

Durable Continuous-Flow Mechanical Circulatory Support

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1. Introduction

The prevalence of heart failure in the UK is 1 in 35 people aged from 65 to 74 and 1 in 15 people aged from 75 to 84. In Europe, the prevalence is 5 per 1000 people/year or 1–2% of the population. This prevalence increases from around 1% for those under age 55 to >10% for those over 70 years of age. Heart failure accounts for 2% of all NHS hospital bed days and 5% of all NHS medical emergency admissions (NICE 2018). Evidently, it is a major health problem of this century.

Heart transplantation is a very effective treatment for patients with severe end-stage heart failure but it presents challenges and limitations. The limited number of suitable donor hearts and the level of morbidity on the waiting list have led to research into durable forms of mechanical circulatory support. The objective was to build mechanical pumps capable of assisting the left ventricle in its function of pumping blood into the aorta, avoiding major thrombosis and thereby allowing patients to survive in a community setting until a donor heart became available. This required the device to be implantable within the patient's chest, portable, untethered, and electrically powered.

In 1994, the first pneumatically driven left ventricular assist device (LVAD) was approved as a bridge to transplant (BTT) by the FDA. A few years later, a new indication for this type of device was explored in the Randomised Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, where a vented electric LVAD was shown to improve survival, compared to medical treatment, in patients with advanced heart failure who were not candidates for transplantation [1]. These trial data led to the approval of the HeartMate VE LVAD device for destination therapy (DT). A technically improved version of the first HeartMate device, the HeartMate XVE was shown to improve outcomes in DT patients to 61% survival at 1 year compared to 52% for REMATCH [2,3]. Despite the overall survival benefit, half of the patients who recovered with this first-generation pulsatile device experienced significant adverse events, namely, infection, stroke, or pump failure.

2. Continuous-Flow Pumps

The past 30 years have seen progressive improvements in mechanical circulatory support devices. The adverse events associated with pulsatile LVADs were the stimulus for the development of continuous-flow devices. This technology brought several advantages. There has been a significant decrease in the size of the pump and increased durability due to fewer moving parts and the elimination of the need for bioprosthetic valves. This has resulted in better outcomes for destination therapy (DT) patients: 46% of HeartMate II (HM II) patients were alive and well after 2 years, free from disabling stroke or device replacement compared to 11% of HeartMate XVE patients [4]. Until recently, the other widely used continuous-flow LVAD had been the HVAD. The ADVANCE trial [5], an observational study, demonstrated 90.7% success in terms of bridge to transplant (BTT), explant for recovery, or ongoing device support at 6 months for HVAD BTT patients. DT patients were randomised to receive either HeartMate II or HVAD in the ENDURANCE trial, which showed a similar overall event-free survival at 2 years [6].



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The Heart Mate 3 (HM3) is a third-generation LVAD with a fully magnetic levitated, centrifugal flow rotor, which eliminates friction-generating mechanical bearings, thought to contribute to thrombus development in the HM II pump. In the multicentre study of MagLev technology in the MOMENTUM 3 trial, the HM3 was superior to the HM II in terms of event-free survival, with a marked reduction in the incidence of blood-related adverse events, most notably pump thrombosis. Despite the very significant improvement in outcomes, the adverse event profile of contemporary LVADs remains of great concern. These events include right ventricular failure, device-related infections, gastrointestinal bleeding, new aortic regurgitation, and stroke.

3. Patient Outcomes from Observational Studies

Data from the INTERMACS Registry reveal that the survival of patients with continuous-flow LVADs has improved over recent years [7]. Despite the increasing clinical urgency in this population and the higher number of DT LVADs implemented, the median survival time has increased from 46 months in the 2010–2014 era to 54 months in the recent 2015–2019 era.

However, a gap exists between LVAD and heart transplant survival. The one-year mortality after transplant is around 10%. Because donor hearts are a limited resource, there are stricter eligibility criteria for them than for an LVAD. Overall, the treatment of end-stage heart failure with an LVAD consistently improves a patient's quality of life [8,9]. After receiving LVAD support, patients typically experience an improved functional capacity with fewer physical and psychological symptoms. Strong social support from care-givers, family, and friends is associated with a better quality of life after LVAD implantation. Although mental function frequently improves after the provision of LVAD support, patients with continued cognitive dysfunction have a worse quality of life [10].

LVAD patients require very careful monitoring and are subject to frequent hospital admission; more than 30% are hospitalised in the first 90 days, and more than 70% at 12 months [7]. This is invariably due to the occurrence of adverse events. The prevalence of severe events, pump thrombosis, or pump failure has decreased over recent years due to improvements in pump technology, patient selection, and surgical technique. However, infection, right ventricular failure, stroke, and gastrointestinal bleeding remain frequent occurrences and, of course, negatively impact quality of life.

4. Patient Management

The primary goal is to obtain longer survival with a reduction in adverse events. To achieve this goal, it is necessary to prioritise three areas: patient selection, surgical management, and medical management.

The ISHLT has recently renewed its guidelines on the selection of appropriate candidates for durable mechanical circulatory support [11]. The evaluation of patients includes cardiac assessment, judgement of non-cardiac co-morbidity, and a comprehensive evaluation of the patient's social support and psychosocial risk factors. Perhaps most critical of all is the timing of LVAD implantation, and part of this involves the pre-operative optimisation of the haemodynamic performance of the heart. Shared decision making between the LVAD team and the patient, including their caregivers, is very important.

Medical evaluation has to be thorough in order to identify high risk factors on the cardiac side, especially high pulmonary vascular resistance (PVR) and right ventricular failure. On the non-cardiac side, features that can represent a contraindication include haemodialysis, malignancy with a poor 5-year survival or acute malignancy, chronic liver disease, active infection, substantial neurological deficit, and a very poor psychosocial profile.

From the surgical viewpoint, the most common approaches to LVAD implantation are median sternotomy or bilateral thoracotomy. The objective is to provide an unobstructed inflow cannula position in the left ventricle and to position the outflow graft anastomosis so that there is no obstruction or kinking. The malalignment of the inflow cannula can result in thrombosis due to the creation of areas of blood stagnation within the cavity of the

left ventricle. The HM3, which is currently the only available continuous-flow device, is designed so that the inflow cannula is placed in the apex of the left ventricle. Some centres have implanted the LVAD without the use of cardiopulmonary bypass (CPB), but this has not been widely adopted. CPB allows for effective control of the circulation in a patient who is often in a fragile haemodynamic state. It also enables the decompression of the left ventricle and, most importantly, enables the safe de-airing of the heart and pump once the LVAD is implanted.

5. Medical Management to Minimise Adverse Events

Stroke: Ischaemic and haemorrhagic strokes are relatively common and occur at a rate of 0.08–0.27 events per patient year [12]. A stroke can be devastating and is associated with worse outcomes and a reduced chance of receiving a heart transplant for BTT patients. Ischaemic strokes originate not only from atherosclerotic plaques in native arteries but from emboli released by the LVAD, the outflow graft, a cardiac chamber, or the aortic root. It may, therefore, be necessary to optimise the LVAD speed to allow for the intermittent opening of the aortic valve and to maintain adequate anticoagulation plus anti-platelet treatment to reduce thrombus formation. Maintaining the mean arterial pressure below 85mmHg has been shown to reduce the risk of stroke in HM3 LVAD patients.

Right ventricular failure (RVF): The right ventricle is a very compliant thin-walled chamber working in a low-resistance circuit. Up to 40% of patients who receive an LVAD develop RVF early after implantation. Several factors play a role in the development of this complication: the baseline RV function, an increased RV afterload, changes in the cardiac geometry leading to the movement of the interventricular septum, as well as worsening tricuspid regurgitation. There may also be an increase in pulmonary vascular resistance (PVR) and the development of arrhythmias. There is no single solution for these problems, but temporary inotropic or mechanical support of the RV, the use of phosphodiesterase pulmonary vasodilators, optimising the right atrial pressure, and, through echocardiography, avoiding the displacement of the septum into the LV may all be helpful. It is important to try to maintain the sinus rhythm. Most cases of RV failure in this setting are due to hypervolaemia, sub-optimal BP control, or chronic excess VAD speed.

Gastrointestinal bleeding: This is a common problem occurring in up to 40% of patients [13]. The shear stress generated by the blood propelled through the LVAD causes the degradation of von Willebrand factor (vWF). The same shear stress stimulates pro-angiogenic factors which lead to intestinal arterio-venous (A/V) malformation. This has proved difficult to both prevent and treat. Maintaining a stable INR is the most helpful approach. In severe cases, blood transfusion will be required, as well as endoscopy for direct intervention into the A/V malformation.

Drive-line infections: These comprise the most common complication. It is more likely to occur in patients who are under- or over-weight, or if there has been trauma to the drive-line. Co-morbidities such as diabetes and chronic kidney disease are incremental risk factors. The strategies to prevent drive-line infections include the correct placing of the line within the tissue tunnel, using external anchoring to alleviate stress on the skin–drive-line interface, and the use of a standard dressing-change protocol coupled with patient education.

Once a drive-line infection is established, the treatment depends on the organism and on the characteristics of the patient. In most instances, chronic antibiotic treatment is required to achieve control. However, as many organisms produce a biofilm, curative antibiotic treatment is not possible. The only definitive treatment is the explantation of the LVAD and either bridge to transplant or to recovery.

6. Bridge to Recovery

The current consensus is that a small percentage of the overall LVAD population achieves the recovery of LV function to the point where the explant of the device can be considered. Those most likely to recover are younger patients with non-ischaemic cardiomyopathy and a short duration of heart failure symptoms. Among patients who fit this description, 10% will experience an improvement in LV function sufficient to allow explantation. Of those who receive explantation, 80% will experience long-term freedom from the need for transplantation or LVAD re-insertion.

7. Future Directions

Meeting the goal of reducing adverse events is critical to enabling safe and durable continuous LVAD support. If this can be achieved, it will be possible to (a) insert the LVAD earlier in the natural history of heart failure and (b) provide a stable setting for novel treatments involving cell or gene implantation to stimulate cardiac regeneration. There are technical and engineering targets which will soon be achieved. These include a 'smart' LVAD that alters pump flow to meet the physiological demand, and the removal of the drive-line with substitution via transcutaneous energy transmission.

It is also likely that machine learning will enable the development of improved software to enable us to monitor LVAD operating metrics. This will enable the early detection of complications or volume status and arrhythmias. After all, the LVAD is an implantable, wearable device with a built-in computer and a continuous power source and, therefore, an ideal setting for artificial intelligence and machine learning.

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