Mechanical Circulatory Support and the Role of LVADs in Heart Failure Therapy

Allison McLarty
Associate Clinical Professor, Division of Cardiothoracic Surgery, Stony Brook University, Stony Brook, NY, USA.

Supplementary Issue: Heart Failure: An Exploration of Recent Advances in Research and Treatment (A)

ABSTRACT: Heart failure is epidemic in the United States with a prevalence of over 5 million. The diagnosis carries a mortality risk of 50% at 5 years rivaling many diagnoses of cancer. Heart transplantation, long the “gold standard” treatment for end stage heart failure unresponsive to maximal medical therapy falls way short of meeting the need with only about 2,000 transplants performed annually in the United States due to donor limitation. Left ventricular devices have emerged as a viable option for patients as both a “bridge to transplantation” and as a final “destination therapy”.

KEYWORDS: mechanical circulatory support, ventricular assist device, heart failure

Heart Failure
Heart failure continues to be a significant health care problem in the United States. The incidence is over 5.8 million in this country and over 23 million worldwide. The annual cost in the United States is over 39 billion dollars.1 Despite advanced medical therapy and the current cocktail of beta blockers, diuretics, and ACE/ARBs, the diagnosis of heart failure still carries a mortality of 39% at one year and 50% at five years,2 rivaling many diagnoses of cancer. Once readmissions for exacerbations of heart failure recur, survival worsens.3 For this reason, heart transplantation was developed, and since the initial landmark transplant in 1967, with effective immunosuppression, has become the gold standard of therapy for end-stage heart failure with contemporary one- and three-year survival of 90% and 82%.4 However, the number of heart transplants performed annually worldwide has plateaued at about 4,000 because of donor availability, leaving thousands at risk of dying. In addition, the average time on the waiting list for a transplant can be excessive with mortality on the waiting list up to 45%.

The Development of Mechanical Support
For this reason, alternate forms of mechanical support for the failing heart have long been sought. In 1966, DeBakey reported the first successful use of a ventricular assist device (VAD) for post-cardiotomy support.5 The first NIH funded study was conducted in 1978. History documents the inexorable drive toward miniaturized implantable support with the first implantable VAD placed in 1991.6 Industry was an integral partner in product development, and in 2001, the HeartMate XVE was FDA approved as the first implantable VAD for bridge-to-transplantation (BTT).

Outcomes were improved enough for the question to arise as to the applicability of the therapy to patients not eligible for transplantation. This hypothesis was tested in the prospective, randomized multicenter REMATCH trial, where HM XVE implantation was compared to optimal medical therapy for patients not considered eligible for transplant.7 Patients on VAD support had survival at one year increased by 50%. VADs as a form of permanent or destination therapy (DT) were approved by the FDA in 2003.8 Current indications for LVAD implantation as DT include patients (1) with New York Heart Classification Class 4 heart failure, (2) with optimal medical therapy on VAD support had survival at one year increased by 50%. VADs as a form of permanent or destination therapy (DT) were approved by the FDA in 2003.8 Current indications for LVAD implantation as DT include patients (1) with New York Heart Classification Class 4 heart failure, (2) with optimal medical therapy (a)

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CORRESPONDENCE: allison.mclarty@stonybrookmedicine.edu

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in vitro and then in vivo work demonstrated preserved cerebral, renal, and visceral perfusion with continuous flow VADs. The Thoratec HeartMate 2 (HM 2) VAD was the first continuous axial flow pump to be approved by the FDA as first BTT in 2008, and then DT in 2010. This revolutionary design had a single ruby bearing and no valves, and in vitro testing suggested it could work without mechanical failure for a prolonged period. This promise has been fulfilled in clinical practice where the longest survivor in the United States with an original HM 2 implant has been on support for over nine years. This smaller, more durable pump has had a highly favorable impact on survival and outcomes, and one-year survival with the HM 2 VAD is currently above 80%, making it for the first time a viable alternative to transplantation.

Competition is generally healthy in the marketplace. In about 2005, an Australian company developed the centrifugally driven continuous flow HeartWare pump or HVAD. This has the advantage of smaller size, with intrapericardial placement facilitating ease of surgical implant, and once FDA approved in the United States in 2012 as BTT, quickly became a popular alternative to the HM2.

**Patient Selection**

INTERMACS stands for the Interagency Registry for Mechanically Assisted Circulatory Support and is a National Heart, Lung, and Blood Institute (NHLBI)-sponsored database that reflects a partnership between NHLBI, FDA, and the centers for Medicaid and Medicare services. Between 2006 and 2012, over 12,000 patients who received FDA-approved durable mechanical support were entered into the database. This allows analysis of pump performance and patient outcome over time. Importantly, INTERMACS status has been used to classify patients, depending on severity of heart failure. The classification system is listed below by category:

- INTERMACS 1 – critical cardiogenic shock,
- INTERMACS 2 – progressive decline on inotropes,
- INTERMACS 3 – stable but inotrope dependent,
- INTERMACS 4 – resting symptoms but home,
- INTERMACS 5 – exertion intolerant,
- INTERMACS 6 – exertion limited, and
- INTERMACS 7 – NYHA Class 3b symptoms.

Analysis of outcome by INTERMACS category has helped shape current implant trends. Thus, patients in Category 1, the so-called crashing and burning patients, did poorly when implanted with a durable device when in extremis. These patients are now mostly supported with short-term mechanical circulatory support such as extra corporeal membrane oxygenation (ECMO) or the Impella pump. Should they stabilize adequately, they are then transitioned to more durable support. In general, most patients implanted fall into Categories 2 and 3. Studies are currently underway to assess the benefit of earlier implantation in less sick patients (Categories 6 and 7), as in, for example, the REVIVE-IT study. Guidelines have been developed to provide structure to assessing patient candidacy and preparation and care.

**Surgical Technique**

The traditional surgical technique includes the following steps:

- median sternotomy,
- creation of a subdiaphragmatic pocket (for HM 2 only),
- cannulation for cardiopulmonary bypass (CPB),
- anastomosis of outflow graft to lateral wall of ascending aorta,
- initiation of CPB,
- coring of apex of the left ventricle and inflow cannula placement in the left ventricle,
- driveline tunneling and fixation,
- connection of inflow/outflow portions of the pump and deairing of the heart,
- separation from CPB, and
- initiation of pump support with inotropic support.

The most significant perioperative complication after LVAD implantation is right ventricular failure (RVF). Great attention is therefore paid to optimizing and preserving right ventricular function. Several scoring systems have been developed to estimate the risk of RVF post-operatively, and clinical factors such as INR, protein, liver function tests, renal function, and inotropic requirement have been identified as possible predictors of poor prognosis. With careful patient selection and preparation, severe right heart failure (RHF) necessitating right VAD (RVAD) implantation is now relatively rare at our institution. Strict criteria employed pre-operatively include diuresis to central venous pressure less than 15 and inotropic support if warranted by hemodynamic measurement on right heart catheterization. This ameliorates congestive hepatopathy and prerenal uremia from exacerbated heart failure. Intraoperatively, more than moderate tricuspid valve (TV) regurgitation is addressed with a TV annuloplasty (TVA), and patent foramen ovale are closed. Some controversy exists regarding the benefit of TVA at the time of LVAD implantation. Some studies suggest TVA facilitates weaning of RV inotropic support post-operatively but has no survival benefit. Others suggest poorer outcome and survival if TVA is added to LVAD procedure. If sternotomy is the approach used, many surgeons agree that the addition of TVA adds little morbidity to the overall procedure. Where thoracotomy or an off-pump approach is selected, the addition of TVA is not felt to be critical. In general, the heart is not arrested unless attention needs to be paid to a significantly regurgitant aortic valve or stenotic mitral valve. Aortic insufficiency greater than mild is treated with bioprosthetic aortic valve replacement or aortic closure to avoid exacerbation of aortic insufficiency and development of resultant heart failure and ineffective support by the device.

Inotropes are initiated prior to separation from CPB – for example, milrinone, dobutamine, and/or epinephrine. Where
appropriate, inhaled nitric oxide is initiated and then quickly weaned off over 24–48 hours as tolerated. Adjustment of the speed of the pump is performed with echocardiographic guidance, care being taken not to increase too rapidly, displacing the interventricular septum to the left, and generate RHF. Alternate strategies for implant have been described over recent years, including off-pump implantation and implantation via thoracotomy, thus sparing patients a sternotomy.

**Post-Operative Care**

In general, hospital length of stay is decreasing. Time in the ICU immediately post-operatively facilitates weaning of inhaled medications, extubation, and weaning of inotropic support. Early mobilization and ambulation facilitates recovery, and daily physical therapy is essential. Nutrition is also critical; for patients unable to eat soon after surgery, enteral supplementation is initiated early. The device requires anticoagulation and antiplatelet therapy. Many centers bridge with heparin until the patient has achieved, via Coumadin administration, an INR of 2–3. It is our practice to trend LDH and haptoglobin to assess for hemolysis. LVAD education is also critical, and comfort for family with alarms and accessories is essential prior to discharge home or to rehabilitation. Of particular importance is care of the driveline; during dressing changes, sterile technique must be observed. Patients are not discharged until they and their caretakers have mastered this.

**Outpatient Management**

Patients are initially seen weekly in the outpatient center to ensure appropriate wound healing, anticoagulation, and compliance with medical regimen. Ultimately, patients are weaned to a monthly or bimonthly schedule of follow-up. In the Shared Care model, outpatient care is shared by the referring group and the implanting center. Ultimately, the expectation is that patients resume as complete and normal a lifestyle as possible. Quality of life data are accumulated to ensure that the full benefit of the therapy is experienced.

**Complications Unique to VADS**

As experience with VADs has grown, a new set of complications has come to light. Understanding and management of these complications unique to LVADs continue to evolve as the field matures. We will review the following:

- GI bleeds,
- Pump thrombosis,
- Driveline infection,
- Late AI, and
- Late RHF.

**GI bleeding.** The most common complication of LVAD therapy, GI bleeding occurs in 20 to 40% of patients post implant. The etiology has been found to be two-fold.

**Acquired von Willebrand’s factor deficiency (VWFD).** This factor facilitates platelet adhesion to vascular endothelial surfaces. The molecule is composed of four polymers. Continuous flow leads to malformation of multimere 4, which results in ineffective function of the molecule, rendering the patient innately coagulopathic. It has been shown that all patients develop this acquired deficiency within a month or two of pump implantation.

**Mucosal arteriovenous malformations (AVMs).** Decreased or absent pulsatility with increased shear stress leads to subsequent angiodysplasia and the development of mucosal AVMs. The fragility of these capillaries leads to bleeding, which is exacerbated in the anticoagulated patient.

**Treatment**

Treatment predominantly includes cessation of anticoagulation and antiplatelet therapy, and endoscopy with control of visualized bleeding sources. Jejunal or ileal AVMs have made the use of push enteroscopy and capsule endoscopy not infrequently necessary. Medications are also being resuscitated from the past, including agents such as octreotide, thalidomide, and estrogen. Effective use of these agents is morphing from case reports to series. Randomized studies are being undertaken. In addition, manipulation of the pump speed to permit ejection through the native valve is employed in an effort to counteract the effect of lack of pulsatility.

**Pump thrombosis.** Anticoagulation and antiplatelet therapy are necessary to prevent thrombus formation within the mechanical pump. Delayed initiation, inadequate dosing, or cessation of such therapy may be associated with thrombus formation within the pump leading to malfunction or pump stoppage, described as pump thrombosis.

The initial trials leading to FDA approval for the HM 2 mandated an INR of 2–3 and full dose ASA for antiplatelet therapy. Low thrombotic and high bleeding rates led to modification of these standards after approval, and INR of 1.5 with ASA dose 81 mg was felt to be adequate. However, a spike in incidence of pump thrombosis, recently published in 201331,32 and drawing national attention to this troubling and sometimes lethal complication, led to a review of practice across the world of mechanical therapy, and new guidelines have emerged.33

Concerns were voiced that upgrades in the HM 2 pump, eg, sealed bend relief, or a bad batch of bearings were responsible for the apparent increase in pump thrombosis that appeared to have started in 2011. Exhaustive reviews by industry have not confirmed this claim. Other factors felt to be contributory include the advent of DT and approval for implantation of the HM 2 into a broader category of patients – older, sicker, or patients with more comorbidities, any of which may be linked to an increased hypercoagulable state.

Several things have emerged from this conundrum. One is an improved understanding of some of the factors associated with a hypercoagulable state, prompting practitioners who care for patients with VADs to augment anticoagulation in these.
populations: in the settings of infection and obesity, in younger patients, and in females.\textsuperscript{34,35} Also, the surgical option of pump exchange was created, where a subcostal approach to the thrombosed HM 2 pump could obviate the risks inherent in resternotomy. This would be applicable where complications of inflow to and outflow from the pump were excluded. Technical details such as attention to inflow cannula position and outflow graft anastomosis have also been elucidated.\textsuperscript{32,33} Guidelines for the management of patients with suspected pump thrombosis include trending blood tests such as LDH, and haptoglobin, use of ramp echocardiography, and lytic and augmented antplatelet therapy.

**Driveline infection.** Patients with current VADs are tethered by a driveline that emerges from the anterior abdominal wall and is connected to the system controller or portable computer that drives the pump. Care of the driveline is critical to avoid the complication of infection that can have troubling consequences.

Regimens of weekly or triweekly dressing changes are followed by various VAD programs. Patient and caregiver instructions are critical to ensure that sterile technique is strictly enforced. YouTube video has been employed to ensure that continuous education is readily accessible. Shower kits have been provided by companies to facilitate showering regimens.

When infection does set in, however, an aggressive treatment plan is recommended to avoid the need for pump exchange or replacement or urgent transplantation.\textsuperscript{36}

Stepwise augmentation of therapy from oral antibiotics, through intravenous antibiotics to surgical debridement and use of VAC dressing to pump exchange or explant, may be necessary.

**Late aortic insufficiency.** The outflow graft for the LVAD is most commonly placed to the ascending aorta. Flow from this graft is antegrade with some retrograde flow leading to increased pressure in the dependent sinuses of Valsalva. Unrelieved pressure is felt to contribute to leaflet fusion and prolapse of leaflets, leading to the development of late aortic insufficiency or AI. This is found most commonly where pump speed is such that there is little or no ejection through the native aortic valve.

Incidence of late de novo AI has been estimated at as high as 38%,\textsuperscript{37,38} Treatment for the problem includes decrease of flow through the device, increase of flow, manipulation of blood pressure to facilitate afterload reduction and surgery. Surgical techniques have been described from the Park stitch for central coaptation of prolapsing leaflets to valve closure, to valve replacement with a tissue prosthesis.\textsuperscript{24}

**Right ventricular failure.** Late RVF has been estimated to occur in 15–20% of patients undergoing LVAD implant.\textsuperscript{39} This is to be distinguished from acute RVF, which occurs immediately post implant requiring temporary short-term RVAD implantation or prolonged intravenous inotropic support. For patients with late RVF recurrence of CHF symptoms with pedal edema and congestive hepatopathy may recur along with signs of increased tricuspid regurgitation and increasing right ventricular dysfunction. This has been associated with higher mortality, usually from complication of congestive heart failure.

**Conclusion**

The field of the mechanical support for heart failure is rapidly evolving. As technology improves and our understanding and care for the unique complications is enhanced, the indications for implantation may be broadened. Dissemination of information of this important therapy is critical to ensure patients have access to all options in treatment of their advanced heart failure.

**Author Contributions**

Conceived the concepts: AM. Wrote the first draft of the manuscript: AM. Made critical revisions: AM. The author reviewed and approved of the final manuscript.

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