Chapter 3

The Current Status of Heart Transplantation

Babar B Chaudhri

Department of Cardiovascular and Thoracic Surgery and Intrathoracic Transplantation, Sir HN Reliance Foundation Hospital, India

*Corresponding Author: Babar B Chaudhri, Department of Cardiovascular and Thoracic Surgery and Intrathoracic Transplantation, Sir HN Reliance Foundation Hospital, Raja Ram Mohan Roy Marg, Mumbai 400004, India, Tel: +91 7738164236; Email: bchaudhri@mac.com

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Abstract

In this chapter, we hope to give a perspective of the new realities of cardiac transplantation as well as the challenges to sustain services worldwide, and some of the new developments. Topics that will be covered in this review include the changing patient population as well as recent advances in transplantation immunology, donor management, organ preservation, allograft vasculopathy, and immune tolerance.

Keywords

Heart Failure; Transplantation; Mechanical Circulatory Support; Immunosuppression

Introduction

The first human-to-human heart transplant was performed in South Africa in December 1967 by Christian Barnard [1]. The initial animal work was conducted by Alexis Carrel, Frank Mann, Norman Shumway, and Richard Lower [2-4]. The first heart transplant patient, recovered well, initially, but died of pneumonia 18 days later. The second heart transplant recipient was the first to leave hospital and survived for 19 months. These initial transplants were from deceased circulation death donors (DCD), as opposed to the current practice of retrieval from brain stem dead donors (DBD). Experimental work will be discussed looking at the utility of recovering hearts from DCD in the current environment.
Initially, there was a limited understanding of early post-operative complications and an absence of interventions to address acute rejection and opportunistic infections, accordingly results were poor. Allograft vasculopathy as a cause of graft failure and death was recognised when the second recipient died of myocardial infarction 19 months after his heart transplantation [2]. In the UK a moratorium on heart transplantation was declared in 1973 to 1980, but it continued in the US. The recovery of heart transplantation was due to refinement of donor and recipient selection methods, better donor heart management, and the introduction of cyclosporine as the main factors associated significantly improved survival.

Since 1967, in excess of 88,000 total heart transplants have been performed [4]. In this cumulative registry managed by International Society of Heart and Lung Transplantation, 1-year survival is 81%. Thereafter the annual mortality is 4% per year. The half-life for survival is 10 years. Hazards are highest in the first year of transplant, after this the conditional half-life is 13 years (Figure 1). Analysis has shown that more recent cohorts have a better survival.

The causes of death within the first 6 months are mainly due to graft dysfunction and infection. Late loss is due to chronic rejection, chronic allograft vasculopathy and malignancies. 1-year survival is now in the region of 90%, 5-year survival rate is approximately 70%, and a median survival in excess of 10 years, heart transplantation is the gold standard option for selected patients with end-stage heart failure (Figure 2) [5].

Heart transplantation is in evolution. Advances in organ preservation, immune monitoring, and immunosuppressive regimens will lead to further improvement in the quality and the length of life of heart transplant recipients.
The Patient Population

There is an increase in the number of patients who require mechanical circulatory support (MCS) as a bridge to transplantation [5]. This has been driven, particularly in the UK by limitation of the number of hearts for donation, and also to buy time on the transplant waiting list. This is due to an increase in the numbers of non-heart beating donors (DCDs), whereby retrieval takes place in a circulation arrested donor, and the increased survival of head injury patients and those with intracranial bleeds who are treated by a decompressive craniotomy, reducing the pool of donors who have raised intracranial pressure and who have coned, resulting in brain stem death. The net result is a retrieval rate for heart transplantation of around 19%. The risk of having preformed antibodies directed against the donor heart (sensitised patients) is increasingly likely and is particularly challenging as it may increase the risk of rejection and allograft vasculopathy [5–7]. Patients with CHD often have a more complex anatomy and are at an increased risk of perioperative bleeding and mortality [8].

Heart transplantation is now being carried out in older recipients. Older age is now seen as a relative contraindication to heart transplantation [9,10]. The incidence of rejection is usually lower in older recipients while the incidence of infection and allograft vasculopathy appears to be higher [5,9].

More patients with CHD are surviving into adulthood due to improvements in paediatric cardiac surgical techniques. Many of these patients may develop heart failure later in life, despite adequate surgical repair or palliation [8,11]. CHD is one of the strongest risk factors for 1-year mortality after heart transplantation in adults [5,8]. Despite the higher initial attrition, in those who survive 3 years, CHD disease has a 10-year survival advantage independent of age. This high initial attrition rate may be due to challenging anatomical arrangements of the heart and great vessels, adhesions from prior surgery, collateral vessels present in CHD; and a higher incidence of HLA sensitised patients due to multiple transfusions.
Cardiac transplantation has also taken place with ABO-incompatible donors. This has increased the donor pool for infants and reduce the mortality rate among infant on the waiting list for transplantation.

There has also been an increase in the number of patients requiring MCS as a bridge to transplantation [12]. This allows many severely ill adult and paediatric patients to survive until a suitable donor heart is available. Patients with MCS are at increased risk for rejection, infection, stroke, and bleeding. The need for transfusions also increase the risk of pre-sensitization [5-7].

Survival at 1 and 5 years is decreased in patients requiring MCS prior to transplantation, but still higher than 80% and 70%, respectively (ISHLT database) [5]. The need for retransplantation will also become more common in the future. Because of organ availability, retransplantation comprises a small minority (<3%) of heart transplants [5]. Survival rates for retransplant patients are significantly lower, due to allosensitisation, and because of the consequences of years of immunosuppression [5,13,14]. Adverse outcomes after retransplantation include retransplantation early after primary transplantation (<6 months), retransplantation for acute rejection, or early allograft failure [13,14]. If we exclude those patients retransplanted for primary allograft failure and those with intractable acute rejection occurring less than 6 months after transplantation, 1-, 2-, and 4-year survival rates after retransplantation is comparable to those after primary transplantation [13,14].

Recipient criteria for heart transplantation include, severe symptoms despite maximal medical management, the absence of reversible or surgically amenable heart disease, and where estimated 1-year survival is less than 50% [15]. An estimate of functional capacity can be best quantified by measurement of peak O₂ consumption (VO₂max). Patients with low VO₂max (< 12 ml/min/kg) have high mortality even if treated with beta blockers. The recent International Society of Heart and Lung (ISHLT) guidelines suggest that transplantation should be considered for these patients [2]. In addition heart failure prognosis scores to estimate survival, such as the Heart Failure Severity Score may be used. This calculates a survival probability on the basis of the presence of ischaemic cardiomyopathy, resting heart rate, left ventricular ejection fraction, mean blood pressure, interventricular conduction delay, VO₂max and serum sodium concentration [16].

Transplantation eligibility is always considered with regard to risk factors, especially, pulmonary hypertension. Right heart catheterization must be performed in all potential candidates for heart transplantation in order to quantify pulmonary vascular resistance [16]. Right heart failure is a substantial cause of mortality. Right ventricular failure is likely when post implant pulmonary artery pressures exceed 50 mmHg. Patients with chronic heart failure may develop pulmonary hypertension due to elevated left
ventricular end diastolic pressure with elevated left atrial and pulmonary venous pressures. This is a reactive form of pulmonary hypertension and may fall when the cardiac output is increased with inotropes or unloaded with nitrate infusions [16]. The transpulmonary gradient is calculated by subtracting the left atrial filling pressure from the mean pulmonary artery pressure. A fixed transpulmonary gradient in excess of 14 mmHg is associated with greatly elevated risk, and thus this cut off is used in the UK [17].

**Preoperative Preparation**

Donor-recipient matching takes place on the basis of urgency, blood group and size (80% or greater of recipient body weight). Organs are generally not used when the recipient has preexisting antibodies to the donor’s HLA antigens, however there are new advances which will be discussed later in this chapter. The donor heart is assessed by measurement of filling pressures and cardiac output with a Swan Ganz catheter inserted by the organ retrieval team or by direct pressure measurements. Trans-oesophageal echocardiography is sometimes used to support the retrieval assessment process. Conditions precluding use of a donor heart are summarised in table 1. If the donor heart is deemed to be satisfactory, the patient is prepared for surgery.

### Table 1: Exclusion criteria for donor hearts.

<table>
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<tr>
<th>Condition</th>
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<td>HIV positivity</td>
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<td>Significant ventricular arrhythmias</td>
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<tr>
<td>Echocardiographic abnormalities</td>
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<tr>
<td>Significant global hypokinesia</td>
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<tr>
<td>Significant valvular abnormality</td>
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<tr>
<td>Significant coronary artery disease</td>
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<tr>
<td>Any acute malignancy with the exclusion of primary brain cancer (unless craniotomy or ventricular shunt has been performed)</td>
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<tr>
<td>C Inadequately treated systemic infection</td>
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<tr>
<td>Hepatitis B surface antigen positivity, unless recipient is positive</td>
</tr>
<tr>
<td>Significant left ventricular hypertrophy</td>
</tr>
<tr>
<td>Cardiac contusion</td>
</tr>
<tr>
<td>Death from carbon monoxide poisoning with carboxyhaemoglobin level &gt;20%</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
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In the U.S., the organization United Network for Organ Sharing (UNOS) regulates donor heart allocation and prioritises based on the severity of cardiac illness, geographic distance between donor and recipient, length of time on the waiting list, and ABO blood group compatibility [11]. The physiological limit of approximately 4 to 5 h of ischemic time precludes (in the USA) national sharing of donor hearts or matching donor hearts according to human leukocyte antigen (HLA) compatibility [10]. The algorithm for allocation of donor hearts used by the United Network for Organ Sharing was changed in January 1999 to better account for medical urgency and to decrease waiting times for blood type O recipients [18]. In recent years, the widening gap between the number of waiting recipients and the number of donors has resulted
in a continuing trend toward transplanting urgent status recipients and to a liberalization of donor acceptance criteria [19]. Despite these changes, post-transplant survival has remained constant mainly due to advances in treatment [19].

Donor heart acceptance is a 2-phase process. The first step is to rule out any contraindication to heart donation such as significant heart dysfunction, CHD, transmissible diseases, or malignancies (except primary tumors of the central nervous system with low metastatic potential).

The second step is to match a specific donor to a suitable transplant candidate. In heart transplantation, matching is based on ABO blood group compatibility (not identity) and compatibility of body size. Although adult donor hearts must be ABO compatible with the recipient, this concept has been recently challenged in infants (age <12 months) by the successful performance of ABO incompatible heart transplants [11,20]. Matching donor and recipient for size is especially important in pulmonary hypertension. In general, a height and weight difference of up to 20 percent is tolerated; in potential recipients with significant pulmonary hypertension, donor size equal or higher than the recipient is usually recommended. In pediatric patients, in order to address donor shortage, a more liberal strategy utilizing an oversized donor has been advocated by many centres with successful results [11].

Donor characteristics that have been associated with outcome include age, left ventricular hypertrophy, and gender mismatches. The use of older donor hearts (>40 year old) is associated with higher perioperative mortality and a higher incidence of later cardiac allograft vasculopathy [5]. Donor left ventricular hypertrophy, defined by a left ventricular wall thickness greater than 14 mm has also been associated with decreased long-term survival in some studies [21]. Gender mismatch in cardiothoracic transplantation is an adverse risk factor, female donor gender is associated with worse 5- and 10-year survival in male recipients [5]. Donor heart allocation from hepatic C positive patients is also sometimes considered for recipients on an alternate list. Donor hepatitis C virus is associated with a decrease in 1- and 5-year mortality in recipients older than 39 years irrespective of recipient hepatitis C virus status [22]. High volume centres are also associated with better post-transplant outcomes [5], so in an effort to improve survival, the US federal regulatory agencies determined that a heart transplant program must do at least 12 transplants per year to receive federal reimbursement.

### Mechanical Circulatory Assist Devices

In recent years, the use of MCS device in treating patients with end-stage heart disease has increased significantly, as bridge to transplantation and as destination therapy for transplant ineligible candidates. This increase is based on the accumulated experience with new second-generation continuous-flow devices which show signifi-
cant improvements in survival, functional capacity and quality of life [23,24]. On the basis of the Heart Mate II Registry experience (1300 patients), guidelines for the clinical management of patients treated with continuous-flow devices have been published [25]. Risk scoring systems, such as the Seattle Heart Failure Model [26] and the Cumulative Risk Score for 90-Day in-Hospital Mortality [27] and the Destination Therapy Risk Score have been investigated to stratify patients who might benefit from LVAD support [28].

Figure 3: Heartware™ HVAD Fully Implantable LVAD miniaturized centrifugal flow pump.

Figure 4: Heartware™ MVAD Axial Flow LVAD (A), blood flow pathways through the impella (B).

Right ventricle failure is a leading cause of morbidity and death after LVAD implant (incidence of about 35%), and can be very difficult to predict [29,30]. Various means to assess right ventricle function both pre- and postoperatively have been assessed [24]. Right ventricular failure risk scores have been created that stratify the risk of
right ventricular failure (RVFRS) and death after LVAD implantation. One such RVFRS found independent predictors of right ventricular failure to include vasopressor requirement, aspartate aminotransferase >80 IU/L, bilirubin >2.0mg/dL and creatinine >2.3mg/dL [29]. Another study developed a score to predict RVAD need after LVAD placement, which included factors of cardiac index, right ventricular stroke work index, severe preoperative right ventricular dysfunction, creatinine, previous cardiac surgery and systolic blood pressure [30]. More recently the presence of severe TR and a tricuspid annulus of >43mm and right ventricular sphericity have been proposed as predictive of occult RV failure and need for biventricular support.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, which follows all long-term MCS systems in the United States, has defined patient profiles that can help identify risks associated with the timing of implant (Table 3) [31]. In the future, the INTERMACS patient profile would be a useful tool to improve management and outcomes of patients who need VAD implant, and unify criteria for future clinical trials and devices. As more LVAD patients are listed for heart transplant, a competition has occurred for organs between stable LVAD supported registrants and less stable registrants listed status 1A or 1B. A recent study found that stable LVAD patients had significantly less 30-day risk of events compared to other status 1A patients concluding that allowance of 30 days of elective status 1A time should not be allocated to stable registrants with implanted LVADs [32]. As VAD technology improves, further revisions to the allocation system will need to be recommended.

Figure 5: INTERMACS patient profiles and timeframe for initiating mechanical circulatory support with LVAD only.

Temporary MCS are available that can be implanted quickly and simply to normalize cardiac output in patients with severe acutely decompensated heart failure. The CentriMag [33], TandemHeart [34], Impella [35] and Circulite [36]. Clinical trials suggest that treatment of temporary VADs does not necessarily correlate with better survival, but merely comprise a component of treatment leading to
recovery, upgrade to fully implantable systems as a bridge to transplant or destination therapy, or transplantation [37,38].

Table 2: INTERMACS Profile and Description and Time-scale to MCS [25].

<table>
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<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>“Crashing and burning”—critical cardiogenic shock. Within hours</td>
</tr>
<tr>
<td>2</td>
<td>“Progressive decline”—inotrope dependence with continuing deterioration. Within a few days</td>
</tr>
<tr>
<td>3</td>
<td>“Stable but inotrope dependent”—describes clinical stability on mild-to-moderate doses of intravenous inotropes (patients stable on temporary circulatory support without inotropes are within this profile). Within a few weeks</td>
</tr>
<tr>
<td>4</td>
<td>“Recurrent advanced heart failure”—“recurrent” rather than “refractory” decompensation. Within weeks to months</td>
</tr>
<tr>
<td>5</td>
<td>“Exertion intolerant”—describes patients who are comfortable at rest but are exercise intolerant. Variable</td>
</tr>
<tr>
<td>6</td>
<td>“Exertion limited”—describes a patient who is able to do some mild activity but fatigue results within a few minutes of any meaningful physical exertion. Variable</td>
</tr>
<tr>
<td>7</td>
<td>“Advanced NYHA III”—describes patients who are clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. Not a candidate for MCS</td>
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</table>

INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; 
MCS = mechanical circulatory support; 
NYHA = New York Heart Association.

Device miniaturisation, without externalized drive lines connecting the device to a console and longer endurance will be the future trend of mechanical design for long term support. Blood pumps with magnetically levitated rotors has shown satisfactory 1-year survival (Figure 4, and Figure 5) [39]. The smaller size and weight of the continuous-flow devices has allowed an extension of the new VADs into smaller patients. Fully wireless resonant coupling power sources are currently undergoing evaluation, which if successful will greatly reduce the incidence of drive line infections, which is the weakest point of the technology of current fully implantable systems [40].

Figure 6: Syncardia™ Total Artificial Heart, schematic of implant.

Many recent studies have focused on the reversed molecular and cellular alterations, such as improved β-adrenergic responses and decreased calcium-regulating gene expression, in patients using LVAD as a bridge to recovery therapy [41]. Functional recovery has been observed in a subset of heart failure patients [42,43]. Recently, a clinical trial using clenbuterol (β-2 agonist and anabolic agent) and LVAD in refractory non-ischemic heart failure patients, reported recovery of heart function in 60% of patients (n = 20) with non-ischemic cardiomyopathy that allows the pump to be explanted (Harefield Recovery Protocol Study for Patients With Refractory Chronic
Heart Failure, HARPS) [44]. LVAD therapy is associated with decreased collagen turnover and crosslinking and increased tissue angiotensin II. LVAD combined with angiotensin-converting enzyme inhibition results in decreased tissue angiotensin II and collagen cross-linking, normalizes left ventricular end-diastolic pressure volume relationships and is associated with modestly higher rates of bridge to recovery [45]. Other adjunctive treatments including other medications, cell or gene therapy with over expression of SERCA2a might in conjunction with VAD support provide a meaningful alternative therapy in patients with severe heart disease [46].

The total artificial heart (TAH) for circulatory support was designed many years ago and has undergone multiple iterations (Figure 6). It is now, increasingly being used in patients with right heart failure or biventricular failure [47]. It is indicated as a bridge to transplant in patients with INTERMACS 1 heart failure who are at risk of imminent death. Scenarios include stone heart after cardiac surgery, cardiovascular failure after global infarction and acute post-infarction VSD. Clinical experience with TAH (SyncardiaTM) has suggested that it can serve as an alternative for survival with a reasonable complication rate in appropriate candidates with end stage heart failure (Figure 6) [48]. More stable patients can be effectively managed with fully implantable LVAD systems and has limited the use of the TAH.

Advances in Organ Preservation

Heart Retrieval

The retrieval process is a highly organized process as a part of a multidisciplinary, multi-organ retrieval. The assessment takes place with the assistance of a Swan Ganz catheter and occasionally with transesophageal echocardiography to assess function and the presence of valvular disease or other anomalies. After median sternotomy, the pericardium is opened and elevated and the heart is inspected and palpated for size, contractility and anomalies.
The coronary arteries are assessed for damage or palpable coronary artery disease. The inferior vena cava (IVC), superior vena cava (SVC) and ascending aorta are dissected. Heparin is administered. The retrieval commences by cross clamping the aorta as high as possible. Cardioplegia solution (15 ml/kg) is administered via a cannula in the ascending aorta until asystole occurs. The heart is cooled with topical ice-cold saline. The IVC is divided and an incision is made in the left atrial appendage especially if the lung is concurrently retrieved to prevent distension of the LV. After giving cardioplegia, the aorta is divided as high as possible. The pulmonary artery is divided at the level of its bifurcation. The SVC is divided at the level of the azygos vein. If the heart and lungs are to be retrieved, the left atrium is incised at the junction of the left superior pulmonary vein, and extended inferiorly. Care is taken to avoid injury to the coronary sinus. The incision continues inferiorly and then to the junction of the right inferior pulmonary veins and left atrium. By this means the heart is excised with a cuff of left atrium and adequate cuff of left atrium is left continuous with the pulmonary veins to facilitate lung retrieval and subsequent implantation. If the heart alone is to be retrieved, then the pulmonary veins are divided and the intact left atrium is left in continuity with the retrieved heart. Meticulous preservation by administration of adequate cardioplegia and topical cooling is required. The retrieved heart is stored in ice-cold saline, triple polythene bagged and transported in ice to ensure adequate preservation. It is important to expeditiously transport the heart to the implant centre to ensure a tolerable ischaemic time. This is the widely used cold static transportation method. There is an inverse relationship between ischaemic time and post-transplant survival [49].

Figure 8: Organ Care System® (OCS) (TransMedics, Andover, MA, USA). The retrieved heart is cannulated and perfused. Haemodynamic, electrocardiographic and metabolic (pH and lactate) monitoring is performed to assess suitability of the heart. The system can also facilitate ex vivo coronary catherisation.

Longer transportation distances and organ retrieval from sites with limited abilities for pre-retrieval evalua-
tion have to be considered. The development of ex vivo perfusion systems such as the Organ Care System* (OCS) (TransMedics, Andover, MA, USA) (Figure 8) may extend the extracorporeal period by reducing the periods of cold and warm ischaemia, with the possibility to constantly evaluate and interact with the retrieved heart during organ transport. The retrieval process is conducted as previously described with the administration of cardioplegia, and then the heart is placed on an ex-vivo perfusion system where it is reperfused [50]. One of the potential advantages of the OCS* is the ability to perform coronary angiography of the donor heart, if a pre-explantation angiography evaluation is not possible at the donor hospital and if significant evidence for coronary artery disease in the donor heart becomes known, because of the donor’s medical history or after palpation of sclerotic coronary ostia. With the donor heart is still in the OCS*, not only is it possible to measure metabolic parameters and pressures, but even coronary angiography is feasible. With the increasing international demand for donor organs, such ex vivo examinations might play a more important role, because longer transportation distances can be accepted and organs from suboptimal donors without pre-explantation diagnostics may be considered at donor sites with limited diagnostic options. Current organ retrieval in the US is limited to around 500 nautical miles. Ex-vivo perfusion systems allow extended transport time and distances. This could allow national retrieval networks in India and China.

Another recent threat to cardiac transplant is the increased usage of circulation deceased donors (DCD). In the UK in particular this has led to a decline in the availability of brain stem dead donors (DBD). Cardiac transplantation in other health systems is still hindered by the lack of donor organs. The initial experience with transplantation used circulation deceased donor (DCD) hearts. More recently, a cohort of infant hearts were retrieved and successfully transplanted. Concerns on the ethics of the hands off time, which were less than the recommended 10-15 minutes once cardiac arrest had taken place [51].

The impact of donor cardiac arrest on orthotropic heart transplantation was investigated using the United Network for Organ Sharing database (UNOS) [51]. In 856 out of a total of 19980 cases, the donors from the UNOS series, had histories of cardiac arrest, and in the remainder, there was no history of donor cardiac arrest. The unadjusted 1-, 5-, and 10-year actuarial survival rates between the arrest and the non-arrest groups were not significantly different. Multivariate logistic regression demonstrated no difference in survival in the donor arrest group at 30 days, 1 year, or 3 years. Furthermore, the adjusted Cox proportional hazard model for cumulative survival also showed no survival difference between the 2 groups. If standard recipient and donor transplantation criteria are met, a history of donor cardiac arrest should not prohibit the potential consideration of an organ for
transplantation [52].

A severe donor organ shortage leads to the death of a substantial number of patients who are listed for transplantation. The use of hearts from donors after circulatory death could significantly expand the donor organ pool, but due to concerns about their viability, these are currently not used for transplantation.

Short-term extra corporeal circulation with in situ normo-thermic machine perfusion (MP) may allow reanimation and resuscitation of the previously arrested heart in DCD donors. This has been demonstrated in rat and porcine models. Porcine DCD hearts after 29 min of warm ischemia can be reanimated using in situ extracorporeal circulation [53].

For DCD hearts, a strategy of pre-reperfusion cardioplegia, followed by continuous warm blood perfusion, is superior to cold storage. These results suggest DCD hearts may be more suitable for transplantation after continuous warm blood perfusion than after cold storage. Although cold storage is a time-tested method for the preservation of hearts during the ex vivo transport interval, its disadvantages are highlighted in hearts from the extended criteria donor. In contrast, transport of high-risk hearts using hypothermic machine perfusion provides continuous support of aerobic metabolism and ongoing washout of metabolic byproducts. Perhaps more importantly, monitoring the organ's response to this intervention provides insight into the viability of a heart initially deemed as extended criteria. Obviously, ex vivo perfusion introduces challenges, such as ensuring homogeneous tissue perfusion and avoiding myocardial oedema. Though numerous groups have experimented with this technology, the best perfusate and perfusion parameters needed to achieve optimal results remain unclear [54].

**Advances in Surgical Techniques**

Heart transplantation may be done with an orthotopic technique, with the donor heart implanted in the mediastinum in place of the native heart or a heterotopic techniques with the donor heart implanted beside the native heart in parallel with it. This was done to mitigate against the risk of early graft failure which was high in the early era of heart transplantation. Heterotopic transplantation is rarely done today, however there are two possible indications for heterotopic heart transplantation; patients with elevated pulmonary hypertension in whom the donor right ventricle would be unable to tolerate the increased afterload; and significant size mismatch (donor/recipient weight ratio >75%), especially seen in paediatric patients and patients with irreversible elevation in pulmonary hypertension.

The biatrial technique for orthotopic heart transplantation was first performed in a dog model by Lower and Shumway in 1960 [55]. Preservation was provided by the
use of topical hypothermia induced by immersion of the graft in iced saline [3,55]. Sievers et al. [23] described a variation of the orthotopic procedure termed the bicaval technique where the donor right atrium is attached directly to the inferior and superior vena cava and the left atrial anastomosis is done as a cuff. Compared with biatrial approach, the bicaval approach results in less disruption of the atrial geometry, better right ventricular function, less tricuspid and mitral regurgitation, and less sinus node dysfunction [57].

The operative steps are as follows: Through a mid-line sternotomy, the diseased heart is exposed. Following full systemic heparinisation, cannulation for cardiopulmonary bypass is accomplished with a straight aortic cannula, high in the ascending aorta. Venous cannulation is via a right angle or straight cannula directly into the superior vena cava or through the posterior right atrium into the superior vena cava. Inferior vena cava cannulation is accomplished through the posterior right atrium. Certain situations, such as recipient instability or difficult mediastinal dissection may need femoral cannulation for cardiopulmonary bypass.

When the donor heart is close to the operating room the ascending aorta is cross-clamped and the diseased heart is excised. An incision is made in the right atrial appendage. This is extended inferiorly, anterior to the inferior vena cava cannula and towards the aorta root. The left atrium is entered through the superior limb of the fossa ovalis. The aorta and pulmonary arteries are transected just above their ventriculo-arterial valves. The interatrial septum is divided down to the coronary sinus, which demarcates the atrioventricular groove. Resection of the heart results in cuffs of left atrium, SVC, IVC, aorta, and pulmonary artery. Prior to implantation, the donor heart is inspected for a patent foramen ovale, which is closed by direct suture, and any other anomalies. Further myocardial protection in the form of 1000 ml of cold blood cardioplegia may be given into the donor heart via its clamped aortic root. The implant procedure begins with anastomosis of donor and recipient left atria (Figure 9). Using a 4/0 polypropylene monofilament suture, the anastomosis starts at the level of the left atrial appendage. Care is taken to align the interatrial septum. A transmitral vent is placed prior to completion of the left atrial anastomosis to vent the left ventricle and stop it from distending. Cardiac cooling may be augmented by running cold Ringer’s solution through this vent during implantation. The next anastomosis is to the donor and recipient aorta. The donor aorta is left long so that there is little tension on the anastomosis, and so it can be manipulated to allow inspection of the suture lines on completion of the transplant. This is done with continuous 4/0 polypropylene monofilament suture. At this point the heart can be deaired via a needle vent placed in the ascending aorta, and reperfusion begun with warm, leukocyte filtered blood
at a carefully controlled pressure. Prior to release of the cross clamp, 500 mg of methylprednisolone is given intravenously. The next anastomosis is the PA, this is done with continuous 5/0 polypropylene. The pulmonary artery should be trimmed short. If the pulmonary artery is left too long, distortion can occur with reestablishment of normal right ventricular contraction. The final anastomoses are between the respective inferior and superior vena cavae, with continuous 5/0 polypropylene, tied down initially to prevent purse stringing of these low pressure structures. When the patient has been rewarmed there follows at least 30 min of reperfusion. An isoprenaline infusion is commenced, pacing wires are placed on the surface of the heart and the patient is weaned from cardiopulmonary bypass. Protamine is administered to reverse the effects of heparin and haemostasis is performed, followed by closure.

Despite the use of the bicaval technique, tricuspid regurgitation remains a problem early and late after heart transplantation. Adding a tricuspid annuloplasty ring to stabilize the annulus, to the transplant operation has been recently shown to decrease the incidence of tricuspid regurgitation and may even improve survival [58].

Figure 9: Commencement of the donor/recipient left atrial anastomosis. A coronary sinus catheter may be placed.
(Reprinted with permission, Elsevier Limited).

Recent advances in organ preservation may also lead to further improvement in outcomes. One of the most promising new technologies is normothermic organ preservation, which provides warm blood perfusion of the donor organ, potentially decreasing reperfusion injury and graft dysfunction. If proven effective, this technology may decrease early graft failure and allow increased utilization...
of available organs. Its potential to decrease ischemic time may also give greater opportunity for prospective cross-matching in heart transplantation [59].

**Immunology of Transplantation**

Immunological barriers remain central in transplantation medicine. An evolving understanding of the pathways involved in immune activation has led to many breakthroughs in transplantation medicine, including the development of novel immunosuppressive agents.

![Image of multiple signaling pathways](image)

**Figure 10:** The alloimmune response requires activation of multiple signaling pathways.

The first signal is provided when antigen-presenting cells and antigens activate the T cell receptor. Co-stimulation (signal 2) occurs when CD80 (B7-1) and CD86 (B7-2) on the antigen-presenting cells engage CD28. Both signals activate important signal transduction pathways (calcineurin, RAS-mitogen-activated protein kinase [MAP-K] pathway, and the nuclear factor-kappa B [NF-kB] pathway). These pathways lead to expression of many molecules, including interleukin (IL)-2 and IL-15. Interleukin-2 and other cytokines then activate the “target of rapamycin” pathway to provide the trigger for cell proliferation (signal 3). AP-1 “ activating protein 1; CDK “ cyclins-dependent protein kinase; IKK “ serine-threonine protein kinase; JAK3 “ Janus kinase 3; MHC “ myosin heavy chain; mRNA “ messenger ribonucleic acid; mTOR “ mammalian target of rapamycin; NFAT “ nuclear factor of activated T cells; PKC “ protein kinase C; S-1-P “ sphingosine-1-phosphate; TCR “ T cell receptor. Adapted, with permission, from Halloran [61].

T cell lymphocyte activation plays a central role in the alloimmune response (Figure 9). The alloimmune response starts with the activation of antigen-presenting cells of donor (usually dendritic cells) and host origin. Once activated in the graft and surrounding tissue, these cells migrate to secondary lymphoid organs where they engage alloantigen-reactive naïve T cells and central memory T cells [60-62]. Naïve T cells and memory T cells may recirculate in the secondary lymphoid organs or un-
dergo clonal expansion and differentiate into effector cells when activated. Direct antigen presentation to antigen-experienced cells by donor cells such as graft endothelium may also occur [61,63].

T cell activation requires the stimulation of at least 3 signal pathways (Figure 2) [61]. The first signal originates from the interaction between the major histocompatibility complex/peptide complex and the T cell receptor/CD3 complex. Antigen-presenting cells, provide co-stimulation when the CD80 and CD86 (B7) interact with the CD28 on T cells. Co-stimulation is also influenced by the interaction of CD80 and CD86 with CD152 (CTLA-4) as well as the interaction of CD40 and CD154 (CD40 ligand). These signals lead to the activation of 3 transduction pathways: the calcium-calcineurin pathway, mitogen-activated protein kinase pathway, and the nuclear factor-kappa B pathway [61,64]. The activation of these pathways leads to the expression of interleukin-2 as well as molecules such as CD154 and CD25. The third signal of the alloimmune response occurs when interleukin-2 and other cytokines activate the target of rapamycin pathway that leads to cell proliferation and differentiation and, therefore, a large number of effector cells.

B cells are also activated when antigens interact with B cell receptors, usually in secondary lymphoid organs and possibly in the transplant organ. B cell activation is also mediated through the interaction between B and T cells through CD40/CD40L and B71-2/CD28 as well as CTLA-4– and CD20-mediated activation. Complement and inflammatory mediators are also activated and contribute to the alloimmune response [61].

Rejection takes place by both cellular and antibody-mediated processes [65-67]. Antibody-mediated rejection (AMR), is usually associated with hemodynamic compromise at presentation and a greater risk of allograft vasculopathy and mortality [66,67]. In cellular rejection (CMR), effector T cells mediate an inflammatory response leading to infiltration of the myocardium by activated macrophages, effector T cells, and plasma cells. The characteristic lesion of CMR consists of mononuclear cells invading the myocardium. CMR is classified into 3 classes depending on the extent of cellular infiltration and myocyte damage. In the internationally accepted grading system for cellular rejection, ISHLT grade 2R or higher is considered clinically significant cellular rejection [68,69].

Antibody-mediated rejection occurs when alloantibody against donor antigens targets capillary endothelium [65-67]. Although the significance of AMR is increasingly recognized, no firm consensus has yet been reached on its recognition and diagnosis either histopathologically or immunologically [69]. Antibody-mediated rejection is usually diagnosed histologically by demonstration of capillary injury with endothelial cell swelling and intravascular macrophage accumulation. Positive immunofluorescence for AMR namely, CD68+, C4d, or C3d com-
plement fragments supports the diagnosis [69]. Positive immunofluorescence for both C4d and C3d complement fragments may be associated with clinical allograft dysfunction [70].

**Immunosuppression**

Immunosuppression prevents or treat rejection. It also minimises the risk of infection or cancer. Immunosuppression works by blocking lymphocyte activation or response pathways, depleting lymphocytes, or diverting lymphocytic traffic [61,71]. In the early 1980s, the introduction of cyclosporine was followed by a significant improvement in survival of heart transplant recipients (Figure 8).

Induction therapy is the use of more intense immunosuppression in the initial days after transplantation. This provides intensive immunosuppression when the alloimmune response is also most intense. It may also be used to permit delayed initiation of calcineurin inhibitors (CNIs) for maintenance immunosuppression in patients with significant renal failure (RF). Induction immunosuppression essentially is with: 1) depleting antibodies (e.g., polyclonal antibodies [horse or rabbit antithymocyte globulin], anti-CD3 antibodies [OKT3], human monoclonal anti-CD52 [alentuzumab]); or 2) nondepleting antibodies (e.g., anti-CD25 antibodies [daclizumab, basiliximab] or fusion proteins (e.g., CTLA4-Ig [LEA29Y]) [72]. A survival benefit of induction therapy not been clearly established, however [72–74]. OKT3 use may be associated with a greater risk of lymphoproliferative disorders [72,75]. Induction agents are probably most useful in highly sensitised patients or patients with severe RF at the time of transplantation.

Standard triple therapy for maintenance immunosuppression comprises corticosteroids (usually prednisolone), a CNI (cyclosporine or tacrolimus), and an antiproliferative agent (usually mycophenolate mofetil). Prednisolone is used early after heart transplantation and usually tapered to low doses or withdrawn during the first year. Withdrawal of steroids may take place early within the first month after or late between 6 to 12 months post-transplant. Late steroid withdrawal may have the advantage of maintaining more intensive therapy in the first 6 months when the risk of rejection is still high [11,76,77]. There is a strong interest in minimizing steroid use in children, as it impairs growth. The use of tacrolimus in heart transplantation has steadily increased, and it now is the most commonly used CNI [5,78] and is associated with a decreased incidence of rejection episodes, although a survival benefit has not been clearly demonstrated [79]. Tacrolimus is favoured over cyclosporine in the presence of a higher risk of rejection. Preliminary data suggest the safety of tacrolimus monotherapy in heart transplantation [78]. The use of mycophenolate mofetil has replaced the use of azathioprine. Molecular target of rapamycin inhibitors or
proliferation signal inhibitors (sirolimus and everolimus) have been shown to decrease the progression of allograft vasculopathy and cancer as well as provide resistance to rejection [80-82]. Poor wound healing is, a serious side effect associated with sirolimus and to a lesser degree with everolimus and limits its use [83].

In patients with established allograft vasculopathy, sirolimus may decrease the progression of allograft vasculopathy and possibly lead to reversal of the process [81,84]. In patients with severe renal failure (RF), calcineurin-free regimens (combining sirolimus and mycophenolate mofetil) late after transplantation can improve renal function without increasing the risk of rejection [85,86]. Belatacept, a costimulatory signal inhibitor could represent an alternative to CNIs [87]. In a phase II multicenter noninferiority trial in de-novo renal transplant recipients, Vincenti et al. [87] showed that there was no significant difference in acute rejection rates between belatacept and cyclosporine. Belatacept treated patients demonstrated significantly lower rates of tubular atrophy and interstitial fibrosis. Clinical trials of belatacept are ongoing in renal transplantation. If proven efficacious and safe, belatacept will most probably undergo investigation in heart transplantation. Individualization of immunosuppression with better immune monitoring and pharmacogenomics will eventually play a greater role in optimisation of therapy [88].

Methods for managing acute rejection are also changing. The management strategy for acute rejection depends on the histological type of rejection (cellular vs. AMR) as well as its severity (hemodynamic compromise and/or high histological grade) and history of prior immunosuppression and rejection episodes. A high-dose corticosteroid (3-day course of methylprednisolone 1 g daily) is used for significant cellular rejection (>2R ISHLT classification) or any rejection-associated hemodynamic compromise. Lymphocyte-depleting agents such as antithymocyte globulin are also considered in patients with hemodynamically compromising or high-grade (3R) cellular rejection.

Severe AMR with haemodynamic compromise is usually treated with high-dose corticosteroids and plasmapheresis followed by intravenous immunoglobulin or rituximab (a B-cell-depleting monoclonal anti-CD20 antibody). T cell depleting antibodies such as antithymocyte globulin are sometimes added to help modulate the interaction of T and B cells. Studies assessing the best treatment strategy for AMR are currently in progress [67].

Recurrent rejection is challenging to manage. Photopheresis may reduce the risk of subsequent hemodynamic compromise rejection and/or death from rejection when initiated for patients with high rejection risk [89]. Total lymphoid irradiation has also been shown to decrease the chances of subsequent rejection but may be associated with a greater risk of lymphoproliferative disorders [90].
Transplantation across blood groups

Transplantation of hearts from ABO-incompatible donors is contraindicated because of the risk of hyperacute rejection mediated by preformed antibodies in the recipient to blood-group antigens of the donor. This contraindication may not apply to newborn infants, who do not yet produce antibodies to T-cell–independent antigens, including the major blood-group antigens. In particular, stimulation by T-cell–independent polysaccharide antigens, such as the capsular components of bacteria (e.g., pneumococci), does not elicit a serum antibody response early in life [92]. Similarly, the production of antibodies to the carbohydrate blood-group antigens begins at the age of six to eight months, in infants of susceptible genotypes, as a cross-reactive immune response after the colonization of the gut with polysaccharide-bearing Escherichia coli [92].

Serum isohemagglutinin titers are measured before and after transplantation. Plasmapheresis, immunoadsorption or administration of soluble carbohydrate antigen is used as well as plasma exchange during cardiopulmonary bypass. Standard immunosuppressive therapy is used, and rejection is monitored by means of endomyocardial biopsy. Despite the eventual development of antibodies to antigens of the donor’s blood group in some infants, there is usually no damage to the graft. The absence of antibody production or its delay beyond the time expected because of early immunosuppression may be evidence of partial B-cell tolerance induced by exposure to donor antigens during the maturation of the immune system [93]. It is also thought that accommodation occurs. This term originally describes endothelial cell resistance to antibody-mediated rejection after ABO-incompatible kidney or experimental xenograft transplant. In both cases, the endothelial antigens that are the targets of the antibody response are mainly carbohydrates [33,66]. The use of ABO-incompatible donors has resulted in the mortality rate among infants on the waiting list declined from 58 percent to 7 percent.

The particularly devastating effects of both hyperacute and delayed antibody-mediated rejection, in heart transplantation, have meant that it is mandatory to avoid situations in which antibody-mediated rejection may occur. HLA compatibility is not the principal determinant of outcome in cardiac transplantation, sensitised patients who have antibodies to the donor’s HLA antigens before transplantation are at high risk for graft loss due to humoral rejection, however. To identify patients at risk for donor-specific alloreactivity, cardiac transplantation candidates are screened for antibodies that are reactive with lymphocytes from a panel of volunteers representative of the major HLA allotypes; these antibodies are collectively referred to as PRAs. Patients with high PRA levels are con-
sidered sensitised to various alloantigens and require donor-specific T-cell cross-matches before transplantation to exclude the presence of lymphocytotoxic IgG antibodies against donor class I HLAs, which can cause early graft failure resulting from complement-mediated humoral rejection [94,95]. Because a positive donor-specific T-cell cross-match is a contraindication to transplantation, sensitised candidates have longer waiting times and higher mortality rates while waiting for organs [97,98]. In addition, the presence of preformed anti-HLA antibodies predicts poorer long-term outcome, including an increased number of cellular rejections, earlier coronary allograft vasculopathy (CAV) onset, and decreased long-term graft survival compared with nonsensitised patients treated with standard triple-drug immunosuppressive regimens. These complications seem primarily related to the presence of preformed antibodies against allogeneic HLA class II molecules and may reflect an underlying state of CD4 T-cell allosensitisation to class II antigens [98-101]. The proportion of highly sensitised patients on cardiac transplant waiting lists has increased as a result of widespread use of left ventricular assist devices (LVADs) and more patients undergoing retransplantation [102]. Whereas alloreactivity in retransplant candidates, blood product recipients, and multiparous women is a result of repeated B- and T-cell exposure to alloantigens, the high frequency of alloreactivity in LVAD recipients seems to result additionally from polyclonal B-cell activation. This activation is attributable to selective loss of Th1-type cells through activation-induced cell death and unopposed production of Th2-type cytokines [103,104]. Interventions in sensitised recipients have focused on therapies aimed predominantly at Ig depletion and B-cell suppression [105,110]. Recent studies suggest that pooled human intravenous Ig is an effective modality to reduce allosensitisation [81,82]. Postulated mechanisms include the presence in intravenous Ig of anti-idiotypic antibodies [111,112], antibodies against membrane-associated immunologic molecules such as CD4 or CD5 [114,115], or soluble forms of HLA molecules [116,117]. The authors investigated the effects of intravenous Ig on serum reactivity to HLA class I molecules in LVAD recipients and compared these effects to those obtained with plasmapheresis, an alternative modality for alloreactive antibody reduction [96]. Viable modalities include immunoadsorption, rituximab and cyclophosphamide. Furthermore intravenous pulse cyclophosphamide therapy, together with pretransplantation intravenous Ig as part of a CyA/steroid-based regimen in sensitised cardiac allograft recipients, is extremely effective and safe for decreasing recipient serum and cellular alloreactivity, shortening transplant waiting time, and reducing allograft rejection.
Post-Transplant Immune and Functional Monitoring

Immune monitoring of cardiac transplants relies on the use of the endomyocardial biopsy, drug level monitoring, and echocardiography. Many patients may still present with rejection, infection, or drug toxicity despite having the desired level of immunosuppression. Endomyocardial biopsy is the gold standard for the diagnosis of rejection and has been so for many years. Its value is limited by significant sampling error and most centres now limiting routine endomyocardial biopsies to <5 years [119].

Many studies have demonstrated that abnormal diastolic parameters of allograft function represent sensitive, although less specific, markers of cellular rejection [120,121] >10% change in maximal systolic or diastolic tissue Doppler velocity of the posterior wall of the left ventricle was a sensitive and specific marker of cellular rejection (grade >2 in the previous classification). Elevation in BNP is also associated with cellular rejection [122]. Therapeutic monitoring of drugs are very useful in the post-transplant surveillance period. Principally CNIs are monitored closely at C0 and now at C2 intervals [123,124].

Gene expression profiling (GEP) is also useful in identifying rejection [125-128]. Gene expression profiling may also be useful for rejection surveillance in heart transplant recipients. In the CARGO (Cardiac Allograft Rejection Gene Expression Observation) study, a multigene algorithm based on the expression of 20 genes, weighing the contribution of each gene, resulting in a score from 0 to 40. Scores below threshold indicate a very low likelihood of moderate-to-severe acute cellular rejection on endomyocardial biopsy (ISHLT grade >3A/2R). These tests have yet to become a major part of clinical practice as further studies are ongoing to assess the safety of routine GEP instead of biopsies (ongoing IMAGE [Invasive Monitoring Attenuation Through Gene Expression] study) [128]. There are also direct immune assays that monitor antibody production and T cell function [6,129,130].

Anti-HLA donor-specific antibodies are associated with increased incidence of early and severe allograft rejection and late development of cardiac allograft vasculopathy and decreased survival [6,132,133]. The importance of non-HLA antibodies is also being increasingly recognised [6]. HLA sensitization is a well-recognized risk factor for rejection. T cell functional tests have also been recently introduced (ImmuKnow, Cyclex Inc., Columbia, Maryland) [134].

In future, comprehensive monitoring is likely to rely on a combination of multiple methods including, biopsy with histopathology, graft functional monitoring with imaging modalities and B-type natriuretic peptide (BNP), drug level monitoring, genomic markers of rejection,
donor-specific antibodies monitoring, and direct immune function assays.

**Cardiac Allograft Vasculopathy**

Transplant vasculopathy and malignancy are the most important causes of death after 1 year [5]. Significant allograft vasculopathy is found in many patients at 5 years [5,7]. It is characterised by diffuse intimal hyperplasia affecting the epicardial vessels and the microcirculation [7,135-137].

Non-immune risk factors for allograft vasculopathy include hyperlipidemia, hypertension, diabetes mellitus, homocysteinemia, older donor age, and donor brain stem death [5,138,139]. Immune risk factors include HLA donor/recipient mismatches (especially HLA DR mismatches), recurrent cellular rejection, AMR [66,121,138]. Viral infections, especially cytomegalovirus, are also important [140].

Intravascular ultrasound may be used to aid diagnosis and follow-up of allograft vasculopathy [139,141]. Progression of intimal thickness of more than 0.5 mm during the first year is a powerful predictor of all-cause mortality, myocardial infarction, and later angiographic abnormalities [141]. Management of allograft vasculopathy focuses on the aggressive management of risk factors such as hyperlipidemia and the use of proliferation signal inhibitors such as sirolimus [81,142]. Statin therapy decreases allograft vasculopathy and improves mortality [143,44]. Percutaneous revascularization of allograft vasculopathy is limited by the diffuse nature of the disease [85]. Re-transplantation is also considered in selected patients with severe allograft vasculopathy.

**Advances in Heart Failure Management**

Most recommended therapies for heart failure which reduce mortality [146] cause reverse remodeling (Table 2) [147]. β-adrenergic receptor blocker and angiotensin-converting enzyme inhibitors (ACEI) decrease mortality by 31% and 20% respectively [146]. β-adrenergic receptor blockers improve b-adrenergic response, sarcoplasmic/endoplasmic reticulum calcium ATPase gene (SERCA2a) upregulation and calcium handling of myocytes, whereas ACEIs decrease interstitial fibrosis through reducing myocardial collagen content and left ventricle mass [147-154]. Aldosterone antagonists can reduce mortality by a further 25% by reducing fibrosis and augmenting the impact of ACEI [150,155]. The Eplerenone Study indicated that early initiation of eplerenone is associated with better outcomes [156], however, aldosterone antagonist therapy is probably underused in heart failure patients [157].

Elevated heart rate is also risk factor for cardiovascular events in heart failure. The SHIFT trial with ivabradine added to standard heart failure therapy with optimal doses of b-blockers was shown to improved survival and
reversed left ventricular remodeling [158].

New therapies, in the research domain, inhibit GMP-specific 3', 5'-cyclic phosphodiesterase [159,160] upregulate the SERCA2a gene [161], block calcium/calmodulin dependent kinase II [162], alter protein kinase C isoform a [163], alter transient receptor potential channels [164], or affect transforming growth factor α pathways [16].

Patients with heart failure often have regions of delayed myocardial activation and contraction, leading to cardiac dyssynchrony. Cardiac resynchronization therapy (CRT) is reported to be able to improve symptoms and the quality of life, reduces complications and the risk of death in patients with heart failure and cardiac dyssynchrony [166-169].

A major hallmark of patients with heart failure is abnormal calcium cycling into and out of the sarcoplasmic reticulum of cardiomyocytes. Overexpression of SERCA in the presence of high concentrations of α agonists have been shown not to increase the incidence of arrhythmias or after-contractions in isolated rabbit myocytes [173, 174]. Multiple studies have revealed that reduced SERCA2a expression and decreased phospholamban phosphorylation both contribute to this impairment by raising the concentration of Ca2+ in the cytosol during diastole and reducing it during systole [175,176]. Recently, gene therapy in human subjects, targeted on SERCA2a has been proven to be safe with trends toward clinical improvement [161]. Research that has flowed from lab based SERCA2a overexpression has led to a clinical trial, SERCA2a which will examine the functional effects of overexpression of SERCA2a in a patient population with a fully implantable LVAD and CUPID2 will assess whether gene therapy to increase SERCA2a is safe and can improve quality, length of life, and reduce emergency hospital admissions, for heart failure patients.

Conclusions

Heart transplantation is associated with excellent long term outcomes and is the gold standard solution for intractable end stage heart failure in eligible patients. What limits its impact, overall, is the limited availability of donor organs. The development of ventricular assist devices has mitigated against this, to some extent. Subsequent device iterations with further miniaturisation and continuous flow have resulted in effective bridge to transplant solutions. The presence of an externalized drive line exposes the VAD recipient to infections, however, which may precipitate urgent listing for heart transplant in the bridge to transplant candidate and may limit the life span of the destination therapy candidate. Fully implantable driveline free systems will definitely enhance the utility of these systems in these settings. As our knowledge of molecular medicine increases, manipulation of key proteins implicated in the pathophysiology of heart failure such as SERCA2a may allow some recovery of the myocardium in patients with heart failure to the extent that transplan-
tion may be deferred or the LVAD explanted.

Another important issue is to find solutions to the low numbers of donors, which, as discussed, is further pressurised by the increased usage of DCD donors. Ex vivo perfusion systems are one answer to facilitate transport across large distances and allow the heart to be evaluated with a considerable reduction in ischaemic time. Furthermore, systems in evolution in experimental models to allow reanimation of the DCD heart need to be translated into the clinical retrieval process. In situ perfusion of the DCD donor with ECMO is particularly attractive followed by ex vivo perfusion during transport.

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