

Cardiopulmonary transplantation: current practice

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Abstract. Heart-lung transplantation has become an effective form of therapy for end-stage cardiopulmonary disease. Early results have steadily improved, and a 1-year survival rate of over 60% is now expected. The fact that lungs can be preserved for an extended period allows organs to be procured almost anywhere and this, in turn, has slightly improved the availability of organs for transplant. A diagnosis of lung rejection remains imprecise and progress still needs to be made in this area. Obliterative bronchiolitis of a variable degree remains the major medium-term complication, probably representing chronic graft rejection. Although long-term progress cannot yet be predicted, heart-lung transplantation remains the only option for a normal life for this special group of patients.

Key words: Heart - Lung - Heart-lung transplantation.

Certain aspects of heart-lung transplantation have changed rapidly in recent years. After the establishment of heart transplantation as a definitive form of treatment for end-stage cardiac disease, the use of combined heart and lung transplantation for terminal heart and lung disease has increased since its first successful clinical application in 1981 [22]. As early experience with single-lung transplantation had been disappointing, primarily because of failure of the bronchial anastomosis, it appeared that heart-lung transplantation would also become the procedure of choice for patients with end-stage lung disease without cardiac failure. Recently, however, encouraging results have been obtained with single-lung transplantation for noninfective fibrotic

lung disease [9] and with double-lung transplantation for other end-stage pulmonary conditions [26]. A choice of procedure allows the rationalization of transplant requirements for each patient and optimal use of available donor organs.

Although the early success of the clinical application of heart-lung transplantation is now an established reality, the long-term results and complications associated with each of these procedures cannot yet be fully analyzed. The high incidence of late pulmonary damage in heart-lung transplantation is a cause of concern and will probably also be seen in other forms of pulmonary transplantation, although the late results of these procedures have not yet been reported.

History

Prior to the establishment of a heart-lung transplantation program at Stanford in 1981, many attempts at experimental and clinical cardiopulmonary replacement had been made. In 1946, Demikhov [11] carried out heart-lung transplantation without bypass on 67 dogs, of which 2 survived for 5 days. Haglin et al. [17] and Castaneda et al. [6, 7] have demonstrated the ability of primates to breathe spontaneously after complete denervation of the lungs. Other workers had previously shown that lower mammals were incapable of a normal respiratory pattern following complete lung denervation. The first human heart and lung transplant was done by Cooley et al. [8] in 1968. Operating on an infant with a complete atrioventricular canal in which repair was not feasible, he carried out heart-lung transplantation with bilateral bronchial anastomoses. The child succumbed as a result of respiratory failure 14 h after transplantation.

Other clinical heart-lung transplants have been attempted by other groups [1, 24], but also with only very short-term survival. The introduction of cyclosporin and the development of a simplified operative technique allowed the Stanford group successfully to begin a clinical program of combined heart-lung transplantation in 1981.

Clinical single lung transplantation was first reported by Hardy et al. [18] in 1963. Many other surgeons then attempted this procedure, but there were no long-term successes. Up until 1983, of 38 patients undergoing single-lung transplantation, the longest survival was 10 months, 8 of which, however, were spent in the hospital [32]. Failure of these early clinical attempts was associated with sepsis and dehiscence of the bronchial anastomosis with or without the development of rejection. The steroid-sparing effect of cyclosporin and the ability to protect the bronchial anastomosis with a pedicle of omentum [23] has allowed the reintroduction of single-lung transplantation by the Toronto Group. A complementary omentopexy is probably also required to secure the tracheal anastomosis in double-lung transplantation, as the potential for a coronary-tracheal collateral circulation is lost with this procedure. Early clinical success with this procedure for end-stage pulmonary conditions has also recently been reported [26].

Recipient selection

The main experience in heart and lung transplantation has been with patients suffering from either primary pulmonary hypertension or Eisenmenger's syndrome. Further experience allowed the successful application of the technique in other forms of pulmonary vascular disease and in patients with end-stage chronic lung disease. In the future it may be possible to offer some of these patients double-lung transplantation alone, allowing the retention of the native recipient heart and thus reducing the risk of the accelerated atherosclerosis seen in cardiac allografts.

The selection of suitable recipients is critical. Potential candidates must have either a prognosis of less than 1 year or a markedly reduced capacity for exercise (New York Heart Association category III or IV). Young patients without evidence of concurrent systemic disease are most likely to survive the operation and to have a successful rehabilitation. Previous extensive thoracic surgery is a contraindication. The presence of coexistent systemic disease that may be independently life-limiting must also be regarded as a contraindication. Peptic ulceration,

bleeding diatheses, or abnormal renal or hepatic function are considered reasons for exclusion because of the need for perioperative anticoagulation and the postoperative administration of steroids and cyclosporin. The psychological status of the recipient is also of primary importance.

The heart-lung donor

The number of suitable organ donors for heart-lung transplantation is small. Occasionally, the situation arises where pulmonary but not cardiac function is well maintained following brain death but, more commonly, the converse is true. Our own experience suggests that suitable heart-lung donors represent 5%-10% of those appropriate for heart donation alone. The donor must be free of thoracic injury and infection, with a clear chest radiograph. Gas exchange must be adequate, and we stipulate a minimum PaO₂ of 100 mmHg on an FiO₂ of 40%. Cardiac function must also be well maintained without the need for major inotropic support. Matching of the donor and recipient depends upon ABO compatibility, height and weight similarities, and a comparison of the chest circumference and transthoracic diameters of the chest radiograph between donor and recipient.

Once a donor is provisionally accepted, close liaison is maintained between hospitals to maintain the donor organs in satisfactory condition prior to harvest. Fluid administration is kept to a minimum, replacing only urinary losses with a small additional amount for insensible losses. The central venous pressure should be maintained below 10 cm H₂O. If cardiovascular instability occurs due to massive diuresis, desmopressin may be given. Additionally, small doses of phenylephrine may adequately maintain the circulation until the donor operation is complete. The donor bronchial tree is given close attention. Pulmonary toilet using soft, sterile, rubber suction catheters is carried out regularly. Aspirates are sent for gram stains and culture. The final decision regarding donor suitability will be made by the harvesting team. Once this decision has been made, close liaison must be maintained with the recipient center in order to synchronize the preparation of the recipient with the arrival of the donor organs.

Donor operation

Following the mediastinotomy, the donor heart and lungs are carefully inspected. The great vessels are circumferentially mobilized and the thymus and

pericardium, including the phrenic nerves, are excised. Particular care is exercised in the dissection of the trachea to minimize the disruption of the collateral coronary tracheobronchial circulation. After the preliminary heart and lung dissection, kidney, liver, and pancreas donor teams mobilize the abdominal organs. Once the preparations are complete, organ removal is carried out, beginning with the heart-lung block.

Catheters for instillation of cardioplegia and pulmonary flush solutions are inserted into the ascending aorta and the pulmonary artery, respectively. The superior vena cava is ligated and divided and the inferior vena cava clamped. The aorta is cross-clamped and 1000 cc cold cardioplegia solution is administered into the aortic root. The pulmonary flush consists of 60 cc/kg cold modified Collins' solution infused over 4 min into the pulmonary artery with the aid of a single roller pump. Although other methods of organ procurement are in current use, the crystalloid flush technique is extremely simple and has given highly satisfactory results for ischemic periods of up to 4 h. During flush infusion, ventilation is continued with unwarmed room air but without any positive end expiratory pressure, aiding the distribution of the perfusate. Topical cooling by thoracic lavage with copious amounts of cold electrolyte solution is also done.

Once the cardiac and pulmonary infusions are complete, the trachea is clamped and stapled, with the lungs held in a state of 50% inflation. The trachea is divided above the stapling line, and the heart-lung block is removed by dividing the great vessels and using electrocautery to complete the dissection of the posterior mediastinum. Once out of the body, the organs are transferred to a cold electrolyte storage container for transportation.

Recipient operation

Following the median sternotomy, the pleural cavities are inspected for adhesions. The thymus is removed and the pericardium opened. A cardiopulmonary bypass using bicaval cannulation and ascending aortic return is set up and the patient cooled. The aorta is cross-clamped and the heart allowed to fibrillate. It is then excised in a manner similar to that used for heart transplantation, leaving a large aortic remnant and right atrial cuff. Each lung is removed separately after the construction of a pedicle consisting of a ribbon of pericardium carrying the phrenic nerves. The posterior wall of the left atrium is removed along with the pulmonary veins.

After removal of the diseased heart and lungs, the donor organs are brought to the operative field. Initially each lung is passed beneath the appropriate phrenic nerve pedicle into the respective pleural cavity. Implantation of the donor organs requires three anastomoses: tracheal, right atrial, and aortic. The tracheal anastomosis is carried out first, using a continuous 3-0 polypropylene suture. Subsequently, the right atrial and aortic anastomoses are carried out, again using single-layer, continuous polypropylene suture techniques. Once all anastomoses are complete, the heart is de-aired and the aortic cross-clamp is removed. Gentle ventilation with oxygen tensions not exceeding 40% enable the discontinuation of the bypass. A small dose of isoproterenol is commonly required to maintain a satisfactory donor heart rate.

Complications

The main technical difficulties of heart and lung transplantation are the removal of the diseased heart and lungs while effecting primary hemostasis, protection of vital nerves, and construction of a sound airway anastomosis. These complications will be discussed separately.

The use of dissection with electrocautery and the ligation of all bronchial arteries in the posterior mediastinum minimizes postoperative bleeding. Once the recipient organs have been removed, careful hemostasis must be accomplished since visualization after the new organs are in place may be impossible. Previous surgery enhances the chances of severe bleeding, which has led to a high early mortality in such patients and should be considered a contraindication for both heart-lung transplantation and double-lung transplantation. Postoperatively, attention is given to the coagulation profile, and necessary corrections are made by the administration of blood products. Reexploration is sometimes necessary, but the aim should be to ensure primary hemostasis.

It is mandatory to preserve the phrenic, recurrent laryngeal and vagus nerves during the dissection and removal of the recipient organs. A paralyzed diaphragm, atonic stomach, or paralyzed vocal chord is a source of major morbidity in the early and late postoperative period. A pericardiophrenic pedicle is constructed throughout the length of the phrenic nerves in order to protect them from injury. The recipient pulmonary artery is not completely removed. A button of pulmonary artery is left in the region of the ligamentum arteriosum to safeguard the recurrent laryngeal nerve. Retention

of the posterior pericardium and careful dissection in the vicinity of the esophagus prevents injury to the vagus nerve.

Before the introduction of cyclosporin, broncho-pleural fistula was a major cause of early death following single-lung transplantation [32]. The ability to avoid the use of steroids, which impair bronchial anastomotic healing following transplantation, has allowed a reduction in tracheal or bronchial anastomotic failure problems. In combined heart and lung transplantation, no additional measures to secure the tracheal anastomosis have been found necessary. The potential for a collateral coronary-bronchial and pulmonary artery-bronchial circulation may aid in the healing of the tracheal anastomosis [23]. Neovascularization from mediastinal tissue surrounding the tracheal anastomosis may also be responsible for improved tracheal healing associated with heart-lung transplantation. In single- or double-lung transplantation, tracheal anastomotic integrity is secured by the use of an omental wrap encircling the tracheal or bronchial anastomosis.

Early postoperative care

The immediate postoperative care of the heart-lung transplant recipient is similar to that required after routine cardiac surgery. The patient is allowed to awaken from anesthesia and is weaned from the ventilator after the first 24–48 h. Ideally, extubation should be achieved within this time to reduce the risks of exogenous pulmonary infection. A vigorous diuresis is maintained in the early postoperative period, using IV furosemide to achieve a negative fluid balance rapidly and return the recipients to their preoperative weight. Chest drains are not removed until at least 48 h postoperatively in order to accommodate the increased drainage associated with the posterior mediastinal dissection. Prophylactic antibiotics are given until the chest drains are removed.

Following extubation, oral nystatin and low-dose cotrimoxazole are given as prophylaxis against candidal and pneumocystic infestation. Patients are closely monitored for infectious complications, and reverse barrier nursing is continued until the patients are extubated and the chest tubes removed. In the denervated lung, secretions in the lower bronchial tree do not induce coughing. Active physiotherapy and expectoration exercises are therefore begun as soon as the patient has been extubated. Patients are mobilized as soon as feasible; they begin a rehabilitation program with increasing ambulatory exercise and cycle ergometry.

Immunosuppression begins preoperatively with an oral dose of 6 mg/kg cyclosporin and 2 mg/kg

azathioprine. Methylprednisolone, 500 mg, is injected IV at the time of organ implantation, and a further 375 mg is injected in divided doses over the first 24 h. Following this, steroids are not given until 2 weeks postoperatively to reduce their deleterious effects on tracheal healing. Cyclosporin is continued following the operation at a dosage adjusted to achieve whole blood trough levels of 200 ng/ml. After 2 weeks, prednisone is introduced at a dose of 0.2 mg/kg daily.

The diagnosis of rejection following heart-lung transplantation is difficult. The initial promise of the endomyocardial biopsy as a monitor of lung rejection has not clinically been confirmed. Asynchronous heart and lung rejection has been documented both in experimental models [28] and clinically [15], and the diagnosis of lung rejection remains imprecise by current methods. The appearance of the chest radiograph is clinically most sensitive although not specific for the changes of rejection. An early pulmonary infiltrate may represent infection, rejection, or the implantation response [29]. The implantation response is now less commonly seen. Occurring 1–5 days after transplantation, it appears to represent the edematous pulmonary response to denervation, the disruption of lymphatic drainage, or inadequate preservation. Its management consists of the promotion of a diuresis to minimize any hydrostatic component. This dehydration may result in hypovolemia and renal insufficiency, and cyclosporin dosage must be carefully monitored. The presence of infection is excluded by means of negative viral, bacterial, and fungal cultures of bronchial secretions. Infections must be treated according to the results of culture and sensitivity, and if doubt exists, broad-spectrum antibiotic cover is advisable.

Viral infections, especially reactivated or donor-transmitted cytomegalovirus disease, have produced a fulminant picture of pulmonary infiltration and worsening respiratory failure in the early weeks after transplantation, and constant vigilance for this pathogen must be maintained [27]. Increasing antibody titers and the ability to detect cytomegalovirus-associated antigen rapidly in bronchoalveolar lavage fluid allow a diagnosis to be made [5]. There has been increasing evidence from other solid-organ transplantation that prophylaxis against cytomegalovirus by treatment with acyclovir and hyperimmune globulin may reduce the impact of this serious infection [25, 30]. In addition, the therapeutic use of ganciclovir for cytomegalovirus has shown promising results. Drug-induced neutropenia, however, may occur [12].

The exclusion of infection or the implantation

response as a cause of radiological opacity allows a diagnosis of acute rejection to be made more firmly. Rejection is characterized by fever, leukocytosis, and pulmonary infiltrates on the chest radiograph. The X-ray changes may appear much worse than would seem compatible with the degree of dyspnea experienced by the patient. Bronchoalveolar lavage, although important in the diagnostic evaluation for infection, has been rather unhelpful in the differentiation of infection and rejection. Transbronchial biopsy is also of little value. Open-lung biopsy may occasionally be necessary, although its use is not without attendant risks to the immunosuppressed patient. Acute rejection is initially managed by optimization of both cyclosporin and azathioprine therapy. If this fails to produce an adequate response, 1000 mg methylprednisolone is injected IV for 3 days. In refractory cases, antithymocyte globulin may be necessary to reverse the process.

Results

In both the Stanford and Pittsburgh series, operative mortality has been directly related to inadequate hemostasis [14, 19]. The risks of previous cardiothoracic surgery were well demonstrated. If the immediate risks of surgery are overcome, successful rehabilitation can be anticipated. Overall, a 1-year survival rate of over 60% should be anticipated [13]. Close surveillance for infection or rejection is maintained following the patient's discharge from the hospital. After 1 year posttransplantation, near-normal pulmonary function is seen, apart from a mild restrictive ventilatory defect, which is probably associated with postoperative chest wall rigidity rather than pulmonary changes. An improved quality of life and exercise tolerance have been clearly documented following heart-lung transplantation [31].

Ominously, late changes in pulmonary morphology have been found in up to 50% of recipients in the Stanford series, although to a lesser extent than documented in the Pittsburgh experience [4, 16]. The morphological changes consisted of an obliterative bronchiolitis [2], and these changes reportedly seem to occur together with an accelerated atherosclerosis of the pulmonary and coronary circulations [10]. Controversy exists as to whether this represents a process of rejection or some other etiology. Primate heart-lung autotransplants do not seem to manifest changes of obliterative bronchiolitis [20], although this has been documented in canine lung autotransplants [21]. The condition is preceded by repeated episodes of apparent chest infections, although sputum and bronchoalveolar lavage cultures may be negative. Viral and bacterial

pathogens have been found in biopsy and postmortem specimens. Previous cytomegalovirus infection would seem to increase the risk of occurrence of obliterative bronchiolitis.

Functionally, obliterative bronchiolitis presents as a mixed obstructive and restrictive ventilatory defect. Hypoxemia is uniform. Chest radiography may be normal, although on occasion peribronchial thickening and lower-zone micronodular opacification may be seen. Symptomatically, the patient suffers increasing exertional dyspnea, which may progress rapidly. Early treatment by augmented steroid dosage may reverse the symptoms and functional changes, but relapse may occur [3]. In late cases, an inexorable decline in pulmonary function occurs and consideration of retransplantation must be given, especially as accelerated graft atherosclerosis occurs simultaneously. Those patients not afflicted with this condition can expect to have a continually improving quality of life. Investigation into the causes, prevention, and treatment of this complication is continuing in order that the early promise of heart and lung transplantation may be fulfilled.

In the long term, heart and lung transplant recipients can expect to suffer a number of complications also seen after heart transplantation alone. These include accelerated graft atherosclerosis, renal failure secondary to chronic cyclosporin toxicity, and the long-term effects of steroids, such as osteoporosis, obesity, and glucose intolerance. Further progress is also necessary in a number of areas in order to reduce perioperative mortality. The supply of donor organs must be increased and the methods of detecting rejection and preventing long-term complications improved. Some alternatives to long-term cyclosporin therapy are required to prevent the long-term nephrotoxic effects of this drug.

Despite these requirements for further improvement of this therapeutic maneuver, combined heart and lung transplantation has provided, for the first time, a method of treating irreversible pulmonary failure with or without cor pulmonale. The dramatic benefit sustained by the majority of patients provides an adequate stimulus to continue to refine this technique such that it benefits a larger population of patients.

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