Left ventricular assist device implantation strategies and outcomes

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Abstract: Over the past 15 years, the field of mechanical circulatory support has developed significantly. Currently, there are a multitude of options for both short and long term cardiac support. Choosing the appropriate device for each patient depends on the amount of support needed and the goals of care. This article focuses on long term, implantable devices for both bridge to transplantation and destination therapy indications. Implantation strategies, including the appropriate concomitant surgeries are discussed as well as expected long term outcomes. As device technology continues to improve, long term mechanical circulatory support may become a viable alternative to transplantation.

Keywords: Mechanical circulatory support (MCS); left ventricular assist device (LVAD); heart failure

Introduction

Mechanical circulatory support (MCS) encompasses a spectrum of devices designed for partial or complete replacement of cardiac function. Appropriate device selection depends on the long term goal of support, nature of cardiac dysfunction, acuity of presentation, and expected duration of support. In general, critically ill patients require immediate stabilization with inotropes or short term MCS before consideration for implantation of a durable device for long term support. A separate article in this issue will cover short term support options, so this discussion will focus on long term support.

More than 15 years ago, the goal of long term MCS was inevitably heart transplantation, with an occasional case of recovery allowing device explantation. As devices have improved, destination therapy (DT), planned long term dependence on MCS without plans for transplant, has become a viable option (1). Bridge to candidacy (BTC) describes patients who are not candidates for transplant at the time of implant due to a potentially reversible issue. DT patients tend to be older and have more comorbid conditions than bridge to transplant (BTT) patients, with BTC an intermediate between the two (2). In clinical practice these categories are fluid, with patients moving in both directions on the indication spectrum, leading some to question the utility of identifying a strategy at the time of implant (3). While the dichotomy of BTT or DT is in some ways artificial, it is imperative to assess patients' candidacy for transplant prior to implant and how MCS fits into their goals of care (4).

Device choice

Most patients with end stage heart failure have severe left ventricular systolic dysfunction. Left ventricular assist devices (LVADs) are designed to support these patients. The most common configuration for a left ventricular assist device (LVAD) requires a cannula in the left ventricle which supplies blood to the pump, and an outflow graft which returns blood

to the ascending aorta. Early generation devices maintained the pulsatile nature of the cardiac cycle, termed pulsatile flow (PF). These devices had multiple moving parts and therefore were unfortunately prone to mechanical failure. Continuous flow (CF) devices are smaller and more durable, and have revolutionized the field over the last 10 years. Thoratec's HeartMate II was the first widely used CF device, and has the most clinical experience worldwide. It is an axial flow device, meaning the flow of blood is parallel to the axis of the rotor. The rotor is suspended by mechanical bearings, which are a potential source of mechanical failure as well as thrombus formation (5). Alternatively, centrifugal flow pumps have a 90 degree angle between inlet and outlet blood flow, with the rotor's axis of rotation aligned with inlet flow. Centrifugal flow devices can be suspended by hydrodynamic and magnetic forces, eliminating the need for bearings. HeartWare's HVAD and Thoratec's next generation device, HeartMate 3, are both centrifugal pumps. The HVAD is substantially smaller than the HeartMate II allowing for intrapericardial placement as well as implantation via thoracotomy. Smaller devices are compatible with smaller patients, which have expanded the number of patients who are candidates for MCS including increasing numbers of pediatric patients.

Currently, the HeartMate II LVAD is approved for both BTT and DT in the U.S (6,7). The HVAD is approved only for BTT (8). The HVAD DT trial, ENDURANCE, has been presented in abstract form and found the HVAD was not inferior to the HeartMate II, full publication and FDA approval are still pending (9). Thoratec's HeartMate 3 is designed to reduce thromboembolic complications, a combined BTT and DT trial has started enrolling patients. HeartWare's next generation device, MVAD, is an even smaller CF device, and a clinical trial is planned in the coming year.

While the majority of patients can be supported with an LVAD, patients requiring biventricular support pose serious challenges. Identification of patients at risk for right ventricular (RV) failure following LVAD placement is not as straightforward as it seems, as evidenced by the myriad published pre-operative risk scores (10-13). Patients with evidence of renal and hepatic dysfunction (elevated creatinine, blood urea nitrogen, aspartate aminotransferase, and bilirubin) are at increased risk of post-operative RV failure. Patients requiring more aggressive pre-operative support, such as vasopressors, multiple or high dose inotropes, mechanical ventilation, intra-aortic balloon pump, and extra-corporeal membrane oxygenation, are at

higher risk. Hemodynamic indicators of risk include higher central venous pressure and pulmonary vascular resistance, higher central venous pressure to pulmonary capillary wedge pressure ratio, and low RV stroke work index [(PA mean – RA mean) × CI/HR]. Finally, echocardiographic risk factors include RV size, particularly in relation to LV size, severity of RV dysfunction, and severity of tricuspid regurgitation (TR) (14). Intraoperative events certainly contribute to RV dysfunction as well, including positive pressure ventilation, hypoxia and hypercapnia, cardioplegia, excessive bleeding, coronary embolism, RV injury during sternotomy, and protamine.

Further complicating the biventricular support dilemma is the fact that the majority of RV failure can be successfully managed medically with inotropic support, pulmonary vasodilator therapy, and careful management of volume status. This makes it quite challenging to prospectively identify patients who will require a right ventricular assist device (RVAD). Configurations vary for RVADs, with either right atrial or right ventricular inflow cannulation and pulmonary artery outflow. Failure to wean from cardiopulmonary bypass mandates RVAD placement. If RV function is expected to improve, a short term RVAD can be used with plans for explant in the weeks after surgery. If RV function is not expected to recover, or if RVAD wean is not successful, the HeartWare HVAD has been used as a long term RVAD (15,16). Progressive RV failure despite medical management in the days following surgery can be more difficult to recognize and intervention is more complex. Percutaneous RVADs are available for short term support, including the CardiacAssist TandemHeart and Abiomed Impella, as well as both short and long term surgical options above. Primary RV dysfunction with relatively preserved LV function is a difficult clinical problem; HVADs have been used in this situation in limited numbers with some success (17).

The Syncardia Total Artificial Heart (TAH) is another option for long term biventricular support (18). Both ventricles are removed during implantation, making it a good option when LVAD or BiVAD support is problematic such as restrictive or hypertrophic cardiomyopathy, refractory ventricular arrhythmias, ventricular septal defects, and complex congenital defects. Obviously, myocardial recovery is not an option with TAH. TAH is approved by the U.S. FDA for BTT, with plans for evaluation as DT in the future.

Concomitant procedures

Patients who present for long term MCS often have

associated cardiac pathology including ventricular arrhythmias and valve dysfunction. Additionally, some patients have had previous corrective surgery including replaced valves or coronary bypass grafting. When assessing cardiac disease at the time of LVAD placement it is important to consider which conditions will improve with MCS and which may worsen over time. Adding concomitant procedures at the time of VAD implantation increases operative time and may increase patient risk of adverse outcomes (19,20). As such, appropriate patient selection has been the subject of recent studies (19-25).

A competent aortic valve is critical to maximize the utility of the LVAD. An incompetent valve will permit a closed loop circulation of blood through the left ventricle and fail to perfuse the rest of the body. With this in mind, aortic valve surgery is one of the most frequently performed concomitant procedures at the time of LVAD placement (20). Isolated aortic stenosis does not need to be addressed at the time of LVAD placement unless there is associated aortic regurgitation. Longitudinal studies have demonstrated that aortic insufficiency often develops over time, presumably from the continuous negative pressure generated in the left ventricle by the LVAD. Mild AI may progress to severe if given enough time. Many surgeons elect to treat aortic regurgitation particularly in DT patients for any finding that is more than 'trace'.

There are several different surgical options for an incompetent native aortic valve. One can either exclude the valve by sewing a pericardial patch across the ascending aorta above the valve or make the valve itself competent. The latter can be accomplished by replacing the valve with a new bioprosthetic valve or with a repair stitch through the valve leaflets. These techniques were examined in a retrospective review of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACs) data and found that excluding the aortic valve was associated with higher mortality rates when compared to repair of the valve (21). Further, suturing the valve, while associated with shorter cross-clamp and bypass time, was less durable than valve replacement for aortic insufficiency. Mechanical aortic valves are generally replaced with a bioprosthetic valve or excluded due to the potential thrombogenicity of the leaflets. Interestingly, in explanted hearts of patients who have had an LVAD and bioprosthetic valve, the leaflets of the valves are often fused. This is important to consider in patients who are being evaluated for bridge to recovery as their aortic valves may need to be addressed at the time of LVAD explant.

The LVADs require a widely patent mitral valve to allow for unobstructed flow into the ventricular cannula. In the case of mitral stenosis, mechanical valvuloplasty or even mitral valve replacement may be necessary. As with the aortic valve, previously placed mechanical mitral valves are also closely evaluated. While not essential, many favor replacing the mechanical valve with a bioprosthetic to avoid potential complications of thrombosis of the valve. Mitral regurgitation (MR) usually does not need to be addressed at the time of LVAD implantation as it is generally overcome once the ventricle is unloaded, though it may be considered for organic MR particularly if recovery is a possibility (22).

TR is commonly seen in patients who are undergoing LVAD placement. Regurgitation either results from associated right ventricular dysfunction or as a result of indwelling leads from a pacemaker or internal cardioverter-defibrillator. In some series it has been found that 50% of the time TR will improve with LVAD placement and mechanical offloading (23). However, recovery can be difficult to predict and as severe TR can exacerbate RV dysfunction, so many surgeons elect to repair the tricuspid valve at the time of LVAD placement. Although tricuspid valve repair does not require full cardiac arrest, Robertson *et al.* in review of over 2,000 patients found that a tricuspid valve procedure at the time of LVAD did not reduce mortality and was, in fact, associated with worse early postoperative outcomes in patients with moderate to severe TR (24).

A patent foramen ovale (PFO) is present in up to 25% of the population. In normal physiologic conditions there is minimal shunting of blood through the PFO and that blood which is shunted is in a left to right fashion. Once an LVAD is placed the left ventricle is off loaded and an open PFO can result in a right to left shunt with clinical hypoxia. Percutaneous cardiac procedures requiring trans-septal puncture such as left atrial ablations can leave behind sizable atrial septal defects. PFOs and other atrial septal defects are surgically closed at the time of VAD placement.

Ventricular tachyarrhythmias are common in patients with end stage heart disease. They are seen in patients preoperatively as well as after LVAD placement. While relatively well tolerated, ventricular tachycardia can result in further right ventricular dysfunction and should be addressed when possible. Preoperative mapping and intra-operative treatment with cryoablation can be helpful in patients with preoperative ventricular arrhythmias. For patients who are unable to have preoperative mapping, concomitant cryoablation of the left ventricle to fixed anatomic points such as the mitral valve or apical LVAD

Table 1 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles

Profile	Hemodynamic status
"Crash and burn"	Critical cardiogenic shock
"Progressive decline"	Inotrope dependence with continued deterioration
"Stable but inotrope dependent"	Stable on mild to moderate doses of inotropes, but failing to wean from them
"Recurrent advanced heart failure"	Possible weaning of inotropes but experiencing recurrent decompensation
"Exertion intolerant"	Comfortable at rest but intolerant to activity
"Exertion limited"	Able to do some mild activity but fatigues easily with any meaningful exertion
"Advanced NYHA class III"	Clinically stable with a reasonable activity despite previous decompensation that is not recent

NYHA, New York Heart Association.

inflow cannula has been shown to eliminate postoperative ventricular arrhythmias (25).

Outcomes

As experience with MCS for management of patients with advanced heart failure continues to grow, a larger number of patients are being considered for these therapies. Careful selection of patients who will benefit from the technology is important. A clear understanding of the predictors of post implant mortality is essential to guiding device selection and post-operative management.

CF pumps have become the mainstay of MCS devices since 2008. The shift from earlier PF devices to CF has led to improvements in patient survival. The INTERMACS is a United States interagency registry for FDA approved MCS devices sponsored by the National Heart, Lung and Blood Institute (NHLBI) and partnered with the FDA, centers for medicare and medicaid services, clinicians, scientists, and industry representatives. The INTERMACS registry reports an 81% 1-year post implant survival for CF LVAD and 57% for CF BiVAD. This is compared with a 65% 1-year survival with PF LVAD and 45% with PF BiVAD. Risk factors for death in patients with CF devices include older age, higher BMI, critical pre-operative illness, DT strategy, renal dysfunction, right heart dysfunction, and history of cardiac surgery (26).

Patients entered into the INTERMACS registry are categorized into seven profiles ranging from level 1-critical cardiogenic shock, to level 7-advanced New York Heart Association (NYHA) III heart failure (*Table 1*). Patients who are critically ill at the time of MCS device implant, INTERMACS levels 1 and 2, have significantly higher 30-day mortality when compared with patients at levels 3 and 4. The major causes of early mortality are infection

and multi organ failure (26,27).

In the recent era of CF devices, mortality in the most critically ill patients remains high. In a small multicenter analysis of patients treated at the University of Minnesota, Columbia University, and University of Pittsburgh, survival to hospital discharge post LVAD implant was 70.4% for patient implanted at INTERMACS level 1, 93.8% at levels 2 and 3, and 95.8% at levels 4-7. There was also a long term survival advantage in patients implanted at INTERMACS level 4-7, 95.8% survival at 36 months versus 51.1% for those at INTEMACS level 1 (28).

The proportion of patients receiving devices for DT has increased from 14.7% in 2006-2007 to 41.6% in 2011-2013 (26). Teuteberg *et al.* investigated how intended strategies at time of LVAD implant influenced outcomes. Two-year survival after primary LVAD implant was 77.7% for BTT, 70.1% for BTC and 60.7% for DT strategy (2). The survival difference between BTT and DT patients is in large part affected by the difference in patient characteristics between these two groups. Patients implanted for DT are generally older and have more comorbidities, and when device complications arise, transplant is not usually a "bail out" option. Interestingly, in this study 14.6% of patients with initial intent of DT were listed for transplant or deemed eligible for transplant at 12 months. At 2 years 6% of DT patients had been transplanted (2).

CF LVADs account for all MCS devices implanted for DT and more than 95% of all primary MCS devices since 2010. Actuarial survival has reached 80% at 12 months and 70% at 24 months. Despite increasing experience with these devices, survival post implant has remained unchanged over the two eras of CF devices, 2008-2010 and 2011-2013 (26). Over this same time period we have seen a dramatic increase in the number of patients implanted for DT, and we know that long term survival is lower in this group compared with

BTT patients. We may not be seeing an overall improvement in survival with increased experience because of this increase in DT implants.

After LVAD implant, mortality risk is most significant during the post-operative hospitalization, especially in patients implanted at INTERMACS levels 1 and 2 (26,28). Post implant, mortality risk rapidly decreases and becomes constant around 3 months. There is a late phase of gradually increasing mortality risk after 18 months and out to 5 years which seems to correlate with increasing risk of infection and multisystem organ failure (26). During the early post implant phase, the major cause of death is multi organ failure, and the risk persists out to 4 months. After the first 3 months and out to 48 months, neurological complications are the predominate cause of death. Additionally, multiple pump replacements have a detrimental effect on survival. Compared with 80% survival at 1 year after initial implant, 1-year survival after second implant is 65% and 50% after the third (26).

Patients requiring biventricular support have substantially worse outcomes than patients requiring left ventricular support only, and overall survival in patients receiving BiVAD or TAH is inferior to CF LVADs. One-year survival for CF BiVAD is 57%, 45% for PF BiVAD, and 59% for TAH (26). The increased mortality risk associated with BiVADs is mostly driven by severe right heart failure and the resulting critical illness and sequela. Cleveland *et al.* prospectively evaluated 1,706 patients enrolled in the INTERMACS registry to determine whether the BiVAD or the patient with right heart failure dictates the inferior outcome. Those patients undergoing BiVAD implant had significantly more end organ damage, higher incidence of mechanical ventilation, lower systolic blood pressure and cardiac index, and higher right atrial pressure when compared with patients receiving isolated LVADs. There were also a higher percentage of INTERMACS level 1 patients undergoing BiVAD implantation, 55% versus 26% in the LVAD group. Additionally, bleeding and neurologic complications and device malfunction were greater in the BiVAD group (29). When biventricular support is required, the type of device used does not significantly impact survival. Kirsch *et al.* assessed 383 patients receiving BiVADs and TAHs from 2000 to 2010, looking for differences in survival during support and after transplant based on the type of device used. They found a trend towards improved survival in patients requiring longer support, ≥90 days, with the TAH, but no significant difference. Similar to LVADs, major causes of death included multi organ failure, neurologic

complications, and infection (30).

INTERMACS data shows the adverse event rates with CF LVADs have been significantly lower than with previous PF devices, particularly with device malfunction and infection. Interestingly, the incidence of pump thrombosis in CF devices, primarily HeartMate II, has increased over time (26). This is an important phenomenon to recognize not only because device exchange increases readmissions and cost during MCS therapy, but there is also a detrimental effect on survival with every subsequent device exchange (26,31). Investigators at the Cleveland Clinic, Washington University, and Duke University further studied the problem of HeartMate II device thrombosis. Between 2004 and March 2011, the incidence of pump thrombosis was 2.2% at 3 months post implant, and increased to 8.4% by January 2013, with substantially increased associated mortality. At 180 days, mortality was 35.6% in patients with confirmed pump thrombosis versus 16.8% in those without. Patients with pump thrombosis managed medically, 6-month mortality was 48.2%. Unfortunately the cause of this recent increase in pump thrombosis remains unknown (32). Possible contributors include less aggressive anticoagulation regimens, both early post-operatively as well as long term (33-35). There is some evidence that intermittent aortic valve opening reduced the late incidence of aortic insufficiency, which led some centers to reduce LVAD speeds (36). Cannula and pump position has also been linked to increased pump thrombosis rates (37). The ongoing PREVENT trial is designed to study patient, implant, and device factors contributing to HeartMate II LVAD thrombosis.

Conversely, bleeding is another common complication of MCS devices. The most common reason for readmission post implant is bleeding, most frequently gastrointestinal bleeding. Although gastrointestinal bleeding is a common and serious cause of morbidity, it has not been found to significantly affect mortality from LVAD support (31,38). Patients who have had bleeding events, however, are more likely to have subsequent thromboembolic and hemolysis events. In one multicenter study, thromboembolic and hemolytic events were 7.4 times more frequent in patients with prior gastrointestinal bleeding, likely due to changes in anticoagulation management (31,39,40).

Health related quality of life (HRQOL) is poor in patients with advanced heart failure undergoing MCS device implant and significantly improves in the post implant period. Patients with worse INTERMACS profiles have worse perceived HRQOL measured by the EQ-5D-3L survey

compared with those at higher INTERMACS profiles. Across all INTERMACS profiles, the majority of patients experience problems with mobility and usual activities prior to implant. By 12 months after implant of CF LVADs, the frequency of problems (mobility, usual activities, self-care, pain, and anxiety/depression) is decreased and similar across all INTERMACS profiles (41). This significant improvement in HRQOL after LVAD placement is also seen in older patients and those undergoing implant for DT (42).

The proportion of LVADs implanted with BTT strategy has dramatically decreased in recent years (31,36), but at the same time, more and more patients receiving heart transplants in the United States are bridged with MCS devices, up to 30% and rising (36). The likelihood of transplant after LVAD implant correlates with implant intent, with 37% likelihood of transplant at 12 months in those with BTT strategy and 20% with BTC strategy (31). LVAD related complications have a significant impact on timing of transplant and post-transplant outcomes. The number of BTT patients receiving transplants for urgent 1A status due to LVAD complications has risen over the last decade, from 20-40% to 55-85% (36,43,44). Post-transplant survival is worse in patients with device related complications. In one study, 3-year post transplant survival was 77.9% in patients with device related complications versus 82.7% in those without. Specifically patients with device related infections, as opposed to other device related complications such as thromboembolism and malfunction, had a higher mortality rate compared with transplanted patients without previous device complications (44).

CF LVADs significantly decompress the LV, and thereby induce reverse remodeling of the myocardium as evidenced by decreased LV end diastolic diameter (LVEDD) and decreased severity of MR. Reverse remodeling appears to begin almost immediately and is sustained during LVAD support. One study found an average reduction in LVEDD of 13.3 mm 1 month following LVAD implant and sustained reduction at 6 months. The severity of MR substantially improved over this same time, with 76% of patients having moderate or severe MR pre-implant and only 8% with moderate or severe MR at 1 month post implant (45). Stulak e*t al.* additionally demonstrated a late survival benefit in patients with pre-operative moderate to severe or greater MR and in patients with larger LVEDD, >69 *vs.* <59 mm (22). Hemodynamics also improve post LVAD implant, with a notable decrease in central venous, pulmonary artery, and pulmonary capillary wedge pressures and increase in cardiac index (45). These studies suggest that patients with severe LV dilation and MR benefit the most from LV unloading with CF LVADs.

Despite reverse remodeling, myocardial recovery leading to LVAD explant is infrequent and the rate of sustained recovery after explant is variable. In a retrospective analysis of the data obtained from 1,108 patients in the HeartMate II BTT and DT trials, only 1.8% of patients underwent LVAD explant for recovery. Those with successful explant tended to be younger, under 40 years of age, and female, with non-ischemic cardiomyopathies of less than 12 months duration. Of the explanted patients, 15% required re-implantation within the first 2 months. At a median follow-up of 510 days, the remaining recovered patients had a mean ejection fraction (EF) of 42% and were NYHA functional class I or II (46). Other studies have shown similarly low rates of myocardial recovery, but those who do recover tend to be younger, female and have non-ischemic cardiomyopathy (47,48).

Birks *et al.* evaluated the effect of pharmacologic therapy with LVAD mechanical unloading on LV reverse remodeling and sustained recovery after LVAD explant. This group combined clenbuterol, a $\beta2$ agonist which induces a physiologic hypertrophy, with typical heart failure therapies, and two thirds of their patients with a HeartMate I device were successfully explanted with good long term results. Next they conducted a small prospective study on patients with dilated non-ischemic cardiomyopathy undergoing HeartMate II implant. Patients were initially treated with lisinopril, carvedilol, spironolactone, digoxin, and losartan at target doses. Once LVEDD was <60 mm at a reduced LVAD speed of 6,000 rpm, carvedilol was replaced with bisoprolol and clenbuterol was added. Of the 20 patients studied, 63% were explanted, and freedom from death or recurrence of heart failure in this group was 83% at 3 years (49). This group recently published data on an additional 22 patients who were successfully explanted after an average of 1.2 years of support and pharmacotherapy with lisinopril, carvedilol, spironolactone and losartan. At 2 years, freedom from death, transplant, or re-implantation was 81% (48). Both of these studies show significantly higher rates of myocardial recovery and device explant than is commonly reported. One potential difference is the rigorous algorithm followed for myocardial recovery testing. LVADs are rarely implanted for bridge to recovery, and after implant for BTT or DT, underlying myocardial function is not regularly evaluated. More frequent testing may lead to increased rates of recovery and explant (26,31,49,50).

Conclusions

The field of MCS has undergone dramatic changes in the last decade, and rapid technological advances will drive further changes in the years to come. Appropriate MCS strategy is critical to optimal patient outcomes, and allows the field to serve a steadily growing population with end stage heart failure. Long term MCS may eventually be a viable alternative to transplantation, which would allow allocation of limited donor hearts to patients who cannot be adequately supported mechanically.

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Footnote

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