, fresh frozen plasma may be needed after CPB. Recent laboratory and chest radiograph results should be sought to assess renal, hepatic, and pulmonary function, which may be deteriorating secondary to low cardiac output.

Preparing for heart transplantation is similar to preparing for any cardiac case involving CPB, with a few special considerations (Box 1). Sterile technique is particularly important because the patient will be immunosuppressed post-operatively. Adequate large-bore intravenous access (typically more than one) and full hemodynamic monitoring with arterial cannula and pulmonary artery catheter are routine. Many anesthesiologists prefer when possible to place the arterial cannula and pulmonary artery catheter before induction so that a complete hemodynamic assessment can be made before and during induction of anesthesia. A long sterile sheath should be placed over the pulmonary artery catheter to allow its withdrawal from the heart before cannulation of the superior vena cava for CPB. If the hemodynamic status is marginal or tenuous, initiating or increasing inotropic support before inducing anesthesia should be considered. It is important to keep in mind that there is significant down-regulation of the β receptors in the recipient heart of most transplant candidates, which decreases the responsiveness

Box 1. Key points in preparing for a heart transplant

Antifibrinolytic administration (aprotinin or aminocaproic acid)
Anticoagulated with warfarin?
Antirejection drugs ordered?
Be prepared to deal with acute right heart failure
Cardiac reflex responses absent after CPB
Current level of cardiovascular support
Feeding status
Long sheath for the pulmonary artery catheter
Special antibiotics ordered?
Stable or deteriorating cardiovascular status?
Use direct acting cardiac drugs after CPB

to a given dose of β agonist drugs such as dobutamine and epinephrine. Because the donor heart will be denervated after CPB and bradycardia is a frequent problem, a direct-acting β agonist drug should be available. Many centers use isoproterenol for this purpose because of its lack of α and vasoconstrictive effects on the pulmonary vasculature, but dobutamine and epinephrine may be used as well. Heart transplant recipients receive antirejection drugs (eg, corticosteroids, cyclosporine, and azathioprine) preoperatively, and these should be given as ordered by the transplant team. In addition, special antibiotics may be ordered in consideration of the patient's immunosuppressed state.

When not contraindicated, transesophageal echocardiography (TEE) is used during cardiac transplantation at many centers. TEE provides valuable information about the recipient heart, such as the presence of intracardiac thrombus or patent foramen ovale, especially in patients who have been awaiting transplantation for some time and have not had a recent evaluation. TEE is also useful in maintaining a stable hemodynamic status before CPB by detecting early deterioration of ventricular function or increasing valvular regurgitation. TEE is also very helpful in weaning the patient from CPB and managing the hemodynamics of the donor heart.

Previous procedures

Some heart transplant candidates have had previous operations that have an impact on their transplantation. Previous heart surgery, most commonly coronary artery bypass graft, will lengthen the time it takes to prepare the recipient to receive the donor heart and increase the risk of bleeding during and after surgery. The usual precautions and preparations for repeated procedures such as multiple large-bore intravenous access, immediate availability of blood before sternotomy, and the application of external defibrillator patches are taken in these cases. At many centers, patients may have had ventricular assist devices (VAD) implanted to maintain them until a donor heart becomes available [7]. The time from VAD insertion until transplantation can vary from a few days to many months, and removing these devices along with the recipient heart can add considerable complexity and time to the procedure. Previous exposure to aprotinin needs to be considered because reexposure within 6 months increases the chance of anaphylaxis [8]. Readministration of aprotinin within this time should be done with extreme caution and only once CPB can be instituted expeditiously, in case of cardiovascular collapse. Some transplant candidates will have had pacemakers or cardiac defibrillator devices implanted. These patients should be interrogated before surgery to determine their status and settings. Generally, the defibrillator function of implanted cardiac defibrillators should be turned off before the operation begins to avoid malfunction from electrocautery interference. These devices are often surgically removed at the end of the operation after the chest has been closed.

Induction and maintenance

Ideally, the heart transplant recipient will be in the operating room with hemodynamic monitors in place when the harvesting team sends word to proceed with induction. Which drugs are used is less important than the way they are used, and the same principles apply as with any cardiac case with poor ventricular function. The key is to achieve a stable, sustainable hemodynamic state before starting surgery by adding or adjusting support. Many heart transplant patients will have recently eaten and need a rapid sequence induction to prevent aspiration. When full-stomach precautions are not needed, the induction should proceed slowly and cautiously. Etomidate may offer some advantage as an induction agent in terms of hemodynamic stability compared with thiopental and propofol [9]. These drugs are usually combined with a modest dose of opioid such as fentanyl and a neuromuscular blocking agent. Some anesthesiologists have successfully used a high-dose opioid induction with or without benzodiazepines for heart transplantation [10,11]. Hypotension caused by decreased vascular tone may be treated with α agonists such as phenylephrine, but drugs with positive inotropic effects (eg, epinephrine or norepinephrine) should be implemented quickly if the response is not satisfactory. Cautious use of the Trendelenburg position and volume administration may also be needed.

Maintenance of anesthesia before CPB may be accomplished with a combination of a potent inhalation anesthetic agent and modest doses of opioid or a high-dose opioid technique [12]. Most heart transplant recipients tolerate induction and maintenance of anesthesia before CPB without major untoward events. Some form of antifibrinolytic therapy (eg, aprotinin or aminocaproic acid) should be started before CPB in most cases. Heparin is administered when the heart is exposed before cannulation. The pulmonary artery catheter is withdrawn from the heart into the sheath before the superior vena cava is cannulated for CPB. Heart transplantation is carried out through a median sternotomy incision, using CPB in much the same way as other common cardiac surgical procedures are performed, such as coronary artery bypass graft and valve replacement.

Orthotopic heart transplantation

In orthotopic heart transplantation, the recipient's diseased heart is removed, and the donor allograft is inserted anatomically in its place. After the sternotomy, the ascending aorta is cannulated close to the aortic arch, venous return cannulae are inserted into both the superior and inferior cavae, and the patient is placed on CPB. The cavae are encircled with tourniquets to isolate all of the venous return from the heart, the ascending aorta is clamped close to the aortic arch, and the recipient heart is then excised. There are two techniques of orthotopic heart transplantation: the classic or biatrial method and the bicaval method. In the classic method, the recipient's right atrium is divided through the body, leaving its posterior aspect in situ (Fig. 1A). In the bicaval method, the recipient's entire

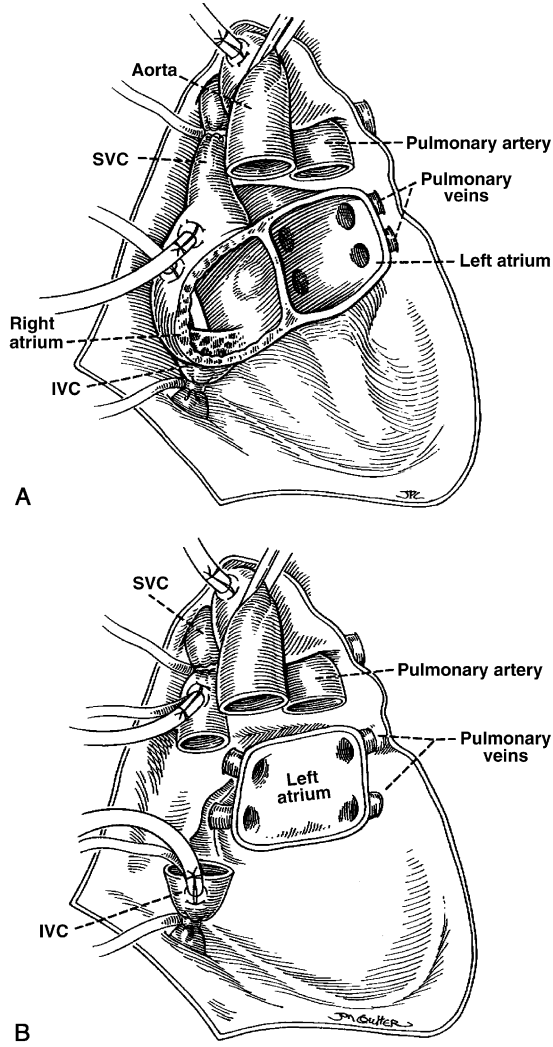

Fig. 1. Orthotopic heart transplantation. (*A*) Classic or biatrial suture line after removal of recipient heart. Posterior aspects of right and left atria remain in situ. (*B*) Bicaval suture line after removal of recipient heart. Entire right atrium is removed leaving only the posterior aspect of the left atrium in situ. *Abbreviations:* IVC, inferior vena cava; SVC, superior vena cava. (*From* Quinlan JJ, Firestone S, Firestone LL. Anesthesia for heart, lung, and heart transplantation. In: Kaplan JA, Reich DL, Konstadt SN, editors. Cardiac anesthesia. 4th edition. Philadelphia: WB Saunders; 1999. p. 993; with permission.)

right atrium is removed by dividing both the inferior and superior vena cavae proximal to the atrium (Fig. 1B). There is some evidence [13,14] to suggest that the bicaval technique may result in fewer postoperative rhythm problems and less tricuspid regurgitation. The left atrium is divided, leaving its posterior aspect and the pulmonary veins of the recipient in situ. The great vessels are then divided,

and the recipient heart is removed. The donor heart is then placed in the pericardial well and attached to the recipient with left atrial and right atrial (or bicaval) suture lines, and then the donor pulmonary artery and donor ascending aorta are anastomosed end-to-end to the recipient's artery and aorta. When the aortic anastomosis is completed, the aortic cross clamp is removed from the recipient aorta, ending the ischemic time of the donor heart.

Heterotopic heart transplantation

Heterotopic heart transplantation is a rarely performed procedure in which the recipient's heart remains in place, and the donor heart is attached to its right side so that the flow in each is in parallel, permitting the recipient's heart to continue to pump blood, particularly through the lungs (Fig. 2). This procedure is primarily reserved for patients with pulmonary hypertension as a strategy to avoid acute right heart failure in the unconditioned donor heart and in cases in which there is a marked difference in size of the donor and recipient [15,16].

Weaning from cardiopulmonary bypass

The heart transplant patient is prepared to come off CPB similarly to any other cardiac case. The patient is warmed, and the lungs are suctioned and ventilated. A

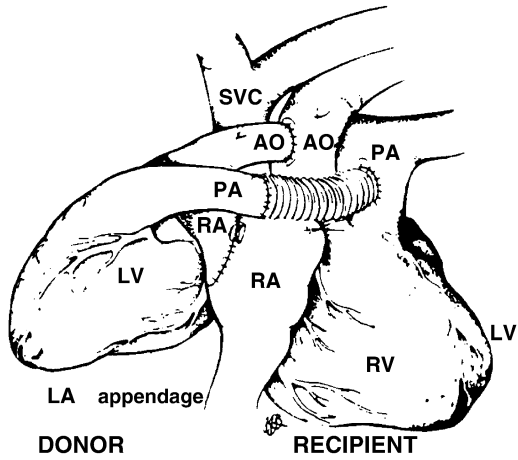

Fig. 2. Heterotopic heart transplantation. The entire recipient heart remains in situ, with the donor heart attached to its right side in such as manner that flow through the two hearts is in parallel. *Abbreviations:* AO, ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC superior vena cava. (*From* Cooper DKC, Lanza LP. Heart transplantation: The present status of orthotopic and heterotopic heart transplantation. Lancaster (UK: MTP Press; 1984; with permission.)

recent arterial blood gas result is reviewed, and abnormalities are corrected. Caval tourniquets are released, and suture lines are inspected for bleeding. The cardiac chambers are examined with TEE, and air-evacuating maneuvers are performed.

It is important to remember that the implanted donor heart is denervated so that reflex-mediated heart rate responses to hemodynamic changes will be absent, and drugs acting indirectly on the heart through the nerves will be ineffective. It usually takes several minutes for spontaneous rhythm to return in the donor heart after completion of the aortic anastomosis and release of the aortic cross clamp. Infusion of a direct-acting, chronotropic drug such as isoproterenol may be used to speed the process. It is sometimes possible to discern two sets of P waves after cardiac transplantation, one set from the donor heart and the other from the posterior walls of the recipient atria, which remain in situ. The latter set is isolated from the donor heart by the suture line and is of no consequence. Pacing may be needed, at least initially, to achieve an adequate heart rate, usually 90 to 110 beats per minute.

Vasoactive and inotropic drugs are used as needed to discontinue CPB after heart transplantation, much as in other types of cardiac operations. Short-acting, easily titratable drugs are used when possible. An indication of the vasomotor tone is given by the mean blood pressure at full flow on CPB. If the mean blood pressure is lower than 60 mm Hg, a vasopressor may be needed, but if it is above 80 mm Hg, a vasodilator is used. The condition of the recipient heart before CPB has no bearing on the contractility of the donor heart, which may range from excellent (requiring minimal or no support) to extremely poor (requiring maximum support). Generally, the longer the ischemic time of the donor heart, the poorer is its initial function. An infusion of isoproterenol initiated to increase the heart rate will provide significant inotropic support as well. Giving the donor heart a few minutes to recover before trying to discontinue CPB may be helpful, but the negative consequences of prolonging CPB need to be kept in mind. By gradually filling the heart and decreasing the CPB flow while carefully monitoring the arterial and central venous pressures and watching the right ventricle directly in the surgical field and the left ventricle with TEE, it is usually possible to determine whether more support will be needed. Once the majority of the venous return is passing from the right atrium through the right ventricle, it is usually possible to advance the pulmonary artery catheter into the pulmonary artery, a process that may be facilitated by TEE imaging.

Right heart failure

Failure to wean a heart transplant patient from CPB is most commonly the result of right heart failure, which is evidenced by low cardiac output in the face of rising central venous pressure [17]. The right heart can be seen in the surgical field to dilate and contract poorly. TEE shows a dilated, poorly contracting right ventricle and an underfilled, vigorously contracting left ventricle. Severe tricuspid regurgitation secondary to dilatation of the tricuspid valve annulus is

also often seen with TEE. Chronically elevated left-sided filling pressures from heart failure causing high pulmonary vascular resistance (PVR) in the recipient's lungs is an important factor contributing to acute right heart failure after transplantation. The donor right ventricle is unaccustomed to the high afterload and fails acutely. The right ventricle may also be more susceptible than the left ventricle to injury from the period of ischemia between the harvest and reperfusion.

Treatment of right heart failure during heart transplantation has two major components: decreasing the afterload the right ventricle must pump against (PVR) and increasing myocardial contractility. It is also critical, however, to maintain an adequate arterial blood pressure to ensure sufficient perfusion of the right ventricle [18]. Adequate oxygenation and ventilation must be assured to avoid the pulmonary vasoconstricting effects of hypoxia and hypercarbia. The preload of the failing right ventricle is optimized by careful administration of volume while monitoring the central venous pressure and using TEE to detect any increase in tricuspid regurgitation, an indication that the right heart is overfilled and distended. Vasodilators such as nitroglycerine, sodium nitroprusside, prostaglandin E_1, and prostacyclin may be infused to reduce PVR, but they also lower systemic vascular resistance and can cause hypotension. The phosphodiesterase inhibitors milrinone and amrinone increase contractility and decrease pulmonary vascular resistance but often require simultaneous infusion of a vasoconstrictor to maintain arterial blood pressure because they too lower systemic vascular resistance [19,20]. Some anesthesiologists prefer norepinephrine for this purpose because, in addition to an α agonist action, its significant β agonist activity may be additive to the positive inotropic effect of milrinone [21]. Vasopressin may be useful for severe hypotension not responsive to catecholamines [22]. The vasoconstrictors used to increase arterial blood pressure will also increase PVR, and achieving the proper balance of pulmonary and systemic vascular tone can be difficult. Other positive inotropic drugs such as epinephrine, isoproterenol, dopamine, and dobutamine may be used, depending on the heart rate and the vasomotor tone of a particular patient.

The need in certain situations to lower the PVR while maintaining systemic blood pressure has led to other therapeutic strategies. Theoretically, infusing a vasodilator into the central venous circulation and a vasoconstrictor into the left atrium can produce differential effects on the pulmonary and systemic vascular beds because of the rapid clearance by the pulmonary endothelium of catecholamines from the blood. This approach was used successfully to treat acute right heart failure with prostaglandin E_1 and norepinephrine in five patients undergoing mitral valve surgery [23], but an animal model found no significant difference in pulmonary vascular response to central venous and left atrial norepinephrine infusion [24]. More recently, inhaled agents have been used to achieve more selective pulmonary vasodilatation in cardiac transplantation. Inhaled nitric oxide (NO) is a potent vasodilator that has a selective effect on the pulmonary vasculature because of its rapid breakdown in the lung [25]. Administration of NO in heart transplant recipients with pulmonary hypertension has been shown to

reduce PVR and improve right ventricular function after CPB and may decrease the incidence of postoperative right ventricular dysfunction [26]. NO was shown to be more effective than intravenous prostaglandin E_1 for lowering PVR and facilitating weaning from CPB during heart transplantation [27]. There are concerns about toxicity for patients and health care workers exposed to NO [28], necessitating an elaborate device for its administration and monitoring and making its cost considerable. Iloprost, a carbacyclin analog of prostaglandin I_2, can be aerosolized and has been given in an inhaled form to treat severe pulmonary hypertension [29]. One study [30] showed that inhaled iloprost was more effective than low doses of NO in decreasing PVR without decreasing systemic blood pressure in heart transplant candidates. Iloprost has also been shown to decrease pulmonary vascular resistance in patients immediately after cardiac surgery, including heart transplantation [31]. The role of inhaled iloprost in treating acute right heart failure during heart transplantation seems promising, but further study is needed.

When cardiac failure after heart transplantation is severe and refractory to medical intervention, mechanical assist devices may be needed. Although it is usually believed to be a left heart assist device, intra-aortic balloon counter pulsation may be helpful in acute right heart failure by improving perfusion to the right ventricle and may provide the support needed until the donor heart function improves [32]. In cases with extremely poor ventricular function after transplantation, right, left, or biventricular assist devices may be needed to support the circulation depending on which ventricle is failing. The rationale of VAD insertion in this setting is that there may be a relatively quick recovery of ventricular function. One large center [33] has found that almost half of the patients requiring VAD support after heart transplantation can be weaned but usually within 4 days, after which time the prognosis is very poor.

Management after cardiopulmonary bypass

Once the heart transplant patient has been weaned from CPB and the caval and aortic cannulae have been removed, protamine is given to reverse the heparin. Many patients have post-bypass coagulopathy and may require transfusion of platelets, cryoprecipitate, or fresh frozen plasma. Diagnosis and treatment of this condition for heart transplantation is similar to other cardiac surgery procedures. Careful monitoring of the hemodynamics is continued through chest closure, and adjustments are made as needed in the support. Cardiac transplantation patients typically need chronotropic and inotropic support for a few days in the intensive care unit after which time the infusions are weaned as tolerated. Up to 25% of patients may require permanent pacemaker implantation to treat bradycardia after transplantation [34]. Once the patient has achieved stable hemodynamics and there is no significant bleeding, consideration can be given to decreasing sedation and weaning ventilatory support.

Postoperative care in the hospital involves continuation of antirejection therapy and careful observation for signs of acute rejection, which is best diagnosed by endocardial biopsy and treated by increasing immunosuppression until the rejection subsides. Biopsies are routinely performed every 1 or 2 weeks for the first few months after transplantation. After the early postoperative period, opportunistic infections become a more likely problem because of chronic suppression of the immune system.

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