

92 Heart and lung transplantation

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FURTHER READING

FURTHER READING

Miller L, Birks E, Guglin M et al . Use of ventricular assist devices and heart transplantation for advanced heart failure. *Circ Res* 2019; 124 (11): 1658–78. - Vieira JL, Mehra MR. Heart transplantation candidacy . *Curr Opin Organ Transplant* 2021; 26 (1): 69–76. Young KA, Dilling DF . The future of lung transplantation. *Chest* 2019; 155 (3): 465–73.

Future perspectives

Future perspectives

Contemporary immunosuppressive therapies and modern surgical and perioperative techniques have all contributed to improved outcomes. The principal innovations being investigated for the future are aimed at increasing donor availability and improving the long-term survival. Xenotransplantation has been extensively investigated with the use of transgenic pig hearts. In 1964, Hardy performed a xenotransplant using a chimpanzee heart that beat for 90 minutes before failing, and in 1984 infant Stephanie Fae Beauclair (often referred to as Baby Fae) famously lived for 21 days after receiving a baboon heart. Gene-editing techniques that allow modification of antigen expression are among the biggest technological breakthroughs to support the resurgence of xenotransplantation. Knockout pigs that lack swine leukocyte antigens to reduce organ immunogenicity have led to pig-to-primate allograft survival of up to 945 days. Despite the technical and scientific challenges the first contemporary pig-to-human transplant was undertaken in 2022 at the University of Maryland, USA, with good early clinical xenograft function using a pig heart with 10 genetic modifications, including four knockouts (three responsible for rapid antibody-mediated rejection of pig organ and one to prevent excessive growth) and six human genes added to increase the likelihood of acceptance. Rejection in the medium and long term and the hazard of infection transmission with porcine retroviruses remain of concern. The problems faced by xenotransplantation could be overcome by organ engineering. Decellularised extracellular matrix scaffolds of hearts can be created by removing cellular tissue then repopulating with autologous cardiac cells. Automatic contractility has been demonstrated. In addition to finding new sources of donor organs, improvement of long-term survival remains a priority. New agents to - more favourable side-effect profile remain under investigation. The induction of tolerance of the recipient immune system to donor antigens has promise and T-cell co-stimulation blockade, mixed chimerism (recipient bone marrow engraftment with donor bone marrow cells) and regulatory T-cell infusions are being studied. Personalisation of current immunosuppressants to individual patients may allow for adjustments based on molecular diagnostic techniques to increase efficacy and - reduce side effects. Future perspectives

Bioengineered artificial lung technology using recipient cells grown onto a decellularised lung scaffold is under development and will avoid an immune response; however, it remains a long way from clinical reality. Success would permit lung transplantation without the need for immunosuppression, waiting lists or rejection. Artificial lungs, mimicking the success of VADs in heart transplantation, remain elusive. The physical volume of membrane oxygenators is too great for implantation within the thorax and devices are not durable, lasting weeks rather than months or years. Membranes are thrombogenic and high levels of anticoagulation would be required.

HEART TRANSPLANTATION

HEART TRANSPLANTATION

The incidence of heart failure is increasing as the population ages and coronary artery disease, hypertension and obesity rise. Current medical therapy, including resynchronisation pacemakers and implantable defibrillators, is effective in improving symptoms and survival but many will develop end-stage disease for which heart transplantation remains the gold standard surgical treatment. Experimental procedures by Demikhov in the 1940s and the xenotransplantation of a chimpanzee heart into a patient with intracardiac thrombus by Hardy in 1964 led Lower and Shumway at Stanford University, CA, USA, to demonstrate that the circulation could be maintained entirely by an orthotopically transplanted heart. The first clinical heart transplant was undertaken in 1967 by the South African Christian Barnard, but mortality remained very high until the advent of modern immunosuppressants. Heterotopic heart transplantation, in which a donor heart is transplanted as a biological biventricular assist with the native heart remaining in place, was first used clinically in 1974 but is now seldom used as long-term survival is poor.

Heart retrieval

Heart retrieval

After exposing the heart by median sternotomy and opening the pericardium the organ is thoroughly inspected for contractility and coronary artery disease. Heparin is administered (300 U/kg) and a cannula placed into the aorta. The venae cavae are then occluded, the aorta cross-clamped and cardioplegia administered to arrest and cool the heart. The inferior vena cava (IVC) is vented. When the lungs are retrieved the pulmonary artery will also have been cannulated and the left atrial appendage incised. Cardiectomy is then carried out by dividing the superior vena cava (SVC), removing the cross-clamp and dividing the aorta and pulmonary artery at the bifurcation. The inferior vena caval incision is completed and the heart lifted to expose the inferior wall of the left atrium, which is then circumferentially incised to explant the heart. The interatrial septum is inspected to rule out a patent foramen ovale and all valves are carefully examined. The heart is then placed in a bag filled with cardioplegia solution at 4°C. Two additional sterile bags are wrapped around it. These bags are then placed in a sterile container and then in a cooler for transport.

Figure 92.3 An organ care system that allows retrieved hearts to be perfused with warm oxygenated blood and remain beating during transportation to the recipient hospital. Devices can shorten ischemic time and may be beneficial in higher risk patients. They have facilitated highly successful donor circulatory arrest heart donation to expand the donor pool.

Heart-lung transplantation

Heart-lung transplantation

Combined heart-lung transplantation is an excellent treatment for PAH (Figure 92.10). However resolution of right ventricular dysfunction has been observed consistently after bilateral lung transplantation, making it the favoured option in the vast majority of patients. Currently, the main indication is in congenital heart disease with pulmonary hypertension. Early post-transplant survival remains lower than after lung transplantation. After a peak of activity in the late 1980s, the number of procedures has steadily declined to less than 100 per annum. Organ allocation systems are weighted towards directing hearts and lungs separately to urgently listed patients, making combined heart-lung donor blocks a rarity for these patients.

Introduction

Introduction

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LUNG TRANSPLANTATION

LUNG TRANSPLANTATION

Pulmonary transplantation has made significant advances since the first human lung transplant performed by James Hardy in 1963 in Mississippi, USA. Mortality and morbidity remain high, in part because lungs remain exposed to the environment through the airway. - For patients with end-stage pulmonary disease, lung transplantation can significantly improve both survival and quality of life. Approximately 80% of lung transplants are bilateral, with single-lung transplants and living related lobar transplants undertaken less often. Long-term outcomes for all recipient pathologies are superior with bilateral lung transplantation. Single-lung transplantation cannot be used in diseases where infection may remain in the other lung, such as in cystic fibrosis (CF) or bronchiectasis. -

Learning objectives

Learning objectives

To recognise and understand: The indications and contraindications to transplantation of the heart and lungs The selection of recipients

Lung retrieval

Lung retrieval

Flexible bronchoscopy is first performed to clear mucopurulent secretions or aspiration. After median sternotomy and exposure of the lungs in each pleural space, detailed inspection is carried out for masses, consolidation or contusion. Uniform atelectasis. Lung compliance is also assessed by observing lung deflation when disconnected from the ventilator. Heparin is administered and the main pulmonary artery cannulated. Prostaglandin E (500 µg) is then injected to induce pulmonary vasodilatation and 3 litres of a cold pulmoplegia preservative infusion is initiated. The left atrial appendage is incised to vent the effluent while the lungs are also topically cooled with saline. Lung ventilation continues during flushing to improve fluid distribution and prevent atelectasis. The pulmonary artery is then divided proximal to the bifurcation and the left atrium is incised to create a cuff of left atrium on each side, into which the two pulmonary veins drain. Division of the pulmonary ligament on each side allows the lungs to be removed after inflating them to 25 mmHg and stapling the trachea, the lungs remaining inflated for transportation. A 500-mL retrograde pulmoplegia infusion is carried out into each pulmonary vein to augment preservation and flush out clots from the vasculature. The lungs are then placed into a bag containing pulmoplegia and double-bagged for transport within an ice-packed cooler. Lungs are more resistant to warm and cold ischaemic times and safe transplantation can be undertaken with preservation times of 6–12 hours. As in heart transplantation the use of DCD donors has expanded the donor pool. After the declaration of death the lungs are rapidly retrieved. Lungs are resistant to the effects of warm ischaemia much more so than the heart and outcomes are equal to those obtained with DBD donors. The avoidance of the catecholamine storm and associated inflammation associated with brain death may be particularly advantageous in these cases. The technique for DCD lung retrieval is somewhat different. Five minutes after the declaration of death, bronchoscopy is performed and the lungs inflated. After rapid chest entry the pulmonary artery is quickly cannulated, the left atrium quickly inspected for abnormalities and topical hypothermia is accomplished with ice slush to limit the warm ischaemic time. Most donors involve controlled withdrawal of treatment (Maastricht 3) but uncontrolled DCD (Maastricht 2) donation where failed resuscitation from unexpected cardiac arrest with a declaration of death is followed by heparinisation, the in situ cooling of the lungs and insertion of chest drains with consent for donation and organ retrieval has been shown to be efficacious in Spain. The use of ex vivo lung perfusion (EVLP) is recommended to allow for assessment. Ex vivo lung perfusion This technique involves placing donor lungs into a machine at the recipient centre; the lungs are ventilated and perfused with an electrolyte and protein solution for 2–4 hours, sometimes longer. This permits the reconditioning and evaluation of lungs that may not appear to be useable for transplantation in the first instance. Treatments may be administered that can optimise graft function, such as antibiotics, steroids and immunomodulatory drugs, and biomarkers for poor outcomes can be detected. EVLP may be used for logistic reasons to reduce ischaemic time and in the future it may permit ex vivo therapeutic interventions such as gene therapy. By using perfusates with an

optimised colloid osmotic pressure, pulmonary oedema can be reduced, thereby improving gas exchange. The lungs can be monitored on the device for the development of changes in compliance, airway pressure, pulmonary vascular resistance and perfusate oxygenation. Bronchoscopy can be performed to resolve areas of atelectasis (Figures 92.6 and 92.7). - -

Figure 92.6 Ex vivo lung perfusion. The lungs have been explanted from the donor but may be borderline for acceptance for transplantation. Perfusion, bronchoscopy and ventilation in the system can recondition lungs to a useable state to permit the transplant to proceed. Ventilator Temperature probe in the open left atrium Pressure measurement PA LA Reservoir Leukocyte /f_i lter Haemoconcentrator O , N , CO 2 2 2 Pump Oxygenator Temperature

probe HCU

Figure 92.7 Schematic of a typical ex vivo lung perfusion circuit. HCU, heater-cooler unit; LA, left atrium; PA, pulmonary artery.

With this technique, lungs can be evaluated for function and quality between donation and transplantation with 35–97% of initially unacceptable lungs being used successfully with 5-year mortality rates equivalent to those of conventional transplantation, although some studies have suggested an increase in postoperative ECMO requirements and longer intensive care unit stays. A different EVLP system that involves a portable organ preservation system taken to the donor hospital rather than the recipient hospital has also been shown to have favourable safety and efficacy. Trials have been completed in which EVLP was used in standard criteria donors to assess whether this would lead to improved outcomes but no benefit was demonstrated.

Figure 92.8 The clamshell thoracotomy commonly used for bilateral lung transplantation. Bilateral anterior thoracotomies through the fourth or fifth intercostal space are connected by division of the sternum. This facilitates excellent visualisation of the thorax

Operative technique

Operative technique

Coordination between the retrieval team and the implanting team is of paramount importance to minimise ischaemic time and the duration of cardiopulmonary bypass. A median sternotomy incision is performed and the aorta, SVC and IVC are encircled. After heparin administration the to establish cardiopulmonary bypass. Blood is drained from the ca vae into a reservoir, then oxygenated, cooled to 32°C and returned via a roller pump to the ascending aorta to perfuse the bod y while the heart is excised and the transplant performed (Figure 92.4). Carbon dioxide is insu ffl ated into the pericardial cavity to reduce the risk of air embolism. When the donor heart arrives in the operating theatre, the recipient aorta is cross-clamped and the heart excised by dividing the SVC, IVC, aorta and pulmonary artery . The left atrium is incised, leaving a cu ff of atrium into which the f our pulmonary veins drain. After administering a dose of cardioplegia to the donor heart, the left atrial cu ff is anastomosed, followed by the pulmo - nary artery , aorta and both cavae. Donor and recipient vessels are trimmed to obtain a perfect match in ter ms of length and width. A vent is placed in the ascending aorta for de-airing and the cross-clamp is removed, allowing reperfusion of the heart (Figure 92.5). Steroids are usually administered to reduce rejection. Sinus rh ythm is usually restored but temporary pacing wires are sutured to the heart for heart rate control. After a period of reperfusion (20 minutes for each hour of ischaemic time) to allow myocardial r ecovery , the new heart can be separated from cardiopulmonary bypass gradually , until it has taken over the circulation. Nitric oxide is useful at this stage to reduce pulmonary vascular resistance and protect the right ventricle from dysfunction. Isoprenaline is commonly infused. A transoesophageal echocardiogram can help to assess biventricular function and valvular competence.

Oxygenator Right atrium Reservoir

Figure 92.4 Cardiopulmonary

bypass is used in heart

transplantation and sometimes in

lung transplantation. Blood is

drained from cannulae in the superior and inferior venae cavae to a reservoir, then oxygenated in a membrane oxygenator before return to the ascending aorta via a roller or centrifugal pump. The patient can have their circulation maintained with oxygenated blood while the heart or lungs are explanted during transplantation.

Operative technique

The decision as to whether to use extracorporeal support during the transplant in the form of cardiopulmonary bypass or ECMO during bilateral lung transplantation varies with institutional experience, intraoperative stability and patient selection. Cannulation can be achieved either within the thorax or peripherally via the femoral vessels. A clamshell thoracotomy incision (Figure 92.8) through the fourth or fifth intercostal space is often favoured with division of the sternum, but the procedure may also be performed using separate bilateral sternum-sparing anterior thoracotomies or via median sternotomy . After opening both pleurae the pericardium is opened in preparation for central cannulation and to aid with hilar dissection and retraction of the heart. There are often significant adhesions in the pleural spaces that need dissection, although care not to injure the phrenic or vagus nerves should be exercised. If an elective decision is made for cardiopulmonary bypass or ECMO, heparin is administered and aortic/femoral artery cannulation (direct or via the femoral vein) for venous drainage. Extracorporeal support is generally avoided where possible owing to increased bleeding and an association with ischaemia-reperfusion injury . After releasing the inferior pulmonary ligament, hilar dissection is

carried out and pneumonectomy performed by division of the bronchus, pulmonary artery and both pulmonary veins. A large Satinsky clamp is placed across the left atrium and the individual pulmonary veins are opened and connected, creating a recipient cuff for anastomosis. Recipient lung bronchial secretions are sent for microbiology and the hilum is prepared by circumferentially opening the pericardium to mobilise the left atrium and pulmonary artery. Mediastinal lymph nodes may need excision to facilitate the transplant. Bronchial arteries are ligated to prevent significant bleeding. Denudation of the recipient bronchus should be avoided to limit local ischaemia at the site of the anastomosis. The pleural space is then liberally irrigated with antibiotic or aseptic solutions. The donor lungs are prepared for implantation by obtaining bronchial cultures for microbiology and dissecting the bronchus, pulmonary arteries and the left atrial cuff, into which the two pulmonary veins drain. Importantly the donor bronchus should be cut short just one or two rings from the bifurcation into the upper and lower lobe bronchi to minimise ischaemia at the anastomosis. The implantation is then conducted by sequentially creating anastomoses between the bronchus, the left atrial cuff of the donor lung and the left atrium of the recipient and the pulmonary artery (Figure 92.9). Prior to reperfusion, 500 mg of intravenous methylprednisolone is administered. The pulmonary artery clamp is removed slowly to lessen reperfusion injury and blood is permitted to escape from the left atrial suture line to de-air the vasculature before the left atrial clamp is opened. After a period of ventilation on a low inspired oxygen concentration to reduce oxygen free radical release, the patient is ventilated and weaned from cardiopulmonary bypass or surgery.

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Bronchus Recipient left atrium
Pulmonary artery Donor
pulmonary vein Figure 92.9 Hilum
of the lung during lung
transplantation. A left atrial cuff is
fashioned into which the donor
pulmonary veins drain. This is
anastomosed to the left atrium of

the recipient. The bronchus has been anastomosed already and the pulmonary artery is to be connected next.

phy is used to check de-airing and the patency of the vascular anastomoses. There has been a growing trend in the use of living related lobar lung transplantation for small recipients, especially in restrictive lung disease with low intrathoracic lung volume with two relatives each undergoing lower lobectomy . Results in a limited number of centres have been good but must be balanced against the risk of complications or death in the two donors. Alternatively larger donor lungs can be reduced in size through multiple wedge resections and right middle lobectomy . With this technique, variable outcomes have been reported when using oversized donor lungs with donor-recipient size mismatch.

Outcomes and complications

Outcomes and complications

Survival has dramatically improved with advances in immuno - suppression and perioperative care, with 1-year post-transplant survival of over 90% and a median post-transplant survival of

Pump Aorta Pulmonary artery Right ventricle

approximately 12 years anticipated. Early mortality is 5–10% at 30 days but often higher in those who have a VAD implanted as the device must be explanted with the recipient's heart, increasing the complexity of surgery owing to adhesions and vasoplegia from long-term non-pulsatile flow or infection often being encountered. After surgery most patients do not require rehospitalisation and functional status is good, with many returning to work and having a greatly improved health-related quality of life. Denervation of the heart is an unavoidable consequence of transplantation but, despite this, baseline cardiac function is preserved and increases in cardiac output are mediated by circulating catecholamines and stretch receptors responding to increased venous return with exercise. Early after transplantation, the main causes of mortality include primary graft dysfunction, rejection and infection. Long-term survival is dictated by the development of chronic allograft vasculopathy (CAV) and immunosuppression-related malignancy, diabetes, infection and renal dysfunction. Primary graft dysfunction occurs soon after implantation in around 10% of cases and is the leading cause of death. Low cardiac output and uni- or biventricular failure secondary to ischaemia-reperfusion injury occurs and is associated with older donor or recipient age, female-to-male donation, prolonged ischaemic time (>240 minutes) and donor-to-recipient size mismatch. Escalating inotropic support is needed, some times culminating in the institution of ECMO for circulatory support until the recovery of heart function. Isolated acute right ventricular failure may occur secondary to prolonged ischaemic time, elevated pulmonary vascular resistance, volume overload or donor size mismatch. The use of inotropes and nitric oxide and the optimisation of volume and mechanical support may be required. Three types of rejection can occur after heart transplantation: hyperacute rejection, acute cellular rejection and antibody-mediated rejection. Hyperacute rejection occurs intraoperatively immediately after reperfusion. Cross-matching of blood type and panel reactive antibodies has rendered this very unlikely. Lifelong immunosuppression is required, balancing prevention of rejection but avoiding the adverse effects of malignancy, infection, renal dysfunction, hypertension, diabetes and hyperlipidaemia. Most patients are prescribed triple therapy, consisting of a calcineurin inhibitor (e.g. ciclosporin, tacrolimus), an antimetabolite (e.g. azathioprine) and a tapering dose of steroids. Induction therapy with antithymocyte globulin or interleukin-2 receptor antagonists (basiliximab) is sometimes used but this may increase the risk of infection and malignancy with no survival benefit. The risk of acute rejection is highest in the first 6 months and a regime of routine surveillance cardiac biopsies obtained from the right ventricle via a biptome inserted through the internal jugular vein are carried out. Alternatives to biopsy have been explored, especially the modalities of cardiac imaging, but they have been associated with low accuracy. Gene expression profiling

Brachiocephalic Left common carotid artery trunk Left subclavian artery Superior vena cava
 Ascending aorta Right superior pulmonary vein Right inferior pulmonary vein Left atrium Inferior
 vena cava Figure 92.5 Cardiac transplantation. (a) A left atrial cuff is fashioned, into which the four
 pulmonary veins drain. This is anastomosed to a cuff of left atrium on the donor heart followed by
 anastomosis of the pulmonary artery, aorta and both venae cavae to complete the implant Arch of
 aorta Superior vena cava Pulmonary artery trunk Left atrium Right atrium Inferior vena cava (b) .

Current median survival after pulmonary transplantation is 6.2 years. In recipients who survive the first year the median survival is 8.3 years and this is associated with a significant improvement in quality of life. The main cause of postoperative mortality is primary graft dysfunction in which florid pulmonary oedema occurs with diffuse alveolar damage resulting from ischaemia-reperfusion injury. In survivors this is also associated with later dysfunction of the graft in the form of bronchiolitis obliterans syndrome (BOS). The pathogenesis is highly complex and involves acute-phase cytokines that are involved in inflammation that are upregulated or augmented in response to ischaemia or reperfusion and donor-specific characteristics such as infection, transfusion, barotrauma or smoking.

Summary box 92.6 Complications of lung transplantation

Immunosuppression after heart and/or lung transplantation, nitric oxide to improve ventilation-perfusion mismatch and diuresis. Support with ECMO is highly beneficial to allow for lung protective ventilation with eventual weaning when the lung injury recovers. Infections are the second highest cause of mortality within 30 days. Most centres use broad-spectrum antibiotics in the postoperative period based on bronchoalveolar lavage specimens from both the donor and recipient lungs. Using donor lungs from hepatitis B core-positive

donors is feasible with a low risk of transmission. Rejection commonly occurs after lung transplantation. Immunosuppression is used postoperatively to prevent acute rejection as well as CLAD by inhibiting T- and B-cell proliferation and activation. Agents similar to those used after heart transplantation are commonly utilised but generally greater immunosuppression is needed compared with other organs because of the increased susceptibility of the lungs to rejection, and this significantly increases the risks of drug toxicity such as renal failure, diabetes and hypertension. Induction therapy may be given as in heart transplants but is not universally applied and side effects such as major infection and malignancies limit its use despite evidence of a survival benefit. Acute cellular rejection occurs in around 30% of patients - in the first year and is characterised by an acute decline in pulmonary graft function without any other cause. Diagnosis is confirmed histologically using scheduled transbronchial biopsies and is based on the presence of perivascular and interstitial mononuclear cell infiltrates. Pulsed high-dose steroid therapy is the mainstay of treatment with modified or augmented immunosuppression in resistant cases. Antibody-mediated rejection is a separate entity in which DSAs directed towards donor HLA are present with neutrophil margination, arteritis and evidence of complement activation (C4d) present on histology. Treatment strategies focus on using plasmapheresis to deplete circulating DSAs, intravenous immunoglobulin and rituximab. Despite this a poor outcome is expected with a 1-year survival of less than 50%. CLAD (which includes BOS) limits long-term survival after lung transplantation and has a prevalence of 50% at 5 years. It leads to a significant fall in lung function and treatment options are limited but may include extracorporeal photopheresis combined with augmented immunosuppressive regimens and total lymphoid irradiation. Pirfenidone is being investigated as a possible option. In advanced CLAD, retransplantation can be considered. Gastro-oesophageal reflux disease is very common after pulmonary transplantation and has a strong association with the development of CLAD. Intraoperative vagal nerve injury, loss of cough reflex, impaired mucociliary clearance and immunosuppression-related gastroparesis may all be implicated. Early fundoplication has been suggested as an option. The bronchial anastomosis is a common site of complications with dehiscence occurring from local ischaemia or infection and stenosis occurring longer term in 5% of cases. Reoperation to cover a defect with an intercostal muscle flap or endobronchial stent insertion for narrowed anastomoses is effective.

Primary graft dysfunction Bleeding Parenchymal and pleural infection Bronchial anastomotic dehiscence or stenosis Vascular anastomotic stenosis or kinking Rejection – acute or chronic (chronic lung allograft dysfunction [CLAD]) Infection – bacterial, viral or fungal – donor or recipient acquired Phrenic nerve palsy Gastro-oesophageal reflux Induction (if used) Antithymocyte globulin/interleukin-2 receptor antagonists (basiliximab) Maintenance Ciclosporin, azathioprine, methylprednisolone

Single Double Figure 92.10 Types of lung transplant. Heart-lung combined transplantation is now rarely performed and is reserved mainly for congenital heart disease associated with pulmonary hypertension. Bilateral lung transplantation is the commonest option and accounts for 80% of transplants performed. Single-lung transplantation can be used in cases where retention of the other lung will not pose a risk from infection, such as fibrotic lung disease or emphysema. Using this option in cystic fibrosis, for example, would be contraindicated. Single-lung transplantation is associated with inferior survival. Lobar transplantation is rarely performed but in experienced centres can provide good results in highly selected patients. In living related donation relatives would donate a lower lobe but risk complications.

Recipient selection

Recipient selection

The primary indication for transplantation is prolonged advanced heart failure despite optimal medical management, often typified by repeated admissions or acute deterioration. Vladimir Demikhov , 1916–1998, Russian pioneer of organ transplantation, performed heart and heart-lung transplantation in animals between 1940 and 1950. James Hardy , 1918–2003, performed the world's first lung transplant in 1963, undertook the world's first heart transplant attempt when he transplanted the heart of a chimpanzee into a dying patient in 1964. Richard Lower , 1929–2008, American pioneer of heart transplantation who, with Shumway , developed many of the techniques required, including the use of hypothermia and the orthotopic technique in Stanford, CA, USA. Instrumental in the use of ciclosporin and in developing techniques of myocardial biopsy to monitor rejection. Norman Shumway , 1923–2006, American pioneer of heart transplantation who, with Lower, developed many of the techniques required, including the use of hypothermia and the orthotopic technique in Stanford, CA, USA. Performed his first human heart transplant in 1968. Christiaan Barnard , 1922–2001, performed the world's first successful heart transplant in 1967 after studying the techniques used by Lower and Shumway . The decision to transplant must take into account the patient's ability to withstand surgery and adhere to long-term treatment. The most frequent indications for heart transplantation in adults are dilated and ischaemic cardiomyopathy . An increasing number of patients with adult congenital heart disease (ACHD) are now considered but need more complex surgery (abnormal anatomy , previous operations) and may have elevated pulmonary vascular resistance and immune sensitisation. There are higher early mortality results after transplantation although the long-term outcome in survivors is excellent. Patients should be within the 'transplant window', being robust enough to survive the operation but their condition and prognosis should warrant the risks involved. As advanced failure can increase risk through the dysfunction of other organs (e.g. cardiorenal syndrome, liver dysfunction) reversible issues that can resolve with the improved cardiac output that transplantation will bring must be identified. Elevated pulmonary vascular resistance (>5 Wood units and a transpulmonary gradient >15 mmHg) is associated with an increased risk of right ventricular failure and mortality after heart transplantation; if irreversible despite vasodilators, this resistance is a contraindication. Age and previous cardiac surgery do not preclude transplantation and neither does diabetes if controlled with an absence of microvascular complications. A body mass index (BMI) >30 kg/m² has been associated with a worse outcome and weight loss is required before listing. Active infection is an absolute contraindication. Patients with chronic infections

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and surgical therapy . Malignancy , other than localised non-melanoma skin cancer, precludes transplantation but patients who have achieved sustained remission following cancer therapy may

become candidates. The presence of circulating antibodies against the allograft (allosensitisation) owing to pregnancy, blood transfusion, previous transplantation and the use of ventricular assist devices (VADs) is associated with worse outcomes and candidates are likely to have an extended waiting time to find a compatible donor. Screening for anti-human leukocyte antigen (HLA) antibodies is routine for all heart transplantation candidates. Psychosocial factors such as substance abuse (including tobacco, alcohol) is a relative contraindication. Relapse of smoking has been associated with a poor outcome after cardiac transplantation. Summary box 92.1 Criteria for heart transplantation

Summary box 92.2 Factors considered in heart allocation

Denton Cooley, 1920–2016, American surgeon, performed the first implantation of a total artificial heart and made major contributions to all aspects of cardiac surgery. Michael DeBakey, 1908–2008, American cardiovascular surgeon, undertook the first surgery to implant an external ventricular assist device for heart failure and developed a classification of aortic dissection.

1.

Impaired left ventricular systolic function

New York Heart Association III (e.g. patient cannot climb one flight of stairs without symptoms)

Receiving optimal medical therapy (maximum tolerated doses of β -adrenergic antagonists, angiotensin-converting enzyme inhibitors, aldosterone antagonists)

Resynchronisation pacing or implantable defibrillator device inserted (if indicated)

Evidence of a poor prognosis, e.g. a. Exercise testing (O_2 max $<12 \text{ mL/kg/min}$ if on β -blockade) b. Elevated B-type natriuretic peptide serum levels c. Calculated Seattle Heart Failure score indicating $>20\%$ 1-year mortality

Biological matching

Blood group compatibility

Appropriate size matching (accounting for recipient sex and pulmonary hypertension)

Need to avoid specific donor HLA antigens in sensitised recipients

Clinical need

Severity of heart failure

Prognosis

Logistic factors influencing ischaemia time

Distance of donor from the recipient centre

Prior surgery in the recipient (multiple sternotomies)

Surgical complexity (e.g. prior VAD, ACHD)

Fairness

Time on the waiting list

Aorta

Pulmonary artery

Left atrium

Right atrium

Coronary artery

Left ventricle

Right ventricle

Left ventricular assist device

Figure 92.1 Typical implantable left ventricular assist device that takes blood from the apex of the left ventricle and passes it through a rotor to a graft anastomosed to the aorta. A driveline crosses the skin to a controller and battery pack providing electrical power.

Recipient selection

Candidates have advanced lung disease with shortened life expectancy and poor quality of life owing to breathlessness and oxygen dependency. The most common indications are chronic obstructive pulmonary disease (COPD), CF, pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD). Organ allocation schemes recognise the last as associated with rapid decline and poor prognosis. Their prioritisation has led to shorter waiting times and a 20–40% reduction in death on the waiting list. The lung allocation score (LAS) is a useful tool to select those most in need of a particular donor lung. Risks are calculated using a set of 17 patient-related variables. Summary box 92.4 Pulmonary diseases and type of transplant

Cystic fibrosis

Bilateral and living related (or cadaveric lobar transplants in small highly selected recipients in experienced centres)

Interstitial (fibrotic) lung disease

Bilateral or single (but

associated with poorer long-term survival) Emphysema/COPD Bilateral or single (but associated with poorer long-term survival) Pulmonary hypertension Bilateral (or rarely combined heart-lung transplantation especially if associated with congenital heart disease)

pulmonary hypertension and the 6-minute walk distance. In deteriorating patients more conventional treatments can be used in some groups before transplant assessment. In COPD endoscopic lung volume reduction is increasingly recognised as a treatment option. Transmembrane conductance regulator modulators have improved outcomes for patients with CF with a reduction in exacerbation frequency and an improvement in quality of life and prognosis. This has resulted in a recent fall in transplantation for CF. In idiopathic pulmonary fibrosis, antifibrotic drugs (e.g. nintedanib, pirfenidone) have slowed the rate of functional decline, but the clinical course remains progressive and unpredictable. Although age should not be considered a contraindication to transplantation it is associated with comorbid conditions that may need to be taken into account. It is unusual to transplant patients over 70 years of age. Previous surgery, such as lobectomy, lung volume reduction or pleurodesis, is not a contraindication to lung transplantation, although inevitably it makes the transplantation operation more challenging with a greater risk of bleeding, phrenic nerve injury, chylothorax and renal dysfunction. A pneumothorax occurring in a waiting-list patient can be managed as required as the choice of intervention is unlikely to affect future acceptance. Untreatable major organ dysfunction, severe atherosclerosis, bleeding diathesis, high or low BMI, severe osteoporosis and chronic infection are all contraindications. In particular, infection with *Burkholderia cenocepacia*, *Burkholderia gladioli* and *Mycobacterium abscessus* can be associated with very poor post-transplant outcomes. For patients infected with hepatitis B and/or C, surgery can occur provided cirrhosis or portal hypertension are absent. Controlled human immunodeficiency virus (HIV) disease with undetectable HIV RNA, and compliance with antiretroviral therapy, allows transplantation to occur. For those with a history of malignancy a low predicted risk of recurrence and a 5-year period of remission are required. With regard to coronary artery disease, percutaneous coronary intervention may be undertaken ahead of transplantation or coronary artery bypass grafting when lung transplantation occurs. The degree of coronary artery disease deemed acceptable will vary but good results have been achieved. In rapidly deteriorating patients who are otherwise excellent candidates a bridge to lung transplantation may be undertaken using ECMO support. This permits ongoing rehabilitation while awaiting a suitable organ and is preferable to ventilation, which is usually a contraindication to pulmonary transplantation as physiotherapy is more difficult, deconditioning likely and the onset of pneumonia and barotrauma more common. Venovenous ECMO can be used in patients with severe hypoxia whereas venoarterial ECMO is used for patients with both hypoxia and haemodynamic instability or pulmonary hypertension. Instituting ECMO, however, is associated with serious and potentially fatal complications, such as bleeding, infection and thromboembolism. Recent series have shown that outcomes from bridging to transplantation can be similar to those transplanted electively despite being far sicker.

SUMMARY

SUMMARY

As the population ages and coronary artery disease, hypertension and obesity increase in prevalence the incidence of heart failure continues to rise. Current medical therapy is effective in improving symptoms and survival but many continue to develop end-stage syndromes. The most critical issue is the growing number of patients on the waiting list and the relatively static donor pool. VADs have emerged as a strategy to bridge patients to cardiac transplantation if they are deteriorating or as durable destination therapy. However complications such as stroke, pump thrombosis and poorer long-term survival remain a challenge. Cardiac transplantation remains the gold standard for the treatment of end-stage heart failure and is associated with excellent outcomes for patients, but it is limited by chronic rejection and the side effects of immunosuppression. Lung donor availability and increased waiting-list mortality are major challenges in pulmonary transplantation, but extended criteria donors can be safely used with good results. *ex vivo* The use of DCD lungs and organs reconditioned with lung perfusion has further expanded the donor pool, the latter technique showing promise for therapeutic interventions in due course. Bridging patients with ECMO rather than ventilation to lung transplantation is successful for those most in need and new allocation systems have been implemented that have led to decreased waiting list mortality, especially in those with fibrotic ILD. Overcoming primary graft dysfunction in the early post-operative period and chronic lung allograft dysfunction in the longer term are the main targets of ongoing research to improve outcomes for lung transplant recipients.

Heart-lung Lobar pulmonary

Ventricular assist devices

Ventricular assist devices

V ADs have had a significant impact. They may be used as a bridge to transplantation, a bridge to recovery (where the device is explanted if the patient's cardiac function improves) or as long-term durable destination therapy. The first total artificial heart implant was performed by Cooley in Houston, Texas, USA, in 1969 with the patient subsequently undergoing heart transplantation 48 hours later. In 1966, DeBakey utilised a left V AD in a patient unable to wean from cardiopulmonary bypass after valve surgery. Current generation devices use continuous non-pulsatile flow technology, which permits small device size, has the rotor as the only moving part and uses electrical rather than the more bulky pneumatic power delivery (Figure 92.1). Patients can now remain on device support for years if necessary, although complications from anticoagulation (stroke, device thrombosis, gastrointestinal bleeding), right ventricular failure, aortic valve regurgitation and driveline infection are common; hospital readmission is frequent. Early mortality is akin to heart transplantation but long-term survival is inferior with 50% survival at 5 years. Given the shortage of suitable donor organs, V AD implantation is an increasingly common approach for those deteriorating on the waiting list to gain time for a suitable donor heart to become available. Future technology improvements are focused on increased biocompatibility, artificially generated pulsatility and avoidance of drivelines. Among patients admitted in cardiogenic shock, venoarterial extracorporeal membrane oxygenation (ECMO) can be used to restore perfusion rapidly via the peripheral femoral artery and vein cannulation and permit urgent heart transplantation to be carried out within days, although the results are inferior (Figure 92.2). Summary box 92.3 Complications associated with VADs

Ventilator Oxygenator Arterial return line (into body) Venous drainage cannula (out of body) ECMO pump pump controller Figure 92.2 Extracorporeal membrane oxygenation (ECMO), which can be used for cardiorespiratory support before or after heart and lung transplantation. Blood is drained from the right atrium via the femoral vein, oxygenated and pumped back to the arterial circulation. In a variation where respiratory and not circulatory support is needed (venovenous ECMO) oxygenated blood is returned to the right atrium via the other femoral vein or jugular vein. Anticoagulation Bleeding – gastrointestinal tract, intracerebral, subarachnoid, extradural Thrombosis Pump obstruction Device failure Infection Driveline, systemic sepsis Structural Aortic regurgitation, tricuspid regurgitation Right ventricular failure Higher risks at transplantation Adhesions, infection, vasoplegia

preservation

preservation

At the time of heart procurement from brainstem dead (donation after brainstem death [DBD]) donors, the heart must be arrested and explanted prior to transportation. There follows a period of ischaemia until the heart is reperfused in the recipient. Allograft ischaemic time is a strong risk factor for post-transplant mortality, especially when it exceeds 3–4 hours, so every effort must be made to keep this time period as short as possible. At retrieval cardioplegic solutions that inhibit the Na^+/K^+ ATPase cell membrane pump or lead to cellular depolarisation and diastolic cardiac arrest are infused into the aortic root to rapidly arrest and uniformly cool the heart. Continuous heart perfusion is an alternative but more expensive and complex method of preservation. This is typified by the widely used Transmedics Organ Care System (Figure 92.3). Rather than being stored in an arrested and hypothermic state, the heart is kept warm and beating. It can be managed with inotropes and monitored through lactate assays, permitting longer transport times. Trials have shown that 30-day post-transplant survival is similar to standard preservation. There is some evidence to suggest that machine perfusion reduces mortality in higher risk donors and recipients and opens the potential for organ modification and improvement. Other systems that utilise cold oxygenated continuous perfusion of a still heart are under investigation. To expand the current donor pool hearts may be retrieved from patients suffering circulatory arrest (donation after circulatory death [DCD]) after the withdrawal of life-sustaining care and proclamation of death (Figure 92.3). The heart is then rapidly retrieved and reperfused in an organ care system before transport and transplantation. Clinical results appear equivalent to conventional donation and this has been a major advance.

More than 80% of potential lung grafts are declined because of concerns over donor history, chest trauma, pneumonia or aspiration. Ideally lung donors should demonstrate standard criteria but in reality only 20% of donors actually meet these values. Those outside of the standard criteria are called extended criteria donors. Experience has shown that these organs can be safely transplanted without detrimental effects on survival or longer term outcome. When oxygenation of donor lungs falls below the standard criterion of 300 mmHg aggressive donor management with alveolar recruitment, ventilatory optimisation, bronchoscopy and diuretics can lead to improvements. Additionally the opiate abuse epidemic in the USA has led to a significant rise in the number of organ donors but with a concomitant increase in hepatitis C infection. Antiviral therapies, however, may enable widespread use of such donors in hepatitis C-negative recipients.

Summary box 92.5 - Standard criteria lung donors

Outcomes are adversely affected by a donor smoking history of an increasing number of pack-years. Recipients of donor lungs from smokers have a higher 3-year mortality and prolonged hospital stay after adjusting for age and oxygenation but this is not a consistent finding and there remains an overall survival benefit to using lungs from heavy smoking donors to reduce waiting-list mortality. Lungs from older donors (>55 years) can be safely used to 70 years old and short-term outcomes of older

donors are - similar in well-selected cases. A history of cancer in the donor does not automatically preclude lung donation. Those with a history of skin cancer , as well as certain low-grade central nervous system tumours, can be used with minimal risk.

Investigations Clear chest radiograph Negative Gram stain of bronchial secretions or purulent secretions Arterial oxygen tension >300 mmHg (inspired oxygen fraction of 100% and positive end-expiratory pressure 5 cmH $_2$ O) 2 History Age <55 years Smoking <20 pack-years No chest trauma No aspiration No pneumonia