Outcomes and complications

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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 V AD 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. Denerv ation 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 cir culating catecholamines and stretch receptors responding to increased venous return with exercise. Early after transplantation, the main causes of mortality include primar y graft dysfunction, rejection and infection. Long-term survival is dictated by the development of chronic allograft vasculopathy (CA V) 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, pro longed 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 reco very of heart function. Isolated acute right ventricular failure may occur second ary to prolonged ischaemic time, elevated pulmonar y vascular resistance, volume overload or donor size mismatch. The use of inotropes and nitric oxide and the optimisation of volume and mechanical support ma y be required. Three types of rejection can occur after heart transplan - tation: 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 r endered this very unlikely . Lifelong immunosuppression is required, balancing pre - vention of rejection but avoiding the adverse e ff ects of malig - nancy , infection, renal dysfunction, hypertension, diabetes and hyperlipidaemia. Most patients are prescribed triple therapy , consisting of a calcineurin inhibitor (e.g. ciclosporin, tacroli - - mus), an antimetabolite (e.g. azathioprine) and a tapering dose of ster oids. 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 r ejection is highest in the first 6 months and a regime of routine surveillance cardiac biopsies obtained from the right ventricle via a bioptome inserted through the internal jugular vein are carried out. Alternatives to biopsy hav e been explored, especially the modalities of cardiac imag - ing, but they have been associated with low accuracy . Gene expression profiling

of blood mononuclear cells is under inves - - tigation and may be promising in the future . Free DNA of donor origin in the recipient’s blood has also been tested as a - means to predict rejection in the transplanted heart. Acute cellular rejection is a T -cell reaction to the donor’s HLA molecules that occurs in 20–40% of patients, most com - - monly during the first 12 months. It is classified based on the severity of lymphocytic infiltrates and myocyte damage and is treated with high-dose corticosteroids . With modern immuno - suppression and the low risk of la te cellular rejection, biopsies are often ceased after 3 years.

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) .

and has a mortality rate of 8%. Donor antigens and recip ient antibodies form an antigen–antibody membrane attack complex that leads to endothelial injury . The diagnosis of antibody-mediated rejection is confirmed by the presence of circulating donor-specific antibodies (DSAs) with evidence of complement activ ation. This is treated with intravenous immunoglobulin, plasmapheresis, antilymphocyte antibodies and high-dose steroids. CA V is a frequent long-term complication of heart trans plantation and the leading cause of late mortality . It has an incidence of 30% at 5 years with a complex pathogenesis involving immunological factors and ischaemia–reperfusion all implicated. Di ff use thickening of coronar y arterial intima occurs, often a ff ecting the entire length of the epicardial vessels and typically extending to the microvasculature. As the heart is denervated recipients do not experience ischaemic chest pain. By the time the patient presents with declining left ventricular function and heart failure, the prognosis is poor. CA V surveil lance by serial coronary angiography often combined with intravascular ultrasound can reliably detect intimal changes early to allow for treatment modification or consideration of retransplantation. Outcomes and complications

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 di ff use alveolar damage resulting from ischaemia–r eperfusion injury . In survivors this is also associated with later dysfunc tion of the graft in the form of bronchiolitis obliterans syn drome (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 suc h as infec tion, transfusion, barotrauma or smoking. Summary box 92.6 Complications of lung transplantation /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Summary box 92.7 Immunosuppression after heart and/or lung transplan tation /uni25CF /uni25CF /uni25CF /uni25CF lation, 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 recover s. 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 speci - mens 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 pr event acute rejection as well as CLAD by inhibiting T- and B-cell proliferation and activation. Agents similar to those used after heart transplantation ar e 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 e ff ects 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 biop - sies 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 neutro - phil margination, arteritis and evidence of complement activa - tion (C4d) present on histolog y . 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 (whic h 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 ar e 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 impli - - cated. Early fundoplication has been suggested as an option. The bronchial anastomosis is a common site of compli - cations 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 e ff ective.

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 re /f_l ux 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 /f_i brotic lung disease or emphysema. Using this option in cystic /f_i brosis, 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.

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