Heart transplantation

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Abstract

Heart transplantation is the definitive treatment for selected patients with end-stage heart failure refractory to medical, interventional and surgical treatment. However, due to a limited number of donor organs, most patients wait a long time for heart transplantation and a significant proportion die or become unsuitable for transplantation while waiting. Although post-transplant survival outcomes continue improving, a fifth of recipients die within 1 year after transplantation. In addition, recipients face constant threats from infection, rejection, malignancy and chronic allograft vasculopathy. Therefore, it is imperative to increase donor heart utilization to reduce waiting list mortality, maintain allograft quality during transportation and optimize post-transplant care to improve outcomes. This review summarizes the process of heart transplantation from recipient and donor selection and matching to post-transplant management with a focus on the surgical aspects, and highlights recent advancements, including the donation after circulatory death programme, mechanical circulatory support, and *ex vivo* heart perfusion.

Keywords Donation after circulatory death (DCD); *ex vivo* heart perfusion; heart transplantation; immunosuppression; surgical technique

Introduction

Since first performed in 1967, heart transplantation has made significant progress and benefited more than 140,000 patients in the last half century.[1] Despite advances in medical treatment, mechanical support and stem cell therapy, heart transplantation remains the gold-standard treatment for selected patients with end-stage heart failure. The median survival for the adult cohort transplanted between 2002 and 2009 has reached 12.5 years.[1] Although annual heart transplant activity is still on a slow rising trend both in the UK and worldwide, it is outstripped by the number of patients on the transplant waiting list. Therefore, cautious liberalization of donor selection criteria, careful review of heart allocation systems, improvement of allograft quality preservation, personalized immunosuppression therapy, and early diagnosis of rejection and chronic allograft vasculopathy (CAV) require ongoing research and innovation. The launch of the donation after circulatory death (DCD) programme in 2014 has contributed to a small increase in heart transplant activities with encouraging early results. However, as of yet, relatively few transplant centres in the world have established DCD heart transplant programmes.

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Pre-transplant preparation

Recipient selection

Recipient-related factors are closely associated with post-transplant survival. This, coupled with a limited number of donor hearts, necessitates careful selection of appropriate candidates. Medical management must be optimized. Assessment of the severity of heart failure, with selection of those with an estimated survival of less than 50% at 1 year, is crucial. The best estimate of functional capacity is by measurement of peak O_2 consumption (VO_2max) during cardiopulmonary exercise testing.

Patients with low VO_2max (<12 ml/min/kg if on beta-blocker, or <14 ml/min/kg if not on beta-blocker) despite maximal tolerable medical treatment have a high mortality rate.[2]

The pre-transplant assessment includes thorough medical history and physical examination, pulmonary function tests, cardiopulmonary exercise testing, blood tests, chest imaging, ECG, stress ECHO, right heart catheterization, screening for malignancy and undiagnosed comorbidities. 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. If reactive, this pulmonary hypertension may fall when the cardiac output is increased with inotropes or the left ventricle is unloaded with nitrate infusions. A fixed trans-pulmonary gradient (mean PA pressure minus left atrial, or 'wedge' pressure) in excess of 14 mmHg is associated with greatly elevated risk, and thus this cut off is used in the UK. The main indications, risk factors, and contraindications are listed in Table 1.[2–4] One of the most important criteria is the patient's willingness to adhere to lifelong immunosuppression therapy after transplantation.

Patients on the waiting list are regularly followed up by the heart transplant team, in order to optimize their medical therapy, review their fitness for transplant, and provide cardiac rehabilitation and psychological counselling. If patients' condition deteriorates, they may be admitted for intravenous diuretics and inotropic support, temporary haemodynamic support, such as intra-aortic balloon pump (IABP) insertion or extracorporeal membrane oxygenation (ECMO), and/or left ventricular assist device (LVAD) implantation. They may also be added to an urgent or super-urgent transplant list, in order to improve their chance of receiving a donor heart in a short period of time.

Donor selection

As donor characteristics and allograft quality influence post-transplant outcomes, less than 30% of the donor hearts are currently procured for clinical transplant.[5] A comprehensive assessment of donor hearts consists of donor characteristics, cause of death, past medical history, social history, inotrope support, blood tests, electrocardiogram (ECG), echocardiogram (ECHO), right heart catheterization and coronary angiogram (if indicated). In addition, the distance between the donor and recipient hospitals and other logistic factors that affect the cold ischaemic time need to be taken into consideration. The donor

Summary of the main indications, risk factors and contraindications for heart transplantation

Indications	Risk factors	Contraindications
• Severe HF symptoms refractory to maximum tolerable medical treatment • Severe coronary artery disease not amenable to interventional or surgical revascularization • Severe ventricular arrhythmias despite conventional therapies • VO_2max $\leq$12 ml/ min/kg on beta-blocker or $\leq$14 ml/ min/kg not on beta-blocker • Estimated 1-year survival <80% based on HF prognosis scoring system, e.g. HFSS	• Age >60 • Congenital heart disease • Previous cardiac surgery, especially heart transplantation • Temporary mechanical support • Mechanical ventilation • Obesity with BMI 30–35 • Smoking in the last 6 months • Frailty	• Irreversible pulmonary hypertension with PVR >5 Wood units or TPG >15 mmHg • Active systemic Infection • Irreversible organ damage/dysfunction • Significant symptomatic cerebral vascular disease • Active malignancy or previous malignancy with high risk of recurrence • Severe cognitive impairment or dementia • BMI >35 • Ongoing drug abuse • Non-compliance with medical advice

HF, heart failure; HFSS, heart failure survival score; PVR , pulmonary vascular resistance; TPG, trans-pulmonary gradient (mean pulmonary artery pressure – left atrial filling pressure).

Table 1

selection criteria differ slightly across centres and countries. The main donor factors of both ideal and extended-criteria reported in the literature are summarized in Table 2.[3,6] All available donor factors should be considered collectively. Among all the donor factors, the most important are left ventricular ejection fraction (LVEF), inotropic support, left ventricular hypertrophy (LVH), cold ischaemic time and donor age.[3] A registry data analysis showed that hearts from donors aged 50 years or over are not associated with worse survival outcome, but higher risk of CAV.[7] Therefore, increased utilization of older donor hearts, especially for older recipients, could be supported.

In the setting of brainstem death, neurogenic shock and catecholamine storm often lead to haemodynamic instability and reversible cardiac dysfunction. Donor management, guided by cardiac output measurement, including fluid infusion, inotropic support and hormonal therapy, may facilitate recovery of heart function and improve organ utilization. Therefore, repeated ECHO is sometimes necessary to reveal the change in heart function after optimization.

As DCD heart transplantation is still in its infancy, the pioneering transplant centres in this field have adopted strict criteria. Only donors $\leq$57 years, with LVEF >50% and who arrest within 2 hours following withdrawal of life support with functional warm ischaemia (time from systolic blood pressure <50 mmHg to administration of cold cardioplegia) less than 30 minutes, are included. In addition to the contraindications listed in Table 2, donors with previous cardiac surgery and sternotomy, known cardiac disease or requiring infusions of adrenaline, dobutamine or noradrenaline >0.3 mg/kg/min, are also excluded.[8] These criteria are likely to be expanded with accumulation of experience.

Another recent advancement to increase the donor pool is to utilize hearts from donors with hepatitis C (HCV). Prior to transplant, the usage of nucleic acid testing to detect viral load in donors provides crucial information about the risk of viral transmission to recipients. After transplantation, the current antiviral therapies are effective to cure HCV viremia, should recipients develop it. Therefore, transplant centres with established protocols to manage post-transplant viremia have started to accept hearts from donors with HCV with encouraging early results.[7]

Donor–recipient matching

Organ allocation in the UK is based on urgency and blood group matching. When assessing donor's and recipient's profiles for risk–benefit analysis of a potential heart offer, gender and size matching are important factors. Female donor to male recipient, especially for recipients with pulmonary hypertension, is associated with the worst mid-term and long-term survival and highest rate of CAV.[3] Similarly, size mismatch is considered as a risk factor for primary graft dysfunction (PGD) and worse long-term survival. The majority of transplant centres use either height or weight for size matching. However, predicted heart mass (PHM), which is calculated from height, weight and age, has been advocated as a promising predictive factor of 1-year and 5-year post-transplant mortality (Figure 1). The recipients of size-matched pairs (PHM difference within 10%) have the best post-transplant survival, and the ones of both undersized and oversized donors (PHM mismatch < −20% or >20%) experienced increased risk of mortality.[1]

Surgical technique

DBD heart procurement

Heart retrieval is a complex process, which requires good communication and co-ordination between cardiothoracic retrieval surgeons, transplant surgeons, abdominal retrieval surgeons, specialist nurses for organ donation and transplant coordinators. The results of cardiac output measurements, filling pressures and optimized inotrope dosages, together with findings from direct inspection and palpation of the donor heart after sternotomy, are reported to transplant surgeons for final decision making.

Once the abdominal surgeons are ready for organ procurement and the transplant surgeons are confident that recipient

Summary of the main donor factors of ideal and extended-criteria and contraindications for heart transplantation

	Ideal Donor	Extended-Criteria Donor	Contraindication
Age	<40	40–70	>70
Cause of death	• Trauma without cardiac contusion, and free wall or IVS rupture	• Cerebrovascular accident • Chest trauma	• Inadequately treated systemic infection • Active malignancy except primary brain tumour • Cardiac contusion, and free wall or IVS rupture secondary to chest trauma
Past medical history	• No significant past medical history	• Hypertension • Diabetes mellitus • Peripheral vascular disease • Hepatitis C	• Malignancy within 5 years except primary brain cancer • Significant coronary artery disease • Cardiomyopathy • Channelopathy or cardiac arrhythmia
Social history	• No drug abuse • Minimal alcohol consumption • Never smoker	• Non-intravenous drug abuse • Alcoholism • Current or ex-smoker	• Active intravenous drug abuse
Inotrope support	No inotrope	Mild level of inotrope	Moderate level of inotrope
Virology results	• No HIV, hepatitis B or C positivity	• Hepatitis C antibody positivity	• HIV positivity • Hepatitis B surface antigen positivity
Echocardiogram			
LVEF	>50%	40%–50%	<40%
IVS	<1.2 cm	1.2–1.5 cm	>1.5 cm
Structural abnormality	• No LVH • No hypokinesia • No valvular abnormality	• Mild to moderate LVH	• Severe LVH • Significant global hypokinesia • Significant valvular abnormality
Right atrial pressure	<10 mmHg	10–20 mmHg	>20 mmHg
Cold Ischaemia Time	<4 hours	4–6 hours	>6 hours

Table 2

heart removal will be completed prior to donor heart arrival, 30,000 units of heparin is infused to the donor systemically. The superior vena cava (SVC) is ligated and the inferior vena cava (IVC) divided just above the diaphragm. Without systemic venous return, the cardiac output soon diminishes. The right superior pulmonary vein is also divided to empty the left side of the heart. A crossclamp is applied to the distal part of the ascending aorta, above the pre-inserted aortic cannula, through which cold cardioplegia solution is administered to arrest the donor heart and flush away the remaining blood and clots in the coronary arteries. Ice-cold isotonic solution is topically applied into the pericardium to reduce the heart's temperature and minimize its metabolic activity during ischaemia. If only the heart is to be retrieved, the pulmonary veins are divided at the pericardial reflection, leaving the left atrium intact. However, if lungs are retrieved at the same time, the left atrium is incised in order to leave adequate cuffs of tissues both around the pulmonary veins and with the remaining heart. The SVC is divided above the ligation; the ascending aorta, just inferior to the right brachiocephalic artery; and the pulmonary artery, at its bifurcation. Immediately after removal from the donor's body, the heart is immersed into cold saline in an organ bag. Two more organ bags with cold saline are applied for packaging before the heart is stored in an insulated box full of ice for transportation.

The equations for PHM mismatch calculation

$$\text{Predicted heart mass (PHM)} = \text{left ventricular mass} + \text{right ventricular mass}$$

$$\text{Left ventricular mass} = a \times \text{Height}^{0.54}\,(\text{m}) \times \text{Weight}^{0.61}\,(\text{kg})$$
$$a = 6.82 \text{ for women; } 8.25 \text{ for men}$$

$$\text{Right ventricular mass} = a \times \text{Age}^{-0.32}\,(\text{years}) \times \text{Height}^{1.135}\,(\text{m}) \times \text{Weight}^{0.315}\,(\text{kg})$$
$$a = 10.59 \text{ for women; } 11.25 \text{ for men}$$

$$\text{PHM mismatch} = [(\text{donor PHM} - \text{recipient PHM}) / \text{donor PHM}] \times 100$$

Figure 1

DCD heart procurement

The DCD heart retrieval process is very different from traditional DBD retrieval. The planned withdrawal of life support usually occurs in the anaesthetic room or intensive care unit. Donor's blood pressure, heart rate and saturation are continuously monitored. Once mechanical asystole occurs, a mandatory 5-minutes hands-off period has to elapse before death can be declared. The donor is then transferred to the operating theatre for organ procurement. It takes an experienced retrieval surgeon about 10 minutes to perform sternotomy and aortic cannulation. Therefore, at least 15 minutes of warm ischaemic insult to the donor heart is unavoidable. In reality, there is an additional warm ischaemic period prior to mechanical asystole when systolic blood pressure drops below 50 mmHg. Therefore, early reperfusion and functional assessment of the donor heart are required before heart transplantation. There are two methods of procurement for DCD hearts, namely normothermic regional perfusion (NRP) and direct procurement and perfusion (DPP).

Prior to establishing NRP, heparin is administered into the right atrium and pulmonary artery, and the aortic arch vessels are divided to prevent cerebral perfusion. With right atrial and aortic cannulation, warm perfusion to cardiothoracic and abdominal organs is restored. During NRP, the heart recovers from the initial warm ischaemic insult. Once the donor is separated from the perfusion circuit, it continues beating to support the circulation and allow for functional assessment by transoesophageal ECHO and Swan–Ganz catheter. The accepted hearts can either be transported with traditional static cold storage or with *ex vivo* normothermic perfusion with the TransMedics Organ Care System (OCS).[5]

The DPP method requires collection of 1.5 litres of donor blood from a right atrial cannula immediately after sternotomy. This bag of heparinized blood, together with the solution provided by TransMedics, is used to prime the OCS. The donor heart is arrested with 500 ml of cardioplegia and rapidly excised. In a bowl of cold saline at the back bench, the ascending aorta is secured to a perfusion cannula, which is then connected to the OCS. Using this procurement method, objective measurement of cardiac function after warm ischaemic damage is not possible. In the UK, due to restrictions placed on the use of thoracoabdominal NRP, all DCD hearts are currently retrieved by DPP.

Implantation

While waiting for the donor heart, the transplant surgeons carry out cardiectomy and prepare the recipient for heart implantation. After sternotomy and dissection of major structures in the pericardium, the recipient is adequately heparinized. Aortic cannulation, and direct cannulation of SVC and IVC with caval snares, are performed to establish cardiopulmonary bypass. If the recipient has undergone previous cardiac surgery, re-sternotomy and adhesiolysis may take a long time. Femoral cannulation may be performed first, in case cardiopulmonary bypass needs to be commenced quickly in emergency situations, e.g. cardiac injury.

Shortly before arrival of the donor heart, a crossclamp is placed across the recipient's ascending aorta proximal to the aortic cannula. The right atrium is then incised anteriorly. The incision is extended superiorly to excise the right atrial appendage and inferiorly towards the coronary sinus. Both the ascending aorta and the pulmonary artery are divided at their roots just above the aortic and pulmonary valves respectively. The roof of the left atrium is opened and thus the left side of the heart is emptied as well, making the rest of cardiectomy much easier. The incision is continued in front of the left pulmonary veins and along the atrioventricular groove. The left and right atriotomy incisions meet at the interatrial septum, which is then partially excised. After removal of the diseased heart, all of the cuffs are trimmed if required and the pericardium is washed.

The donor heart is first examined and prepared at the back table. Special attention is needed to look for a patent foramen ovale and to inspect the mitral valve. An additional dose of cardioplegia may be given, either antegrade through the aortic root or retrograde via the coronary sinus, at this stage. With the standard bicaval anastomosis technique, five anastomoses need to be performed. The donor left atrium is first anastomosed to the remaining tissue of the recipient left atrium, which is connected to the right and left pulmonary veins. Although the sequence of the remaining anastomosis varies, some surgeons prefer performing end-to-end anastomosis of the IVCs next, as its location is the most restricted. The excess length of donor SVC and pulmonary artery are trimmed prior to anastomosis to prevent kinking. The donor aorta, on the other hand, is left long in order to prevent tension on the anastomosis. Before opening the crossclamp, the heart is reperfused with warm blood from the bypass machine and de-aired through an aortic root vent. Atrial and ventricular temporary pacing wires are inserted. Isoprenaline infusion is usually started as a chronotrope. Adrenaline and/or milrinone infusion may be started as well to provide inotropic support. If pharmacological support is inadequate to maintain a satisfactory cardiac output, temporary mechanical support, such as IABP, ECMO or a right ventricular assist device, may be considered. Once the donor heart is beating steadily, and the de-airing is confirmed to be complete by transoesophageal ECHO, the recipient is gradually weaned from the bypass machine. Protamine is slowly given to reverse the action of heparin. The chest is closed after achieving haemostasis.

The implantation technique for DCD hearts is exactly the same as DBD hearts, with the exception that the beating heart on the OCS machine needs to be arrested with cold cardioplegia solution before being transferred to the recipient's pericardium.

Post-transplant management

The recipient is closely monitored in a cardiac surgical intensive care unit post-transplant. The systemic arterial pressure, pulmonary arterial pressure, central venous pressure and heart rate are constantly displayed on the bedside monitor, and cardiac output is regularly measured. With the appropriate level of support, it is recommended to maintain the systolic arterial pressure >90 mmHg, mean arterial pressure >60 mmHg, central venous pressure between 5 and 18 mmHg, pulmonary arterial pressure <30 mmHg, and cardiac indices >2 L/min/m^2. Urine output is a good indication of end-organ perfusion and should be kept >30 ml/h. As the implanted heart is denervated, bradycardia is common in the immediate post-transplant period. This is treated with an isoprenaline infusion and temporary pacing. Good cardiac output is paramount for peripheral tissue perfusion. If cardiac output is unsatisfactory, inotropic agents may be added to increase contractility. Milrinone infusion is also helpful

to reduce pulmonary arterial pressure. If peripheral vasodilatation is present, vasoactive drugs, e.g. vasopressin, should be used. If the cardiac function does not respond to the addition of pharmacological support, ECHO should be considered to rule out tamponade. If severe ventricular dysfunction occurs within 24 hours post-transplant, the recipient is diagnosed with PGD, which is associated with post-transplant morbidity and mortality.[9] PGD is associated with increased incidence of CAV but not acute cellular rejection or development of *de novo* donor-specific antibodies.[10]

In addition to the heart function, the function of other organs needs to be regularly examined through serial blood tests and imaging if indicated. Respiratory failure, stroke, acute kidney injury and hepatic dysfunction are common complications post-transplant.

Immunosuppression

To prevent rejection, heart transplant recipients must take immunosuppressive medications for the rest of their lives. There are four classes of immunosuppressants commonly used and usually several medications from different classes are prescribed in conjunction.

Corticosteroids reduce the inflammatory response by suppressing expression of inflammatory cytokines and cytokine receptors, and inhibiting the T-cell response. 1000 mg of methylprednisolone is typically given preoperatively, another 500 mg just before release of crossclamp during implantation, and further doses of 125 mg every 8 hours in the immediate post-transplant period. It is then switched to prednisolone at 0.5 mg/kg twice a day. As long-term corticosteroids have many undesired side-effects, the dose is gradually tapered. It may be completely withdrawn if there is no evidence of rejection 3 months post-transplant.

Calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, are the main immunosuppressive medications for solid organ transplantation. They inhibit calcineurin from activating the transcription of IL-2 and thus prevent T-cell proliferation and differentiation. The main side effect of CNIs is nephrotoxicity. Hence, CNI trough level and the recipients' renal function need to be closely monitored.

Proliferation signal inhibitors, such as everolimus, a potent mTOR inhibitor, also prevent transcription of cytokines, like IL-2, and inhibit proliferation of T cells and vascular smooth muscle cells. They can be used as an alternative to CNIs for recipients at high risk of developing chronic kidney disease and have an additional benefit of slowing the progression of CAV.

Mycophenolate mofetil (MMF) targets the purine synthesis pathway and inhibits T-cell and B-cell proliferation. Due to its potency, recipients' white cell count needs to be checked regularly.

Adequate immunosuppression is necessary to prevent cardiac allograft rejection. Routine endomyocardial biopsies are performed to diagnose and grade rejection, as clinical presentation is variable and non-specific. Long-term use of immunosuppression leads to serious complications, such as infection, malignancy and CAV. Therefore, it is crucial to provide heart transplant recipients with individualized, combination immunosuppression therapy that is adjusted and optimized to keep rejection at bay while minimizing its adverse effects, regular screening for malignancy, and early diagnosis and treatment of CAV.

New developments

Mechanical circulatory support

The history of mechanical circulatory support (MCS) is longer than that of heart transplantation. The first attempt of MCS was made in 1963 by Dr Liotta's team using an implantable tubular displacement pump to partially support the left ventricle post-aortic valve replacement. With decades of development, the third-generation LVADs, e.g. HVAD (HeartWare) and HeartMate III (Thoratec), that are currently used, include an inflow cannula which is inserted into the LV, a continuous-flow pump which houses a rotor and internal magnet, an outflow conduit which conveys blood to the ascending aorta, and a driveline that connects the pump to an external console (Figure 2). Wireless devices, without a driveline exiting through the skin, are currently under development and should offer a much lower infection risk, as well as being more convenient for patients.

LVADs are implanted in patients with advanced heart failure as a bridge to candidacy, transplant or recovery. For the bridge to candidacy group, LVAD implantation improves end-organ perfusion and reverses reactive pulmonary hypertension, making them eligible to be listed for transplantation.[11] For the bridge to transplant group, LVAD enhances their quality of life and reduces the risks of death and delisting, while waiting for heart transplant.[12] In a selected small number of patients with non-ischaemic dilated cardiomyopathy, myocardial function can recover after a period of LVAD implantation and medical treatment.[13] In patients not suitable to be listed for transplantation, LVAD can be used as a destination therapy.

Short-term survival of LVAD implantation is comparable to that of heart transplantation and continues to improve, but its long-term outcome is inferior. Moreover, it is associated with higher risks of right ventricular failure, bleeding, infection, sepsis, stroke and driveline infection.[13] Patients with LVADs have to take anticoagulation every day and carry the console with them all the time.

Ex vivo organ perfusion/preservation

The cold-cardioplegia/ice box approach has been used almost unchanged for over 40 years. More recently, *ex vivo* organ perfusion has gained much attention as a promising strategy to increase the donor organ pool and improve organ quality. Perfusion systems are designed as transportation devices, assessment tools and/or platforms for delivery of novel therapies to recondition marginal organs.

For the heart, the TransMedics OCS is the only commercially available device available to perfuse the donor heart extracorporeally. It is a portable device that perfuses the coronary arteries with warm oxygenated donor blood to maintain the heart at 34°C in an empty beating state. Perfusate is drained from the coronary sinus into the reservoir where the heart is stored, and pumped through an oxygenator and leukocyte filter before returning to the perfusion cannula connected to the aorta. The aortic pressure, coronary flow rate and temperature are constantly measured and regulated to maintain the optimal preservation state. Blood gas analysis of the perfusate in both arterial and

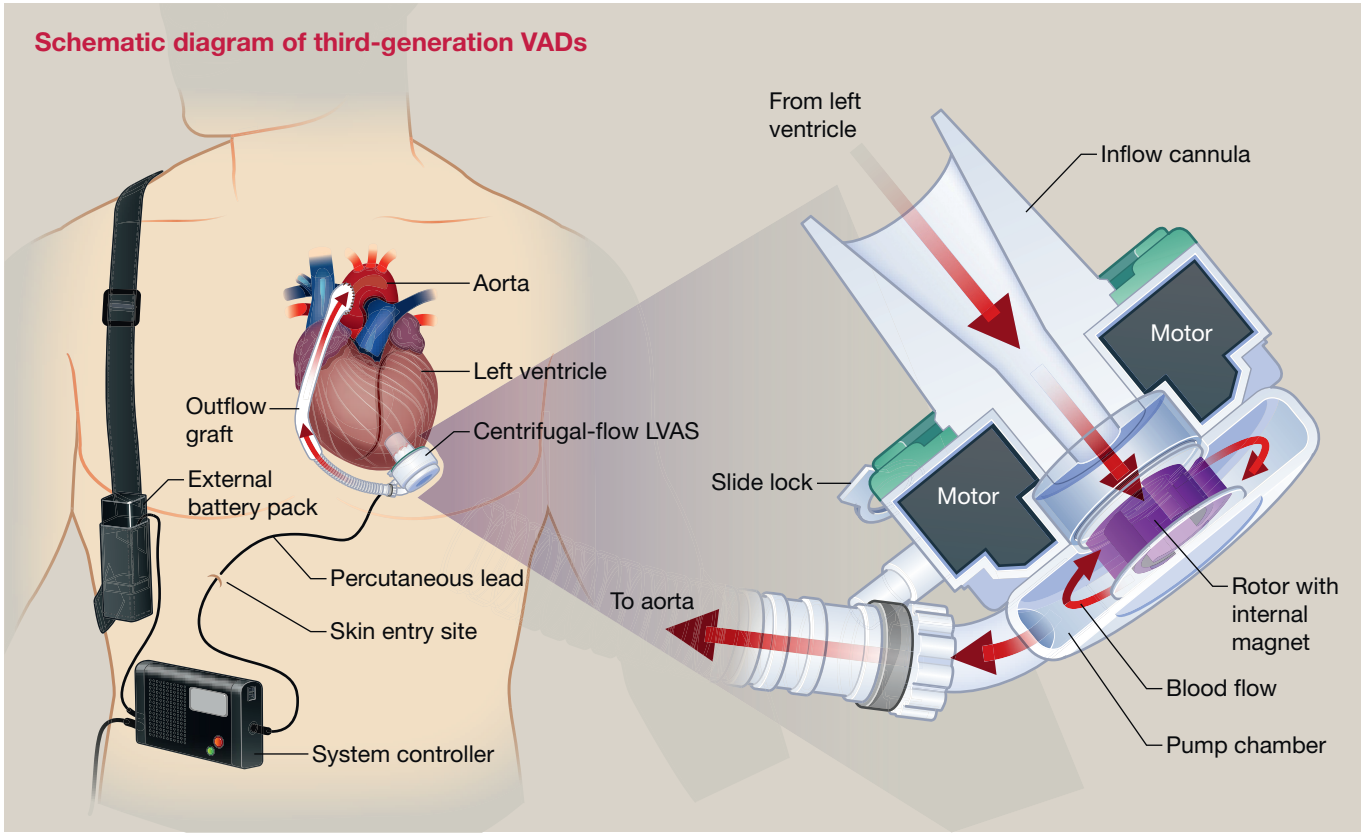

Figure 2

venous lines is regularly performed to assess lactate metabolism as a biomarker of donor heart quality. Previous studies have shown that the OCS is able to preserve donor hearts for up to 10.5 hours followed by successful transplantation, transport DCD hearts (with comparable outcomes to DBD transplantation), and reduce the incidence of post-transplant PGD, rejection, and acute renal failure, without affecting survival rate.[14] By enabling the use of DCD hearts, the OCS has also increased donor organ supply.[15] However, the expensive cost prohibits its wider application and it is currently almost exclusively used for DCD heart preservation in the UK.

Another option is the simple approach of keeping the heart at a very carefully controlled hypothermic temperature (the Paragonix SherpaPak device). Registry data is promising, but there has not been a formal comparative study. There are also hypothermic perfusion devices undergoing early clinical trials, and they offer considerable promise,[15] although results are not yet available.

Research groups around the world are exploring the benefits of both normothermic and hypothermic perfusion, particularly in the context of extended-criteria and DCD hearts, as well as the exciting possibilities of delivering therapies during perfusion. The reduction of ischaemia offered by these devices is likely to both reduce early dysfunction, the commonest cause of death after transplant, and may also increase the range of usable donor hearts. For instance, the deleterious effect of the age of the donor is multiplied by ischaemic insult. If ischaemia is minimized, then older donor hearts, of which there are large numbers, can be more safely used. There are real prospects for an exciting increase in activity, if the next generation of devices can be afforded.

Conclusion

It is exciting and encouraging to witness that research effort, technological advancement, and improved knowledge of donor and recipient selection and post-transplant care, have translated into better clinical outcomes and increased heart transplant activity. However, challenges still remain to expand the donor heart pool, maintain organ quality during preservation, determine reliable biomarkers for donor organ evaluation, and improve post-transplant short-term and long-term outcomes. ◆

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Practice points

- Despite advances in medical treatment, heart transplantation remains the gold-standard treatment for selected patients with end-stage heart failure
- Due to a limited number of donor organs, most patients wait a long time for heart transplantation and a significant proportion die or become unsuitable for transplantation while waiting
- Donor hearts require comprehensive assessment and careful selection of recipients is vital, as donor- and recipient-related factors are closely associated with post-transplant outcomes. "Extended-criteria" donors, for example older donors, and donation after circulatory death (DCD) hearts are increasingly being utilized to increase the donor pool.
- Heart retrieval and implantation requires meticulous coordination to limit the ischaemic time
- For donation after brainstem death (DBD) organs, the donor is heparinized before the heart is arrested using cold cardioplegia, explanted and stored on ice. For DCD hearts, either normothermic regional perfusion is established to reanimate the heart or the heart is directly procured, before transport on the Organ Care System, a normothermic perfusion device
- The recipient is placed on cardiopulmonary bypass before the diseased heart is explanted and the donor heart implanted. Depending on function, the recipient may require pharmacological or mechanical circulatory support when weaning from cardiopulmonary bypass
- Heart transplant recipients require individualized, combination immunosuppression therapy with careful monitoring for rejection and adverse effects
- Left Ventricular Assist Devices (LVADs) are implanted in patients with advanced heart failure as a bridge to candidacy, transplant or recovery
- Recent advances in *ex vivo* perfusion systems, as transportation devices, assessment tools and/or platforms for delivery of novel therapies, may be a promising strategy to increase the donor organ pool and improve organ quality

