Review Article

Invited Paper

PERSPECTIVES IN CARDIAC TRANSPLANTATION: OPERATIVE TECHNIQUES AND EARLY POSTOPERATIVE CARE IN CARDIAC TRANSPLANTATION

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INTRODUCTION

Although heart transplantation has become a popular therapeutic modality in only the last decade, the technical groundwork started in the early 1900s and spanned more than 60 years, ultimately leading to the first successful clinical orthotopic allograft heart transplantation in 1967(1-7). In addition to decades of work refining the operative technique, particularly over the last two decades, significant improvements in cardiac anesthesia and conduct of extracorporeal circulation, and better myocardial preservation techniques have all contributed to excellent operative outcome in heart transplantation. Today it is not unrealistic to expect a surgical mortality of well below 10%.

The following perspectives are based on the author's personal experience encompassing close to 400 heart and lung transplant cases as Director of the Heart and Lung Transplantation Programs at the Oregon Health Sciences University, in Portland, Oregon, U.S.A.

Timing and Logistic of Donor-Recipient Operations

With the scarcity of donors and the tremendous demand of organs, organ procurement is performed at distant donor sites and multiple teams are involved in the harvesting of multiple organs. Close attention to timing of recipient and donor operations in heart transplantation has never been more important. In order to achieve best functional results with the transplanted cardiac allograft, the total ischemic time should be kept to a minimum (8-9). Most centers have tried to keep this period to less than 4 hours, which translates into 3 hours of total transport time (approximately 2000 km of air travel) and an hour of implantation. For severely ill, hemodynamically unstable patients who otherwise might not survive, these time limits are generally extended. With an increasing number of recipients who have had previous open heart surgery (38% of cases at Oregon Health Sciences University), one has to allow additional time for meticulous cardiac dissection and have the recipient ready for cardiectomy as soon as the donor heart arrives. If one is to err in timing, it is best to have more time for the recipient in order not to have to rush the anesthesia and sternotomy in these patients because they are usually critically ill.

The Donor Cardiectomy

Since multiple teams are usually involved in the donor operation, the sequence of events should

be collectively reviewed before starting the procedure and intraoperatively all moves should be made in close collaboration with other teams (10-11). It is appropriate that the cardiac surgeon take the leadership role in the intraoperative management of the donor and direct the fluid and drug therapy as necessary. In extreme hemodynamic instability refractory to therapeutic maneuvers, the heart would take priority over other organs and would be harvested after notifying other teams working on the liver, kidneys, and so on.

It is desirable to have good control of the donor's hemodynamic status, which can be assisted by the use of large-bore intravenous lines, an arterial pressure monitor line and a central venous catheter. The cardiac surgery team may have to insert some of these lines before surgery in smaller hospitals with limited personnel and expertise in donor management.

The heart and other organs are approached through a long mid-line incision from the suprasternal notch to the symphysis pubis. The pericardium is incised and the mid-line incision is deepened in the area where the central tendon of the diaphragm fuses with its inferior surface. After pericardiotomy, the heart is carefully examined for evidence of contusion, coronary artery disease, valvular heart disease, or congenital anomaly. Sanguinous or serosanguinous effusion upon entry into the pericardial space might indicate myocardial trauma and injury.

Once the decision is made to use the heart, the ascending aorta and inferior vena cava are dissected free and controlled with tapes. The pulmonary artery is dissected free to its bifurcation. The superior vena cava is controlled with two heavy silk ties and dissected off the right pulmonary artery underneath it. Further dissection that might disturb the hemodynamic stability is not done and the circulation is supported while the abdominal organs are harvested. Just before harvesting of organs, 30.000 units of heparin are administered intravenously.

Proper myocardial preservation at the time of harvesting is obviously of utmost importance for good cardiac function in the recipient after transplantation. Methods that are used on a daily basis in open heart procedures are used during cardiac harvest and include hypothermia and cardioplegic arrest of the heart. Selective cardiac hypothermia decreases oxygen consumption significantly and this is further enhanced by chemical cardioplegia, since 80% of myocardial oxygen consumption arises from mechanical work (12-13). For this purpose we prepare a cold crystalloid potassium cardioplegia solution (Table-I). This solution is kept at 3° to 4°C before administration.

Table I. Oregon Health Sciences University cardioplegic solution.

Basic Solution	Ringers Solution
K^+ (mEq/L)	25
N^+ (mEq/L)	152
Ca^{2+} (mEq/L)	405
HCO_3 (mEq/L)	25
Glucose (mg/dl)	0.2
pH	7.8
Osmolality (mosmol)	360

When harvesting is begun, the superior vena cava is doubly ligated and divided between ligatures, then the inferior vena cava is clamped right above the diaphragm. The heart is allowed to beat and empty for a few seconds, then the ascending aorta is cross-clamped at innominate artery take-off and the cardioplegic solution (1000 ml) is infused into the aortic root. The right inferior pulmonary vein and the inferior vena cava are transected immediately. During cardioplegic solution infusion, approximately 8 to 10 L of ice-cold physiologic solution is used for topical cooling and bathing the heart. The aorta is transected at the origin of the innominate artery and the main pulmonary artery at its bifurcation. All pulmonary veins are transected and the specimen is removed, rinsed in two basins of balanced electrolyte solution, and packed for transport. Before transplantation the donor heart is prepared for implantation by incising across and connecting the pulmonary veins and trimming the excess left atrial tissue.

The superior vena cava tie is reinforced with a circumferential 4-0 polypropylene suture, as well as the cardioplegia administration site in the ascending aorta. The interatrial septum is inspected for presence of a patent foramen

ovale; if present, this is fixed to prevent a significant right-to-left shunt that might result from temporary right ventricular dysfunction, poor compliance, and elevated right atrial pressures.

In the early 80's, the author and his research team while at Thomas Jefferson University in Philadelphia, developed a chamber with a physiologic bath for a beating, auto-perfused heart-lung preparation. This "Jefferson Chamber" (cover photograph and Fig.I) was used to preserve the heart and both lungs for prolonged periods, with eventual successful transplantation in the laboratory setting. Though other centers in the United States used similar preservation techniques and portable systems for donor preservation, all these were eventually abandoned due to being cumbersome and their complexity. Today, the donor heart is flushed out with cold physiologic solutions and then stored in same and transported in an ice-chest for simplicity.

The Recipient Operation

The patient comes into the operating room after having received all immunosuppressive drugs

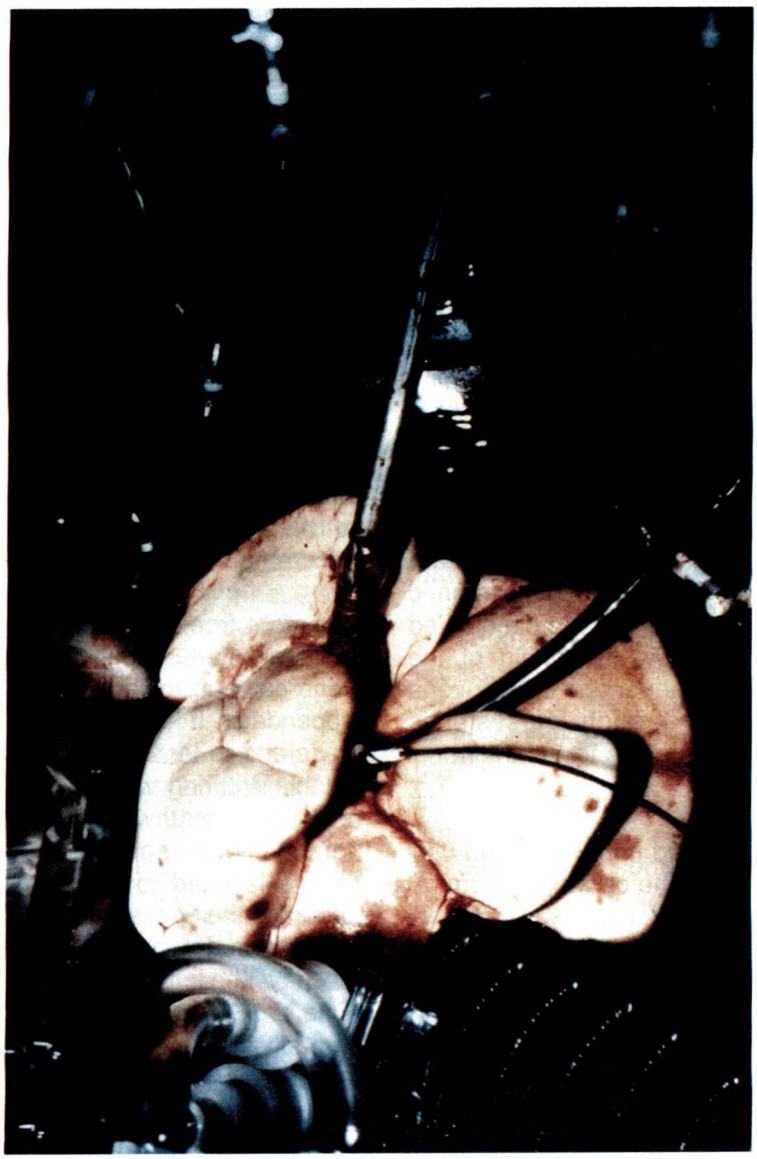

Fig.1: A working, auto-perfused heart-lung preparation in Jefferson Chamber

and prophylactic antibiotics. If a distant donor procurement is to be done, the patient is not anesthetized until the donor heart is visualized and examined. Timing is more critical when the donor is in the transplant hospital or within close proximity. In these cases, particularly if the recipient has had prior cardiac surgery, the recipient is anesthetized, prepped, and draped, and all is ready to make the incision once the donor heart is inspected. The recipient should have one or two large-bore peripheral intravenous catheters, a radial artery catheter, and a left internal jugular vein catheter. Strict sterile technique must be observed at all times during catheter placement. In critically ill patients who have hemodynamic instability, or when weaning from cardiopulmonary bypass is expected to be difficult, a balloon-tipped, flow-directed pulmonary artery catheter should be placed. This catheter can be preserved during cardiectomy and then replaced just before completion of right atrial anastomosis, and before pulmonary artery anastomosis. Postoperatively in patients who have demonstrated instability, this catheter has been invaluable in assessment and management of hemodynamics.

The recipient's heart is approached through a median sternotomy, the pericardial cavity is entered, and the pericardial edges are sutured to wound stockinettes. The aorta and superior and inferior vena cavae are circumferentially controlled with umbilical tapes. Tourniquettes are passed onto caval tapes. After systemic heparinization (3 mg/kg), the aorta is cannulated as distal as possible below the origin of the innominate artery. The superior and inferior vena cavae are cannulated through pursestrings placed on the right atrium close to the interatrial groove.

The recipient's heart should not be excised until the donor heart arrives at the operating room. At that point cardiopulmonary bypass is started, superior and inferior caval tourniquets are tightened down, and the ascending aorta is cross-clamped after the heart empties in a few beats. The core temperature is usually taken down to 26°C.

The native heart is excised starting with an incision at the base of the right atrial appendage on the right lateral wall of the right atrium and close to the atrioventricular junction. A small incision in the interatrial septum is made and a coronary suction catheter is introduced into the left side to decompress the left heart and facilitate the excision. The right atrial incision is carried downward and toward the left side and across the interatrial septum, making sure that the coronary sinus is left on the specimen side and that most of the interatrial septum is left behind. The aorta and the left pulmonary artery are divided close to the corresponding semilunar valves. The incision in the right atrium and the interatrial septum is carried on leftward to the dome of the left atrium and toward the base of the left atrial appendage. The left lateral wall of the left atrium is the last area that is incised, making sure that an adequate cuff of atrial tissue remains in front of the pulmonary veins for suturing without causing pulmonary venous obstruction.

The prepared donor heart is sutured starting with the left upper corner of the left atrial cuff and the base of the left atrial appendage of the donor heart. One arm of a 54-inch long double-armed 3-0 polypropylene suture is carried downward in an over-and-over fashion toward the diaphragmatic surface of the left atrium and then up to the mid-portion of the interatrial septum. The second arm of the suture is carried in a similar manner across the dome of the left atrium to the interatrial septum and this suture is secured on the outside of the left atrium.

The right free wall of the right atrium is incised obliquely starting at the lateral wall of the inferior vena cava up toward the base of the right atrial appendage. It is important to avoid the sinoatrial node and to leave enough of a cuff anteriorly to enable suturing without damage to the node or internodal pathways in the area of crista terminalis. A second 54-inch polypropylene suture is used to anastomose the donor right atrium to the right atrial cuff. This suture is started in the mid-portion of the interatrial septum and overlays the left atrial suture line to some degree. One arm is carried around clockwise to the right lateral wall of the right atrium and the second arm is carried around counterclockwise. This suture is secured on the lateral wall of the right atrium.

Although some advocated performing the aortic anastomosis next and then removing the cross-

clamp, the approach at Oregon Health Sciences University has been to attach the donor and recipient pulmonary arteries in a quiet, bloodless field while the clamp is still on. The anastomosis is started on the left lateral side of the arteries and carried around with a double-armed 4-0 polypropylene suture. This suture is left untied anteriorly to use later during the cardiac resuscitation period.

The aortae are sutured with a double-armed 4-0 polypropylene suture in a similar manner, starting at the left side of the aorta and moving in both directions. The suture is tied down anteriorly. During this anastomosis the patient is rewarmed to 37°C. A separate pursestring is placed at the highest point of the ascending aorta to introduce a large-bore needle to vent intracardiac air during ejection. Ventricular pacing electrodes are placed in the anterior wall of the ventricle. The heart is electrically fibrillated while the ascending aorta is vented and the aortic cross-clamp is removed. Caval tapes and tourniquets are removed; all intracardiac air is evacuated with aspiration of the right superior pulmonary vein and left ventricular apex. The heart is defibrillated while the ascending aortic vent is still open. Varying amounts of time (usually 15-20 min.) are allowed for the donor heart to recover while still on bypass. Quite frequently a continuous intravenous infusion of isoproterenol (0.005-0.01 μg/kg per min) is started to promote sinus rhythm and a heart rate of 100 to 110 beats/min. Infusions of dopamine, epinephrine, and nitroprusside are added as necessary in cases where right or left ventricular dysfunction or both are likely.

Once at 37°C, with normal sinus rhythm and good contractility, the patient is weaned off cardiopulmonary bypass. Protamine is administered to counter-effect the heparin. Decannulation and sternotomy closure are carried out in a routine manner. Two mediastinal drainage catheters and pleural catheters (if these cavities have been entered) are used. The usual cardiac implantation time is 45 to 50 min. and cardiopulmonary bypass time is 90 to 120 min.

Quite cleary, during harvesting of the donor heart and other organs and preparation of the recipient and the actual transplantation operation, there are many little details that must be meticulously attended to in order to secure successful outcome. Precise coordination, collaboration, and communication are never more important.

Reoperations

Most cardiac transplant services treat an increasing number of patients who have had prior cardiac operations due to coronary artery disease, valvular heart disease, or congenital heart defects.

If patients have been on sodium warfarin or heparin preoperatively, consideration should be given to using fresh frozen plasma in the pump prime solution.

Importance of meticulous attention to hemostasis at the time of sternotomy cannot be overemphasized. It is better to stop bleeding on the way in rather than on the way out. Electrocautery is used liberally throughout the procedure. Dissection is carried out to allow enough exposure of the right heart and the ascending aorta to cannulate and initiate cardiopulmonary pypass. In cases where an internal mammary graft is present, only minimal dissection is performed over the left heart. The left-sided dissection and separation of the aorta from the pulmonary artery can be performed once on bypass. The latter is easier once cardiectomy is done because the plane between the two vessels can be better identified. If one encounters multiple proximal vein graft anastomoses, the aorta is transected at the usual level and the proximal sites remaining on the aorta are oversewn. If there are dense adhesions in between the heart and pericardium or the adjacent lung due to felt pledgets, automatic defibrillator pads, electrodes, and so forth, thereby making dissection inordinately difficult, these could be left behind on the pericardium.

After discontinuation of cardiopulmonary bypass, one must be cautious in using blood and blood products. The pulmonary vascular resistance and right ventricular function are delicately balanced in most cases, and overzealous use of blood, fresh frozen plasma, or platelet infusions could tip this balance unfavorably. These should be given only if bleeding is truly excessive.

Early Postoperative Care

Hemodynamic Monitoring and Support

The most common cause of hospital death early after cardiac transplantation is acute right ventricular failure or global biventricular dysfunction with low output syndrome. In cases of early postoperative left or biventricular dysfunction, the cause is likely to be myocardial preservation and usually resolves within 48 to 72 hours. Conversely, patients with prior pulmonary hypertension and increased pulmonary vascular resistance are more likely postoperatively to develop right ventricular dysfunction. The therapeutic manipulations for these two scenarios may require vastly different approaches, which can be greatly facilitated by the use of a balloon-tipped, flow-directed pumonary artery catheter (now used routinely because of the higher risk patients and extended ischemic times). Ischemic injury results in myocardial edema, decreased compliance, and in more severe cases a reduction in systolic function. Both left and right ventricular filling pressures are elevated(14) and it is not infrequent that despite this, additional volume is required to optimize preload (sarcomere length) to improve cardiac output. If filling pressures are already excessive and poor cardiac output persists, a combination of inotropic support and vasodilator therapy is indicated (15-19). In most cases small doses of dopamine or dobutamine are adequate to maintain cardiac output. In patients with elevated systemic vascular resistance, small doses of sodium nitroprusside can be added (Table-II).

In patients with acute right ventricular dysfunction secondary to pulmonary hypertension, the state of the heart is similar to that seen with acute right ventricular infarction. The right ventricle is dilated with impaired contractility, right ventricular output is inadequate to fill the left ventricle, and hypotension ensues(20). In contrast with right ventricular infarction, the pulmonary vasculature is not normal and volume expansion results in additional distension of the right ventricle (which likely has some degree of preservation injury), and further deterioration of hemodynamics. In this case, the primary therapy is inotropic support. If blood pressure can be maintained, systemic vasodilators may be of some benefit for their effects on the pulmonary vasculature. In addition, some groups have used prostaglandin E infusions in this circumstance for more selective pulmonary vasodilation(21).

Table II. Intravenous agents used in the immediate postoperative period.

Adrenergic agents	A-Effect	B-Effect
Dobutamine (2-30 mg/kg/min)	+	++++
Dopamine (2-30 mg/kg/min)	++	+++
Epinephrine (0.025-0.25 mg/kg/min)	+++	+++
Isoproterenol (0.005-0.08 mg/kg/min)	-	++++
Vasodilators	Venous	Arterial
Nitroglycerin (0.3-6 mg/kg/min)	+++	+
Nitroprusside (0.3-8 mg/kg/min)	++	+++

Isoproterenol, a direct-acting beta agonist, is a commonly used drug. It increases the heart rate, causes peripheral vasodilation, and augments the cardiac output substantially. It is not unusual to continue an infusion of isoproterenol for 2 to 4 days postoperatively. In cases where heart rate is refractory to pharmacologic maneuvers, epicardial atrial and ventricular pacing is used to optimize heart rate.

When pharmacologic measures are inadequate in dealing with the low output state, a means of mechanical circulatory assist becomes necessary. The intraaortic balloon pump (IABP) is often extremely effective when the cardiac index is 1.0 to 1.8 L/m^2 and is secondary to biventricular dysfunction. IABP reduces both left ventricular afterload and preload with eventual reduction in myocardial oxygen demand. It augments the coronary blood flow by 30% to 35% by increasing diastolic pressure and improvement in zonal myocardial perfusion. It produces an average increase in cardiac output of 20% to 25% (22-23). In extreme refractory cases of low cardiac output, one might have to resort to the use of unilateral or bilateral ventricular assist systems and/or retransplantation.

Protective Isolation and Infection Control

Based on the initial Stanford experience, most centers used protective isolation to varying degrees. It is important to emphasize that there are currently no supporting data regarding the use of protective isolation in this patient population yet there are studies suggesting the lack of benefit for these procedures(24).

Other infection control measures include the rapid removal of intravenous, intraarterial, and bladder catheters and early extubation to prevent catheter and pulmonary infections. Vigorous pulmonary toilet and early ambulation are also used to prevent pulmonary atelectasis. Frequent surveillance cultures and prophylactic antibiotics to cover common skin bacteria are used in most centers covering the time that catheters are in place. Finally, some centers use prophylactic trimethoprim sulfa and cytomegalovirus globulin for patients at risk.

Immunosuppression

In general, after loading doses of immunosuppression are given preoperatively, it is the author's preference that all immunosuppression is administered by intravenous route in the first 48 to 72 hours to ensure adequate bioavailability. By administering cyclosporine (2.5-3.0 mg/kg) by continuous infusion over 24 hours, therapeutic levels are achieved rapidly and fluctuations are minimal during this time period. No evidence of excessive renal toxicity has been noted using this protocol. Most transplant centers, however, administer cyclosporine via the nasogastric tube immediately postoperatively.

In patients who have moderate or severe renal insufficiency in the immediate or early postoperative period, cyclosporine can be avoided by using the monoclonal antibody to CD3, OKT3. Cyclosporine is then instituted on postoperative day 11.

Miscellaneous Medical Care

Ventilator support with a volume-cycled mechanical respirator is provided for 12 to 24 hours with early extubation if possible. With careful monitoring of fluid status and arterial oxygenation, most patients can be weaned from the respirator within 24 hours of the transplant operation. After cardiac transplantation patients usually require 3 to 4 days in the intensive care unit, another week to 10 days on the hospital ward, and are usually ready for hospital discharge by postoperative day 12 to 14.

Most patients undergoing cardiac transplantation have intravascular as well as interstitial volume expansion. In addition, patients often receive fluid and blood products intraoperatively. As the peripheral vasodilatory effects of anesthesia wear off, to a variable degree, volume is shunted centrally, raising cardiac filling pressures. The maintenance of adequate urine output to compensate for excess volume is therefore required but can be further complicated by the renal vasoconstrictive properties of cyclosporine(25). In patients refractory to large doses of intravenous furosemide, intravenous ethacrinic acid in modest doses (50-100 mg) may be effective in the early postoperative period. Following daily weights is extremely imporant in deciding on the degree of diuresis.

Rehabilitation and Patient Education

All patients undergoing cardiac transplantation, by the nature of their underlying disease, have been sedentary and have suffered severe physical deconditioning. Most centers are therefore aggressive in instituting physical therapy early postcardiac transplantation in an attempt to begin to reverse the deconditioning process. It is not unusual for patients to be ambulating while still in the intensive care setting, and riding a stationary bicycle under supervision 4 to 5 days after the transplant operation. Physical therapy is continued for several weeks after transplantation.

Finally, patient education is instituted as soon as possible while patients are recovering from the operation. No patient is allowed to be discharged without first demonstrating a working understanding of cardiac transplant physiology (as it relates to exercise and daily activities), rejection and infection surveillance, and a complete understanding of the patient's medication dosages, schedules, and side effects.

Conclusions

Over a period of two decades, significant advances have been made in all aspects of cardiac transplantation, including better stabilization of transplant candidates in heart failure, advances in immunosuppression manipulation, and anesthesia in patients with severely compromised circulation. Refinement in operative techniques and better myocardial preservation methods have enabled rapid recovery of the transplanted heart and excellent graft function in most cases in the immediate postoperative period. With continued improvement in postoperative care and medical management of early graft dysfunction, hospital

mortality after cardiac transplantation has continued to decline and approaches levels enjoyed by routine cardiovascular surgery.

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