16.5.5 Cardiac transplantation and mechanical circ

16.5.5 Cardiac transplantation and mechanical circulatory support 3428 Jayan Parameshwar and Steven Tsui

section 16 Cardiovascular disorders 3428 Summary The interaction between heart and kidneys in acute and chronic disease leads to poorer survival and greater hospitalization for patients. The pathophysiology of the cardiorenal illness differs according to clinical scenario and between cases, from CKD- induced arrhythmia to decompensated heart failure causing dialysis-dependent AKI. The management of each scenario is fur- ther complicated by potential nephrotoxicity and altered renal drug clearance. This means that a general guideline for care in cardiorenal syndrome is not applicable, and patients must be as- sessed on a case-by-case basis. FURTHER READING Bongartz LG, et al. (2005). The severe cardiorenal syndrome: ‘Guyton revisited’. Eur Heart J, 26(1), 11–17. Braam B, et al. (2014). Cardiorenal syndrome—current understanding and future perspectives. Nat Rev Nephrol, 10(1), 48–55. Faul C, et al. (2011). FGF 23 induces left ventricular hypertrophy. J Clin

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J Am Coll Cardiol, 44(7), 1393–9. Roberts PR, Green D (2011). Arrhythmias in chronic kidney disease. Heart, 97(9), 766–73. 16.5.5 Cardiac transplantation and mechanical circulatory support Jayan Parameshwar and Steven Tsui ESSENTIALS Cardiac transplantation Cardiac transplantation is the treatment of choice for selected pa- tients with advanced heart failure: median survival exceeds 12 years and recipients enjoy an excellent quality of life, but availability is se- verely limited by shortage of donor organs. The need for lifelong immunosuppression is associated with side effects, including an increased incidence of malignancy. Newer immunosuppressive agents reduce nephrotoxicity and delay the onset of cardiac allograft vasculopathy, but may produce other side effects. Mechanical circulatory support Ventricular assist devices are mechanical blood pumps that work in parallel or series with the native ventricles. First-generation volume-displacement pulsatile ventricular assist devices have been superseded by rotary blood pumps that generate continuous flow. Significant complications include bleeding, thromboembolism, de- vice failure due to pump thrombosis, and infection. Temporary support—several devices are available for use in pa- tients who require support for days to weeks in the intensive care unit: these are invaluable in post-cardiotomy cardiogenic shock and in patients who present in extremis with uncertain viability. Chronic support—implantation of a durable ventricular assist device in patients with chronic heart failure can either be as a bridge to heart transplantation or as permanent support, sometimes referred to as destination therapy. There is evidence that patients with end-stage heart failure randomized to implantation of a ventricular assist de- vice (HeartMate XVE) have improved survival (52% vs. 25% at 1 year) compared to those receiving best medical therapy. A subsequent study randomizing similar heart failure patients between a newer continuous-flow left ventricular assist device (the HeartMate II) and the pulsatile HeartMate XVE showed that survival with continuous- flow ventricular assist devices was even better. Heart transplantation Introduction In 1964 James Hardy transplanted a chimpanzee heart into a 68- year-old man with ischaemic heart failure, but the patient did not survive surgery. The first human-to-human heart transplant was per- formed in Cape Town on 3 December 1967 by Christiaan Barnard; the patient died 18 days afterwards of infective complications. By the end of 1968, 102 patients had received heart transplants in 50 hos- pitals in 17 countries: mean survival was only 29 days and there was widespread disenchantment with the procedure. Only a few institu- tions continued clinical cardiac transplantation during the 1970s, the team at Stanford University under the leadership of Norman Shumway being pre-eminent among them. By the late 1970s, 1-year survival at Stanford had increased to 65%, establishing the place of heart transplantation. The introduction of new immunosuppressive drugs in the 1980s led to further improvement in outcome and an explosion of activity around the world, but during the 1990s there was a decline in the number of heart transplants performed owing to a shortage of donor organs. However, heart transplant activity has

slowly increased again in recent years, probably due to increased use of extended criteria donors. Before transplantation Recipient selection Heart transplantation is the treatment of choice for selected pa- tients with end-stage heart failure. However, the limited number of available donor hearts restricts this treatment to a small fraction of

 potential recipients. Careful selection of patients is therefore cru- cial to make best use of this scarce resource. Patients with New York Heart Association (NYHA) class IIIB and class IV heart failure are best discussed with the local heart failure/transplant centre to opti- mize medical management and to consider high-risk nontransplant cardiac surgery where appropriate (see Chapter 16.13.6). Patients with chronic heart failure should be referred before they develop significant end-organ dysfunction (renal and hepatic) or irrevers- ible secondary pulmonary hypertension. Box 16.5.5.1 summarizes criteria used to select patients for trans- plantation. Haemodynamic assessment, measurement of natriuretic peptides, and the use of cardiopulmonary exercise testing to object- ively quantify functional capacity are all important in estimating prognosis. Box 16.5.5.2 outlines the important contraindications. Matching of donor and recipient Donor and recipient blood groups need to be compatible. Appropriate size matching is also generally thought to be necessary to minimize the risk of donor organ failure. HLA matching is not routinely car- ried out, but there is some evidence that HLA-DR matching results in fewer episodes of acute rejection. The presence of preformed antibodies to HLA antigens is an important consideration, hence selection of an appropriate donor includes ruling out those with the relevant HLA antigens and sensitized patients are likely to have a much longer wait for a suitable donor organ. After transplantation Most patients spend 2 to 3 weeks in hospital after a heart transplant and are fit to return to work after 4 to 6 months. In the first year they need to return to the transplant centre at set intervals to monitor immunosuppression, and to have surveillance endomyocardial biopsies to screen for acute rejection. There is data suggesting that, at least for low-risk patients, a noninvasive monitoring strategy involving gene-expression profiling of peripheral blood mono- nuclear cells may be a safe alternative to endomyocardial biopsy. Immunosuppression Immunosuppression is commenced at surgery and continued for life. The intensity of immunosuppression is greatest early post- transplant, with a staged reduction in the dosage of drugs over the first year. Box 16.5.5.3 lists the agents commonly used for mainten- ance immunosuppression: some units routinely deploy induction therapy with an antibody for the first few days after the transplant. At least 50% of patients can be safely weaned off prednisolone in the first 2 years after heart transplant. Episodes of acute cell mediated rejection (usually confirmed by endomyocardial biopsy) are treated with intravenous methyl prednisolone and are almost always reversible. The importance of antibody-mediated rejection has been increasingly recognized in recent years. Treatment includes antibody removal, intravenous immunoglobulin, and various monoclonal antibodies, but there is no convincing evidence for the efficacy of these regimes. When antibody-mediated rejection is associated with ventricular dys- function, medium-term prognosis is compromised. The presence of donor specific antibodies in the serum may be associated with an adverse prognosis, including early cardiac allograft vasculopathy. Outcome Fig. 16.5.5.1 shows the survival of patients after heart transplant- ation. Median survival now exceeds 12 years in most large centres. Annual mortality after the first year is approximately 2.5% per year. Most patients enjoy an excellent quality of life, with minimal or no functional limitation. Successful pregnancy is possible, with management requiring close collaboration between transplant and obstetric teams. Maternal morbidity is higher than in the general population and there is a higher incidence of small-for-date babies. Teratogenicity does not seem to be a significant problem with the

immunosuppressive regimens used in the 1980s and most of the 1990s (steroids, azathioprine, calcineurin inhibitors), but patients receiving mycophenolate mofetil or sirolimus/everolimus should be Box 16.5.5.1 Indications for heart transplantation • History: recurrent hospital admissions for worsening heart failure • Recurrent symptomatic ventricular arrhythmia associated with severe impairment of ventricular function • Refractory ischaemia not amenable to revascularization and associ- ated with severe impairment of left ventricular function • Functional capacity: persistent symptoms of heart failure at rest or minimal exertion despite optimal medical therapy. Functional capacity measured by peak oxygen uptake on exercise <14 ml kg−1 min−1 (or 50% predicted). For patients receiving β-blockers, a value of <12 ml kg−1 min−1 has been recommended • Biomarkers: persistent elevation of natriuretic peptides • Prognostic scores (e.g. Seattle Heart Failure Model indicating 1-year mortality >20% on optimal medical therapy) Box 16.5.5.2 Relative contraindications to heart transplantation • Active infection—but note that patients with chronic viral infection (e.g. hepatitis B, HIV) may be considered if viral titres are undetectable and there is no organ damage other than to the heart • Symptomatic cerebral or peripheral or vascular disease • Diabetes mellitus with end-organ damage (e.g. nephropathy, neur- opathy, proliferative retinopathy) • Coexistent or recent neoplasm • Severe lung disease—FEV1 and FVC <50% predicted and evidence of parenchymal lung disease • Renal dysfunction with creatinine clearance less than 40 ml min−1 (combined cardiac and renal transplantation may be considered) • Recent pulmonary thromboembolism • Pulmonary hypertension-pulmonary artery systolic pressure >60 mm Hg, transpulmonary gradient ≥15 mm Hg, and/or pulmonary vascular resistance >5 Wood units • Psychosocial factors including history of noncompliance with medica- tion, inadequate support, drug, or alcohol abuse • Obesity (body mass index >35 or weight >140% of ideal body weight) Box 16.5.5.3 Immunosuppressive agents • Calcineurin inhibitor: ciclosporin or tacrolimus • Antimetabolites: mycophenolate mofetil or azathioprine • Corticosteroid: usually prednisolone • Proliferation signal inhibitors: sirolimus or everolimus • Antibody therapy: antithymocyte globulin (ATG), basiliximab, alemtuzumab

section 16 Cardiovascular disorders 3430 strongly advised not to become pregnant and arrangements made to switch to alternative drugs if pregnancy is planned. Complications General complications related to immunosuppression include an increase in opportunistic infection and malignancy, in particular squamous cell carcinoma of the skin and non-Hodgkin’s B-cell lymphoma (which affects 2–4% of heart transplant recipients). Calcineurin inhibitors can cause headaches, tremor, hypertension, nephropathy, and peripheral neuropathy, and exacerbate myalgia/ myositis associated with statin use. Corticosteroids are associated with osteoporosis and diabetes. Ciclosporin can cause hirsutism and gum hypertrophy. Issues particular to cardiac transplantation are described next. Hyperlipidaemia Abnormalities in lipid levels have been reported in up to 80% of pa- tients on standard immunosuppressive drug regimes. Pretransplant abnormalities are common in patients transplanted for ischaemic cardiomyopathy. Use of statins early post-transplant has been shown to delay the onset of cardiac allograft vasculopathy thus increasing late survival, and is now standard practice in most units. Renal dysfunction The most serious side effect of calcineurin inhibitors (CNI) is renal toxicity. Data from the International Society for Heart and Lung Transplantation indicate that about 20% of patients have some de- gree of renal dysfunction at 1 year after transplantation. Afferent renal arterial vasoconstriction is believed to be the cause of early renal dysfunction and is reversible. Late renal dysfunction is re- lated to tubular damage and tends to be progressive, even when the offending drug is discontinued. At least 5–6% of heart transplant recipients progress to require renal replacement therapy in the first 10 years post-

transplant, and their prognosis on dialysis is poor. Judicious use of CNI-free regimes slows the progression to end- stage renal disease and, if introduced early, renal function may im- prove significantly. Selected heart recipients who have developed renal failure but maintained good cardiac allograft function can be considered for renal transplantation. Cardiac allograft vasculopathy This term is used to describe concentric narrowing of the coronary arteries (and sometimes veins) of the transplanted heart. It is be- lieved to be an immune-mediated disease and is also referred to as ‘chronic rejection’, although nonimmune mechanisms probably contribute to pathogenesis. It is the commonest cause of late death after heart transplantation but occasionally presents as a fulminant process that causes death within the first year. Conventional risk fac- tors like smoking and hyperlipidaemia are associated with earlier disease, but cardiac allograft vasculopathy occurs in children and in the absence of other risk factors. The basic pathological lesion is a diffuse and progressive thick- ening of the intima that occurs in epicardial and intramyocardial arteries (Fig. 16.5.5.2). The disease tends to affect the arterial tree diffusely, although there is heterogeneous involvement of different parts of the arteries. The degree of intimal thickening that occurs in the first year (measured by intravascular ultrasonography) is a predictor of the development of angiographic disease and death or retransplantation for cardiac allograft vasculopathy, the risk factors for which are shown in Box 16.5.5.4. Most patients with cardiac allograft vasculopathy present with signs and symptoms of heart failure, although angina can be ex- perienced despite denervation. The disease is commonly first seen during surveillance coronary angiography. Revascularization is rarely feasible because the disease is diffuse, but occasionally pa- tients have focal proximal lesions that are amenable to angioplasty. Intravascular ultrasonography (IVUS) is the most sensitive tech- nique for diagnosis of early disease and most clinical trials of new immunosuppressive drugs include IVUS-derived parameters as an endpoint. The only definitive treatment for cardiac allograft 0 25 50 75 100 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 Survival (%) Years 1982–1991 (N = 21482) 1992–2001 (N = 40097) 2002–2008 (N = 26046) 2009–6/2016 (N = 30824) Adult Heart Transplants Kaplan-Meier Survival by Era (Transplants: January 1982–June 2016) All pair-wise comparisons were significant at $p < 0.0001$. Median survival (years): 1982–1991 = 8.6; 1992–2001 = 10.5; 2002–2008 = 12.4; 2009–6/2016 = NA Fig. 16.5.5.1 Survival was calculated using the Kaplan–Meier method, which incorporates information from all transplants for whom any follow-up has been provided. Since many patients are
still alive and some patients have been lost to follow-up, the
survival rates are estimates rather than exact rates because the time of death is not known for all patients. The median survival is the estimated time point at which 50% of all of the recipients have died. Survival rates were compared using the log-rank test statistic. Adjustments for multiple comparisons were done using Scheffé’s
method. Source data from The International Society for Heart and Lung Transplantation (JHLT 2018 Oct:37 (10): 1155–1206). Fig. 16.5.5.2 Cross-section of coronary artery at autopsy showing marked intimal hyperplasia and obliteration of the lumen.

 vasculopathy is retransplantation, which—given the shortage of donor organs—is an option for only a few patients. Proliferation signal inhibitors may delay the onset and slow the progression of cardiac allograft vasculopathy. Mechanical circulatory support The concept of arterial counterpulsation to unload the heart in sys- tole was introduced in the early 1960s. This led to the development of the intra-aortic balloon pump, which was first applied clinically by Kantrowitz in 1967. In 1966 DeBakey reported the first

suc- cessful clinical application of a true ventricular assist device (VAD) in a 37-year-old woman who could not be weaned from cardiopul- monary bypass following aortic and mitral valve replacement. In 1969 Cooley supported a patient with a total artificial heart for 64 h until a donor heart was available. In 1984 Stanford University re- ported the first successful heart transplant following bridging with a left ventricular assist device (LVAD). VADs are mechanical blood pumps that work in parallel or series with the native ventricle. An LVAD draws oxygenated blood from the left atrium or ventricle and returns it to the aorta; a right ven- tricular assist device (RVAD) draws venous blood from the right atrium or ventricle and returns it to the pulmonary artery. Contexts for using mechanical circulatory support Bridge to transplantation Successful cardiac transplantation provided the stimulus for the de- velopment of devices that could be used to support patients until a suitable donor organ became available. The availability of donor hearts is unpredictable, hence the patient with acute haemodynamic deterioration requires other means of circulatory support when intravenous inotropic therapy cannot maintain adequate perfusion to vital organs. Renal and hepatic functions improve on mechan- ical support, pulmonary vascular resistance falls, nutritional status and muscle strength recover. This buys time for the patient until a suitable donor heart is identified and reduces the risk of subsequent transplantation. Box 16.5.5.5 outlines guidance for use of a LVAD as a bridge to transplantation and factors affecting risk of perioperative complications. Permanent support Depending on definition, the prevalence of severe heart failure be- tween the ages of 65 and 75 years is 0.5–1.2%. Most of these patients will not be candidates for heart transplantation by virtue of age and comorbidity. VADs were originally developed as a long-term treat- ment for heart failure and patients who are not transplant candidates can be considered for this form of therapy. The REMATCH study (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) random- ized patients with end-stage heart failure to best medical therapy or the implantation of the pulsatile HeartMate assist device. Survival at 1 year was 52% in the device group and 25% in the medical group; at 2 years it was 23% and 8%, respectively. Quality of life was sig- nificantly improved at 1 year in the device group, but with a higher frequency of serious adverse events. In the HeartMate II study, patients with end-stage heart failure were randomized to undergo implantation of the pulsatile HeartMate XVE or a continuous-flow LVAD (HeartMate II). The quality of life and functional capacity improved significantly in both groups. Patients implanted with the continuous-flow LVAD had superior ac- tuarial survival rates at 2 years (58% vs. 24%, $p = 0.008$) and signifi- cantly lower adverse event rates. This provides compelling evidence that LVAD therapy can increase life expectancy and quality of life in selected patients with advanced heart failure. Similar outcomes have been reported in the ENDURANCE Study with the HeartWare heart ventricular assist device (HVAD). In a com- parison with the HeartMate II in patients ineligible for transplant- ation, survival at 2 years free of disabling stroke or device removal Box 16.5.5.4 Risk factors for cardiac allograft vasculopathy Immunological • Number of episodes of acute rejection • HLA-DR mismatch between donor and recipient • Anti-HLA donor specific antibodies in the recipient (associated with the deposition of antibody and complement in the vasculature of the allograft) Nonimmunological • Donor age • Recipient age and gender • Coronary artery disease as the cause for transplantation in the recipient • Cytomegalovirus infection • Smoking • Obesity • Hyperlipidaemia Box 16.5.5.5 Guidelines for the use of LVAD as a bridge to transplantation Inclusion criteria • The patient is a candidate for transplantation, or is likely to become a candidate after a period of mechanical circulatory support (bridge to candidacy) • Haemodynamics (usually on IV inotropic therapy); cardiac index <2.0 litres min^{-1} m^{-2}; systolic blood pressure <80 mm Hg; pulmonary capil- lary wedge pressure >20 mm Hg • Progressive end-organ dysfunction (renal or hepatic) due to reduced

perfusion • More than two heart failure hospitalizations in previous 12 months without an obvious precipitating cause Exclusion criteria • Active endocarditis • Multiorgan failure • Life-limiting comorbidities: systemic disease that limits 1-year survival (e.g. advanced or irreversible pulmonary disease), advanced hepatic disease (cirrhosis and portal hypertension), severe peripheral vascular disease, metastatic cancer, and irreversible neurological or neuromus- cular disorders • Severe right ventricular failure (would need BIVAD) Factors increasing the risk of perioperative complications • Age • Prolonged prothrombin time or raised INR • Hypoalbuminaemia • Era of implantation (lower mortality for implants after May 2007) • Centre experience (>15 implants associated with decreased mortality).

section 16 Cardiovascular disorders 3432 for malfunction was 55.4% in the HVAD group and 59.1% in the HeartMate II group. The HeartMate 3 device has shown promising results at 6-month follow-up (86.2% for a similar endpoint), with a lower rate of pump thrombosis when compared with HeartMate II, but longer-term data are not available as yet. The ADVANCE Study com- pared the HeartWare HVAD with the HeartMate II; two-year survival free of disabling stroke was over 55% in both groups. The Momentum study compared the HeartMate 3 device with the HeartMate II. Two year survival free of disabling stroke was 79.5% in the former and 60.2%. There was also a much lower incidence of pump thrombosis leading to pump exchange in the HeartMate 3 group. Bridge to recovery Patients dying from fulminant myocarditis can be supported with mechanical circulatory support and it is not uncommon to see re- covery of myocardial function to the point where the device can be removed. Recovery has also been reported in patients with idiopathic dilated cardiomyopathy. LVADs unload the ventricle to a degree that cannot be achieved by drug therapy, and there is a considerable body of evidence to show that the myocardium recovers at the cellular and molecular level with mechanical circulatory support. Structural improvement detectable by echocardiography occurs much less fre- quently, and clinical recovery to the point where the device can be re- moved safely is rarer still (<10% of patients in most series, although there are intriguing reports of higher rates of clinical recovery from a few centres). Studies are ongoing, but at present implantation of a device in patients with chronic heart failure should be viewed as a bridge to heart transplantation or as permanent support. Short-term support Several devices are available for use in patients who need support for days or weeks. These are invaluable in post-cardiotomy cardiogenic shock and in patients who present in extremis with multiorgan failure. In the latter group, a short-term device may be a bridge to a longer-term device or to heart transplantation, but occasionally patients may improve to the point where the device can be removed and they can be stabilized on medical therapy. This is sometimes described as ‘bridge to decision’. To support patients for periods of a few weeks to several months, the CentriMag device has been widely used with reasonable success. Veno-arterial extracorporeal membrane oxygenation (ECMO) can be introduced at the bedside in critically ill patients to maintain systemic circulation and to afford the opportunity to assess the appropriateness of further therapy. It may also be used to stabilize patients for transport to an advanced heart failure centre for further evaluation. Patients with any of these devices are confined to critical care or a high-dependency area and cannot be discharged from hospital. Types of ventricular assist devices There are many devices available for clinical use. Box 16.5.5.6 shows a classification of devices and examples of each type: a brief descrip- tion of selected devices in each category follows. Rotary ventricular assist devices Rotary devices deploy an impeller spinning at high speed to generate blood flow. An inflow cannula carries blood from the apex of the left ventricle to the device, while the outflow graft is anastomosed to the ascending aorta. They are smaller than the original pulsatile devices, have a

limited blood contact surface with a single moving part, and are silent in operation. Newer pump designs have eliminated mech- anical bearings altogether with the hope that these will be even more durable. Implantation is generally easier than for pulsatile devices and infections are less common, probably because of the less inva- sive surgery and thinner drive line. Rotary devices provide continuous flow and are therefore not ‘physiological’; patients usually do not have a palpable pulse and blood pressure measurement with a sphygmomanometer requires a Doppler probe to detect blood flow. Rotary pumps are preload de- pendent and afterload sensitive. Adequate left ventricular filling is re- quired to ensure sufficient preload and avoid ventricular ‘suckdown’. The absence of valves makes them simpler to operate. However, in the event of pump stoppage, free regurgitation from the ascending aorta back into the left ventricle may occur. Depending on native left ventricular function, some pulsatility may be seen as more blood is delivered to the VAD during ventricular systole. The impeller spinning at speed results in high sheer stress to blood components which can cleave the von Willebrand factor, resulting in an acquired von Willebrand disease. Pump thrombosis is another potential com- plication of continuous-flow devices and all rotary pumps currently require anticoagulation with warfarin and antiplatelet agents. The Thoratec Heartmate II (Fig. 16.5.5.3) is a second-generation device which consists of an axial-flow blood pump with a percutan- eous lead that connects the pump to an external computer controller and power source. The blood pump is a 12 mm diameter straight tube made of titanium alloy containing an internal rotor with helical blades that curve around a central shaft. When the rotor spins on its axis, blood is drawn from the left ventricular apex through the pump and into the ascending aorta. The pump requires a pump pocket in the anterior abdominal wall, has an implant volume of 63 ml, and weighs 350 g. It operates at approximately 8000–10 000 rpm and can generate up to 10 litres of flow per minute. The controller and two batteries are wearable, providing 4–6 h of power. The HeartMate II is approved for clinical use in Europe and the United States of America for bridging to transplant as well as for destination therapy. It has been implanted in over 20 000 patients worldwide, representing the benchmark against which other continuous-flow devices are being compared. Box 16.5.5.6 Classification of devices for mechanical circulatory support Temporary devices • Thoratec CentriMag • Abiomed Impella 2.5; 4.0; 5.0 • TandemHeart • Venoarterial Extra Corporeal Membrane Oxygenation (VA-ECMO) Long-term devices Pulsatile (volume displacement) • Berlin Heart Excor • NuPulse iVAS (investigational device) Continuous flow • Jarvik 2000 • Berlin Incor • HeartMate II and HeartMate 3 • HeartWare HVAD

16.5.5 Cardiac transplantation and circulatory support 3433 The HeartWare HVAD (Fig. 16.5.5.4) is a third-generation cen- trifugal blood pump which contains a wide-bladed impeller with a hydrodynamic suspension. This pump weighs only 160 g, has an implant volume of 70 ml, and does not require an abdominal pump pocket, allowing intrapericardial placement. It operates at 2400–3800 (a) (b) Fig. 16.5.5.3 (a) HeartMate II. (b) Stylized picture of a patient with a HeartMate II LVAD. (a) and (b) Courtesy of Thoratec. (a) (b) Fig. 16.5.5.4 (a) The HeartWare HVAD. (b) Stylized picture of a HeartWare HVAD showing inflow drainage from left ventricular apex and outflow graft anastomosed to ascending aorta. (a) and (b) Courtesy of HeartWare Inc.

section 16 Cardiovascular disorders 3434 rpm and can generate flows of up to 10 litres/min. The HeartWare HVAD is approved for clinical use in Europe and for bridging to transplant in the United States of America. The HeartWare HVAD has been implanted in nearly 10 000 patients worldwide and has pro- duced very favourable clinical outcomes. The HeartMate 3 is a third-generation

centrifugal pump in which the rotor is suspended using magnetic forces. Like the HeartWare HVAD it is placed intrapericardially (Fig. 16.5.5.5). It has been de- signed with large blood flow pathways to minimize shear stress on the blood cells. It also provides some artificial pulsatility. In a ran- domized trial against the HeartMate II device, the HeartMate3 was superior with regard to survival free of disabling stroke and need for pump exchange due to pump thrombosis at 2 years. Outcome of ventricular assist device treatment Clinical outcomes of patients treated with implantable VADs have improved significantly over the last decade. This is a result of better understanding of patient selection criteria, the develop- ment of clinical strategies to minimize perioperative complica- tions, and improvements in device technology. Algorithms have been developed to risk stratify patients preoperatively, allowing targeted medical optimization of high-risk patients before VAD implantation. The introduction of the INTERMACS registry in the United States of America created a template for rigorous data monitoring and audit. Actuarial survival following implantation of continuous-flow LVADs is 80% at 1 year and 70% at 2 years across all indications (Fig. 16.5.5.6). The commonest causes of 30-day mortality are right ventricular failure, multiorgan failure, and neurological events. In the longer term, device-related infec- tion, stroke, and pump thrombosis emerge as the most important cause of death. Multivariate analysis identified older age, greater severity of right ventricular failure, and cardiogenic shock at im- plant as risk factors for death. External battery pack Outflow graft Skin entry site Centrifugal-flow LVAS Left ventricle From left ventricle Inflow cannula Motor Motor Rotor with internal magnet Pump chamber Blood flow To aorta Slide lock Aorta Percutaneous lead System controller Fig. 16.5.5.5 Stylized picture of a HeartMate 3 device, with a fully magnetically levitated centrifugal-flow pump. Courtesy of Abbott Laboratories. 100% Intermacs - Kaplan–Meier survival for continuous flow LVADs (with or without RVAD implant at time of LVAD operation) by device type primary prospective implants: 23 June 2006 to 30 September 2017 Device type LVAD (n = 18745, Deaths = 5895) BiVAD (n = 690, Deaths = 348) 90% 80% 70% 60% 50% % Percent survival 40% 30% 20% At risk 690 18745 231 10288 125 5875 72 3325 46 1891 31 983 10% 0% 0 Shaded areas indicate 70% confidence limits p (log-rank) = <.0001 Event: Death (censored at transplant or recovery) 3 6 9 12 15 18 21 24 27 Months after device implant 30 33 36 39 42 45 48 51 54 57 60 Fig. 16.5.5.6 Kaplan–Meier survival for continuous-flow LVADs (with or without RVAD implant at time of LVAD operation). Primary prospective implants: 23 June 2006 to 30 September 2017. From Kirklin KJ (2017). Intermacs Quarterly Statistical Report 2017 Q3. Exhibit 17: p. 26 http://www.intermacs.org.

 Complications of ventricular assist devices With long-term requirement for anticoagulation therapy and the need for a percutaneous driveline, bleeding and infection re- main the most common adverse events following LVAD implant. Other common complications include arrhythmias, respiratory failure, renal dysfunction, and right heart failure. Patients receiving continuous-flow devices appear to experience significantly reduced incidences of device malfunction, infection, and hepatic dysfunc- tion, but there appears to be a significantly increased risk of gastro- intestinal bleeding with the use of rotary devices, which may be associated with an acquired form of von Willebrand’s disease and reduced pulsatility of the systemic circulation. Stroke remains a sig- nificant complication (ischaemic and intracerebral bleeding) as does pump thrombosis. Recent data suggests that optimal blood pressure control may reduce the risk of stroke. FURTHER READING Barnard CN (1967). A human cardiac transplant: an interim report
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