

Mechanical Circulatory Support as a Bridge to Transplant or for Destination Therapy

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Abstract Mechanical circulatory support (MCS) frequently is used to treat medically refractory end-stage heart failure. Initially designed to be a bridge to transplantation, MCS also has proven itself as a durable therapy for patients who are not transplant candidates. As outcomes for patients with MCS have improved, research interest in device development has flourished, with many new device types under investigation. In addition to improvement of MCS devices, investigational work continues to achieve appropriate patient selection and complication management.

Keywords Mechanical circulatory support · Left ventricular assist device · Heart failure

Introduction

In the United States, there are more than 5 million people with heart failure, and every year 500,000 people are newly diagnosed; as such, 40-year-old individuals have a 20% chance of developing heart failure during their lifetime [1•]. It is estimated that 200,000 patients have American College of Cardiology/American Heart Association (ACC/AHA) stage D heart failure, which is defined as heart failure

symptoms refractory to standard treatment [2]. Despite many advances in recent decades that have specifically antagonized the neurohormonal cascade, improved synchrony, and aborted sudden cardiac death, heart failure continues to carry a grave prognosis. Patients with ACC/AHA stage D heart failure have a mortality approaching 80% at 5 years [2]. Once patients become dependent on inotropic therapy, their 1-year survival plummets to less than 30% [3].

The ideal therapy for the management of heart failure refractory to usual medical care continues to be cardiac transplantation [4]. However, the woeful shortage of organs has made this treatment option untenable for many who are eligible [5••]. Last year in the United States, approximately 5–10 people were on the waiting list for each of the 2200 heart transplants that were performed. In addition, hundreds of thousands of patients who have severe end-stage heart failure are not eligible for a heart transplant due to concomitant multisystem disease, uncontrolled diabetes, continued tobacco use, or psychosocial limitations, but continue to deteriorate.

History of Mechanical Support Devices

The limitations of medical therapy to treat end-stage heart failure, the lack of available organs, and the large number of patients who do not qualify for transplantation despite worsening heart failure symptoms all have spurred interest in mechanical circulatory support (MCS). Initial reports of mechanical support of the heart date to the 1950s, when the work was spearheaded by the development and refinement of cardiopulmonary bypass by Drs. John Gibbon, Walter Lillehei, and John Kirklin. In 1964, the National Institutes of Health instituted the artificial heart program to promote interest in this nascent field. Soon thereafter, Dr. Michael DeBakey [6] reported the first clinical use of a left

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ventricular assist device (LVAD); the competing group lead by Dr. Adrian Kantrovitz [7] followed soon thereafter with their own version.

First-Generation Mechanical Circulatory Support

The first-generation LVADs were pulsatile devices with many moving parts that suffer from frequent device complications; due to their size, these large devices are associated with more frequent infections and are limited to patients with a body surface area of 1.5 m² or greater.

In 1994, the US Food and Drug Administration (FDA) approved the pulsatile ventricular assist device (VAD) HeartMate XVE (later called HeartMate I; Thoratec Corporation, Pleasanton, CA) as the first VAD for bridge to transplantation [8]. The initial study involved 19 patients who were on multiple inotropes, and 84% required intra-aortic balloon pumps (IABP). Of the initial 19 patients, 13 patients were supported to transplantation after a mean wait time of 66 days and three patients died of multisystem organ failure (two of whom had significant right ventricular [RV] dysfunction). The initial anticoagulation strategy with the HeartMate XVE used aspirin with dipyridamole, and no thrombotic events were reported in this study.

The overwhelming success of the HeartMate XVE as a temporary support device to bridge patients to transplant led to a growing interest in the use of this device as a permanent therapy for long-term support as an alternative to transplant. The Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) study, which evaluated the HeartMate XVE against medical therapy in patients with end-stage heart failure, opened the door to the current explosion of interest in mechanical support devices [9]. In this landmark study, 129 patients with New York Heart Association (NYHA) class IV heart failure who were ineligible for heart transplantation were randomized to receive a HeartMate XVE or maximum medical therapy, which in the overwhelming number of cases (> 70%) included intravenous inotropic support. The patients who received the HeartMate XVE had a 48% reduction in the risk of death from any cause. The device group had an estimated 1-year survival of 52% compared with a 1-year survival in the medical therapy group of 25%.

Despite gaining FDA approval, the HeartMate XVE was not widely implanted outside transplant centers due to its large size, the specialized care that all VADs require, and frequent device failure after about 18 months of continued use [10]. Although patients on MCS survived for an average of 258 days longer, they also spent more than 2 months longer in the hospital. They also were more likely to experience fatal outcomes such as sepsis, bleeding, and

device failure. In fact, 41% of deaths in the device cohort were due to sepsis, and a further 17% of deaths were due to device failure, with 10 of the original 68 patients requiring device replacement. Follow-up of 280 patients who underwent HeartMate XVE implantation between 2001 and 2005 yielded similar results to the original REMATCH study [11]. The 1-year survival of these patients was 56%, but the in-hospital mortality after surgery was fairly high at 27%. More disconcerting was that device failure again played a major role in outcome, with 72.9% of patients at 2 years either requiring a device replacement or experiencing a fatal event secondary to device failure. A nonrandomized trial with another first-generation, positive displacement, pulsatile device, the Novacor LVAS (WorldHeart, Ottawa, Canada), also demonstrated improved survival with MCS therapy compared with standard medical care. Use of this device was associated with a significantly greater stroke risk: 62% of patients implanted with the Novacor LVAS suffered a stroke or transient ischemic attack [12].

Second-Generation Mechanical Circulatory Support

The marked survival benefit documented in patients implanted with these devices stimulated research in device improvement and has led to second- and third-generation LVADs. Second-generation LVADs are continuous-flow devices that work with an axial flow mechanism, such as HeartMate II (Thoratec Corporation, Pleasanton, CA) [13], Jarvik 2000 (Jarvik Heart, Inc., New York, NY) [14], and HeartAssist 5 (MicroMed Cardiovascular, Houston, TX) [15]. Due to the presence of a single moving rotor, device wear and tear is less problematic. In addition to their smaller size, second-generation devices require a more limited surgery, are less likely to become infected, and can be used more frequently in patients with small body surface areas.

The HeartMate II was evaluated as a bridge to transplantation in a prospective trial involving 133 patients that were either status 1A or 1B for heart transplantation [16]. At 6 months, 75% of patients ($n=100$) either had been transplanted ($n=56$), continued with ongoing mechanical support and were still listed for transplantation ($n=43$), or achieved cardiac recovery leading to device explant ($n=1$). Actuarial survival was 89% at 1 month, 75% at 6 months, and 68% at 1 year. Interestingly, of the 43 patients who remained eligible for cardiac transplantation, four patients eventually removed themselves from the transplant list due to preference for continued mechanical support. Within the 6-month follow-up period, 25 patients (18%) died; of these, 18 (13.5%) died during the initial hospitalization. Fewer patients experienced device complications, with only five patients (3.7%) requiring device replacement

(two for pump thrombosis). Other complications included bleeding requiring surgery, sepsis, and stroke/transient ischemic attack. Due to the higher thrombogenic potential of the HeartMate II, these patients were maintained on warfarin (with international normalized ratio [INR] goal 2.5–3.5) and aspirin plus dipyridamole. Longer-term follow-up for 18 months in 281 patients with the HeartMate II as a bridge to transplantation yielded similar results to the earlier study [17]. In this trial, 72% of patients successfully underwent transplantation (55.8%), achieved cardiac recovery and had the device explanted (2.5%), or were still dependent on mechanical support and listed for a heart transplant (19.9%). Survival of these patients was even better than those in the initial HeartMate II study with 82% alive at 6 months, 73% alive at 12 months, and 72% alive at 18 months. Device-related dysfunction causing death again was low at 3% ($n=7$), and 11 patients required device replacement. The most common complication continued to be bleeding, which required surgery in 26% of patients. Infection related to the percutaneous lead was present in 14% of patients, and 2% of patients experienced a pump pocket infection. Twenty-five (8.9%) patients experienced a stroke, 15 of which were ischemic and 10 hemorrhagic; 40% of the strokes were fatal.

To further examine the efficacy of second-generation LVADs compared with their first-generation counterparts, a randomized trial of the HeartMate II versus the HeartMate XVE was conducted during a 2-year period [18]. Patients implanted with the HeartMate II were four times more likely (46% vs 11%) to be alive at 2 years without a stroke or another operation due to device complication. Only 10% of patients with the continuous-flow LVAD required pump replacement compared with 36% of patients with the pulsatile HeartMate XVE. Of the 13 replacements of the continuous-flow LVAD, 10 were due to percutaneous lead disconnect/breakage, and a further two patients experienced pump thrombosis. The risk of stroke did not differ between the two cohorts, but the HeartMate II group was treated with aspirin and warfarin with a goal INR of 2.0–3.0, whereas the HeartMate XVE group was treated with aspirin alone. Despite the greater anticoagulation, the risk of overall bleeding did not differ between the two groups, although 30% of patients with the continuous-flow LVAD did experience bleeding that required surgery. The 11% survival free from these two complications at 18 months in the HeartMate XVE cohort was lower than the 23% survival reported in the previously described REMATCH study; this might be explained by the fact that the end point in the REMATCH study did not account for survival free from these complications. In this most recent study, the 2-year actuarial survival rate for the pulsatile LVAD was 24%, which matches up well with the results from REMATCH. The 2-year actuarial survival in the continuous

LVAD cohort was 58%, more than twice that of the pulsatile LVAD cohort. Also of interest was the finding that, although the patients enrolled in this trial were initially deemed ineligible for transplant, 17 patients with the HeartMate II and 9 patients treated with the HeartMate XVE eventually were transplanted once their contraindications to transplant had resolved. Based on these data, the HeartMate II and other second-generation LVADs have gained much wider acceptance. A standardized protocol reviewing issues such as anticoagulation and how to deal with LVAD complications has been published recently to address this growing population and the clinicians who must care for the patients [19••].

Third-Generation Mechanical Circulatory Support

Although outcomes with second-generation LVADs continue to improve, several trials already are underway evaluating third-generation LVADs including HeartWare HVAD, [20], HeartMate III [21] (both manufactured by Thoratec Corporation, Pleasanton, CA), and Synergy (CircuLite, Inc., Saddle Brook, NJ) [22]. Third-generation LVADs continue the trend of providing continuous blood flow but differ from their second-generation counterparts by having a “bearing-less” mechanism for moving blood, usually a magnetically levitated impeller. In addition, these devices continue the march toward miniaturization, with the smallest device in current trials being the size of an AA battery [22].

Patient Selection

Using a classification of clinical intent at the time of implantation, there are four broad indications for an LVAD. The most common indication, the bridge-to-transplant intent, is performed on someone who needs to be supported while awaiting a transplant. The second indication, known as destination therapy, applies to patients with refractory heart failure symptoms who have contraindications for transplant and require MCS. In the third category, bridge to decision, patients have an imminent need for MCS but their candidacy for transplantation requires a reevaluation of parameters that can change with adequate support and improvement of end-organ perfusion. A fourth category, bridge to myocardial recovery, involves the application of active mechanical unloading of the systemic ventricle, exclusively in nonischemic heart failure, to restore myocardial function to a level that can sustain the individual with minimal or no heart failure symptoms after the explantation of the LVAD. Although it was initially thought that the first two categories would be comprised of two completely separate patient populations, it has become apparent that a significant

number of patients potentially could qualify for either transplant or destination therapy, either due to improvement in their comorbidities (eg, obesity, pulmonary hypertension, liver failure) while supported with an LVAD, or because they suffer a complication (eg, stroke, infection) while being supported and then are deemed unsuitable for a transplant.

Understandably, the decision to embark on mechanical support for a patient with a failing heart is a difficult one, and the criteria for referral vary greatly from institution to institution. The initial MCS trials followed patients who were being bridged to transplant and for whom mechanical support was deemed to be their only option of surviving until a heart became available. Once REMATCH results became available, the push for replacing chronic inotropic therapy with mechanical support gained momentum [23]. The results of the REMATCH trial clearly outlined the marked survival advantage of LVADs over chronic intravenous inotropes. Indeed, since REMATCH, there have been no randomized trials proposed that would examine any of the newer LVADs compared with chronic inotropic therapy due to the belief that doing so would be unethical. However, thousands of patients continue to be maintained on intravenous inotropes as both a bridge to transplant and also as destination therapy. Other than patient preference with respect to quality-of-life issues [24], one of the key determinants in deciding to pursue an LVAD is the significant morbidity related to the actual surgery. The REMATCH cohort had perioperative mortality of 31%, although as experience with both the surgery and postoperative care has improved, a few centers have reported perioperative mortality as low as 8.7% [25].

An important next step after defining the patient population that would benefit from mechanical support is to calculate individual risk during the actual surgery, as patients with severe RV failure and end-organ dysfunction have a high in-hospital mortality after VAD surgery [26]. Lietz et al. [11, 27••] examined 280 patients receiving the HeartMate XVE as a destination device and derived a risk score that divided patients into high- and low-risk groups based on platelet count, serum albumin, INR, mean pulmonary artery pressure, aspartate aminotransferase, hematocrit, blood urea nitrogen, and whether they were being treated with vasodilatory therapy or with intravenous inotropes. Patients in the low-risk group had a survival to discharge of 93.7% compared with a survival to discharge of 13.7% in the very high-risk group. The low-risk group had a 1-year survival of 81.2% compared with a 1-year survival of 10.7% for the very high-risk group. Analysis of this patient population affirms that the presence of comorbidities (ie, renal and hepatic dysfunction), RV dysfunction (ie, low pulmonary artery pressure and elevation in liver enzymes), and poor nutritional status greatly increase mortality, which in most cases was secondary to

sepsis (29.5%), multisystem organ failure (12.8%), stroke (9%), and right heart failure (8.4%). Interestingly, the severity of heart failure alone was not predictive of mortality. Due to frequent hepatic dysfunction and high perioperative bleeding risk, another group described the ability of the Model for End-Stage Liver Disease (MELD) score to predict perioperative and 6-month mortality with LVAD placement [28]. Patients with an MELD score greater than 17 had a 6-month mortality that was 2.5 times higher than those with an MELD score less than 17. Both of the above studies primarily looked at patients with first-generation LVADs. A single-center ($n=86$) comparative analysis examining the ability of various risk indices (Leitz-Miller, Columbia, Acute Physiology and Chronic Health Evaluation II [APACHE II], Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS], and Seattle Heart Failure Model [SHFM]) to predict mortality with the newer continuous-flow HeartMate II revealed that the SHFM was superior to the other risk indices in this specific patient cohort [29].

Outcomes

As the perioperative risk with LVAD implantation has improved, less sick patients are being considered for LVAD placement. Though a less sick patient cohort might tolerate surgery much better than a patient in cardiogenic shock, the immediate survival advantage from mechanical support might not be as obvious. Nevertheless, significant improvement in functional capacity could be achieved if a detailed evaluation is performed to identify patients who might derive symptomatic and survival benefit without prohibitive risk. Consideration for LVAD placement has been advocated for patients with a 1-year life expectancy of less than 50% due to the severity of their heart failure and/or symptoms that limit ambulation to less than one block [23]. To further study outcomes in patients with different disease severity, INTERMACS has defined seven different profiles of end-stage heart failure [30]. The profiles range from patients in critical cardiogenic shock to patients with advanced NYHA class III symptoms (Table 1).

The INTERMACS dataset includes follow-up for all MCS devices implanted in the United States since June 23, 2006 [31••]. Centralization of these data allows for long-term follow-up and device comparison, and serves as a historical record for the evolution of MCS. The second annual INTERMACS report reviewed 1092 primary LVAD implants, and currently, there are more than 2500 patients included in the registry. A full 85% of these patients are INTERMACS profile 1 through 3, although the proportion of profile 1 patients has been decreasing as the expansion of LVAD use to a less sick population increases. In addition, the first annual

Table 1 INTERMACS classification of heart failure

| | |
|---------|---|
| Level 1 | Critical cardiogenic shock (“crashing and burning”) |
| Level 2 | Progressive decline on inotropic support |
| Level 3 | Stable but inotrope dependent |
| Level 4 | Resting symptoms on home oral therapy |
| Level 5 | Exertion intolerant |
| Level 6 | Exertion limited |
| Level 7 | Advanced NYHA class III |

INTERMACS Interagency Registry for Mechanically Assisted Circulatory Support, *NYHA* New York Heart Association.

INTERMACS report showed a worse outcome for patients who were implanted in critical cardiogenic shock, or patient profile 1. At the time of the second annual report, there already was a shift toward the use of continuous-flow devices, with 51.6% of all LVAD implants registered as the newer continuous-flow models. That trend has continued with the current registry being comprised of more than 80% continuous-flow models. The 1-year survival for all LVADs has continued to improve, from the roughly 50% 1-year survival reported in REMATCH to 74% reported in the second annual INTERMACS report. Based on data presented at the International Society of Heart and Lung Transplantation annual meeting in 2010, the current 1-year survival for LVADs has continued to improve and is now close to 85% (Kirklin, unpublished data). The risk factors for mortality identified in this registry include age of the recipient, RV function, implantation in INTERMACS patient profile 1 patients, and the use of a pulsatile pump. The improved mortality over the years can be explained by better patient selection, standardized postimplantation care, and more durable devices. However, despite the better outcomes, a few common complications continue to plague MCS devices.

Right Ventricular Failure

One of the main determinants of outcome after LVAD implantation is RV function, which plays a role in postoperative vasopressor requirements and multisystem organ failure. A definition for RV failure in the setting of left-sided MCS has not been fully developed, especially in patients who develop signs and symptoms several months postoperatively. However, perioperatively, a clinically important definition that has been embraced by INTERMACS is the need for RV mechanical support (RVAD) or persistent need of inotropic support for more than 14 days. Clinically important RV failure with compromised perfusion and function of end organs remains a significant factor impacting short- and long-term survival. In a single-center study of

patients with right heart failure, the abovementioned definition identified that 35% of patients implanted with HeartMate VXE and 41% of patients implanted with HeartMate II met the criteria for RV failure, with significantly fewer patients who were implanted with the HeartMate II requiring support with a RVAD [32]. An RV-failure risk score comprised of aspartate aminotransferase, bilirubin, creatinine, and a preoperative vasopressor requirement was able to identify patients at high risk for needing biventricular support and a higher postoperative mortality [33]. However, even the lowest risk group in this study had a 20% incidence of RV failure (compared with an 80% incidence in the highest risk group). A retrospective review of the patients in the HeartMate II bridge-to-transplant trial showed that patients with a central venous pressure/pulmonary capillary wedge pressure ratio more than 0.63, preoperative ventilator support, and elevated blood urea nitrogen were more likely to have post-LVAD RV failure [34]. This study reported 20% of patients with RV failure requiring either an RVAD (6%), early inotropic support (7%), or late inotropic support (7%) and identified a significant survival advantage in the patients who did not develop clinically significant right heart failure. Single-center studies have identified RV stroke work index, pulmonary artery pressure, prior cardiac surgery, serum creatinine, and systolic blood pressure as being predictive of post-LVAD RV failure (Table 2) [35, 36]. Further work needs to be done to truly identify risk factors predictive of RV failure post-LVAD implantation. Perhaps better techniques of RV protection during LVAD implantation need to be further explored as well.

Infection

As in the REMATCH and HeartMate II bridge-to-transplant and destination therapy trials, the INTERMACS registry identified infection as a common adverse event and the cause of death in 16.2% of patients. The newer continuous-flow devices are much smaller and, as the HeartMate II trials showed, these newer devices are associated with less pocket and driveline infections, which had been a source of morbidity and mortality. Once a driveline infection is identified, attempts to treat it with antibiotics can be successful, but the recurrence and possibility of bacterial resistance to antibiotics also have been noted. Anecdotally, cases of pump and other thrombosis postinfection have led to concern that a postinfectious hypercoagulable state can lead to clinically important events in LVAD recipients. Attempts to stabilize the driveline with support devices that minimize driveline movement, and thus minimize skin irritation, also have been reported to minimize driveline infections.

Table 2 Predictors of right ventricular heart failure

| Study | Predictors | Comments |
|---|--|---|
| Matthews et al. [34] | Vasopressor requirement; Aspartate aminotransferase > 80 IU/L; Bilirubin > 2.0 mg/dL; Creatinine > 2.3 mg/dL | 197 patients; 86% pulsatile devices; 20% of patients with a low (normal) score still experienced RV failure |
| Kormos et al. [35] (HeartMate II ^a bridge-to-transplant trial) | Central venous pressure/pulmonary capillary wedge pressure ratio > 0.63; Preoperative ventilator support; Blood urea nitrogen > 39 mg/dL | 484 patients; all HeartMate II (continuous flow) devices |
| Fitzpatrick et al. [36] | Severe preoperative RV dysfunction; RV stroke work index ≤ 0.25 mm Hg/L/m ² ; Creatinine ≥ 1.9 mg/dL; Prior cardiac surgery; Systolic blood pressure ≤ 96 mm Hg; Cardiac index ≤ 2.2 L/min/m ² | 266 patients; 96% pulsatile devices; risk score comprising all of these variables had 83% sensitivity and 80% specificity for predicting the success of isolated LVAD support |

^a Manufactured by Thoratec Corporation, Pleasanton, CA.

LVAD left ventricular assist device, RV right ventricular.

Stroke

Both ischemic and hemorrhagic stroke have been associated with MCS. A primary cerebrovascular event was associated with 14.1% of all deaths in the second annual INTERMACS report [31••]. With the advent of the continuous-flow devices, standard practice has been the use of aspirin and concomitant use of warfarin (goal INR 2.5–3.5 initially, but now 1.5–2.5) [19]. A heparin bridge frequently is used whenever a patient is subtherapeutic, either immediately after implant or before an invasive procedure. Recent data from Slaughter et al. [37] suggest that a heparin bridge might not be needed at all immediately after LVAD implantation. The appropriate anticoagulation regimen that minimizes the risk of bleeding and prevents thromboembolism has yet to be demonstrated conclusively. A tailored approach for thromboprophylaxis with thromboelastography has been reported by several centers, but a prospective multicenter study has yet to be performed. In addition to anticoagulation, the aforementioned hypercoagulable state associated with infection could be playing a role in causing ischemic strokes. Finally, one of the leading causes of hemorrhagic stroke in the general population is the presence of systemic hypertension. Patients with continuous-flow devices have increased diastolic pressure at higher pump speeds and it is becoming increasingly clear that direct Doppler measurement should be used to measure systemic blood pressure (systolic blood pressure approximates the mean with a narrow pulse pressure) and that target blood pressure should be lower. It is our practice to aim for a mean blood pressure no greater than 80 mm Hg and to decrease pump speed or increase the degree of afterload reduction if the mean pressure is higher than 90 mm Hg. However, there are no retrospective or prospective data linking high mean blood pressure on a continuous-flow device and a greater incidence of hemorrhagic stroke.

Bleeding

Bleeding, both at the site of implantation and in the gastrointestinal (GI) tract, is another frequent adverse event associated with MCS devices. The second INTERMACS annual report showed that bleeding was the second most frequent adverse event (after infection) [31••]. Despite this, the bleeding episodes were infrequently fatal and accounted for only 6.7% of all deaths. There have been reports that the use of continuous-flow devices leads to acquired von Willebrand's deficiency, which predisposes to bleeding, especially in the setting of antiplatelet use [38]. Also, the use of continuous-flow devices has led to more frequent incidence of atrioventricular fistulas in the GI tract, a finding also seen in another narrow pulse state, aortic stenosis [39]. As the appropriate anticoagulation strategy evolves with lower INR goals, less frequent use of heparin, and a reevaluation of the role of antiplatelet use, it is likely that these adverse events will become less frequent.

Conclusions

MCS has evolved from a therapy of last resort to rescue patients in postoperative cardiogenic shock to a viable alternative for thousands of patients with end-stage heart failure. The INTERMACS registry allows for centralization of data gathering for the MCS field and already has depicted remarkable trends both in device development and in tracking adverse effects. Additional registries in multiple European nations have been started, and hopefully, an international registry that will allow for the compilation of all data regarding MCS will one day be a reality. In the meantime, progress continues in miniaturization of circulatory support devices that will lead to better operative outcomes, less frequent infections, and higher patient satisfaction.

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