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CURRENT TOPICS REVIEW ARTICLE

Current status of the implantable LVAD

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Abstract With the ongoing shortage of available organs for heart transplantation, mechanical circulatory support devices have been increasingly utilized for managing acute and chronic heart failure that is refractory to medical therapy. In particular, the introduction of the left ventricular assist devices (LVAD) has revolutionized the field. In this review, we will discuss a brief history of the LVAD, available devices, current indications, patient selection, complications, and outcomes. In addition, we will discuss recent outcomes and advancements in the field of noncardiac surgery in the LVAD patient. Finally, we will discuss several topics for surgical consideration during LVAD implantation.

Keywords LVAD · Bridge to transplantation · Destination therapy · Bridge to recovery · Bridge to candidacy

Introduction

The gold standard for the treatment of end stage heart failure remains orthotopic heart transplantation. However, given the ongoing shortage of available organs and the ever-increasing pool of patients, mechanical circulatory support devices have been increasingly utilized for managing acute and chronic heart failure that is refractory to medical therapy. In particular, the introduction and clinical validation of left ventricular assist devices (LVAD) in several pivotal studies have revolutionized the field. With the widespread application of the continuous flow LVAD, 1-year survival is now 80 %, which is approaching that of heart transplantation at 86 % [1, 2]. This is in stark contrast to what was reported in the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial of 2001, where 1-year survival was 52 % [3]. This survival improvement is directly related to a greater understanding of heart failure, improved patient selection for LVAD implantation, refined surgical technique, improved postoperative care, and advancements in LVAD technology, with a general shift away from pulsatile flow technology and toward continuous flow technology. In the Seventh Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report from 2014, greater than 90 % of all assist devices implanted in the US were of the continuous flow type [1].

Although LVAD are associated with a decrease in mortality and an improvement in the quality of life, it needs to be stressed that LVAD implantation is associated with significant complications and device-related problems. In this review, we will discuss a brief history of the LVAD, available devices, current indications, patient selection, complications, and outcomes. In addition, given that a growing number of patients with LVAD are surviving longer and requiring noncardiac surgery, we will discuss recent advancements in the care of these patients undergoing noncardiac surgery. Finally, we will discuss several topics for surgical consideration during LVAD implantation.

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Development of the LVAD and landmark trials

Dr. Debakey is credited with the first successful clinical use of the LVAD. In 1966, he performed a double valve replacement in a 37-year-old female, who then developed postcardiotomy cardiogenic shock. He successfully implanted a pneumatically powered, paracorporeal LVAD from the left atrium to the right subclavian artery. After 10 days of support, the patient recovered and the LVAD was removed [4]. Following this, Dr. Norman implanted the first LVAD as a bridge to transplantation (BTT) in 1978 [5].

The REMATCH trial of 2001 played a pivotal role in the approval of the LVAD as destination therapy (DT) in the US in November 2002 [3, 6]. This landmark study compared patients with advanced heart failure who underwent LVAD implantation versus maximal medical therapy and showed survival to be 52 % versus 25 % ($p = 0.002$) at 1-year. In addition to the survival benefit, the LVAD cohort had a statistically significant improved quality of life when compared to the medical therapy cohort. However, several complications and key limitations of this technology became apparent. The LVAD used in this study was the HeartMate VE, which relied on pulsatile flow technology. The incidence of serious adverse affects was 2.35 times greater in the LVAD group than the medical therapy group. Infection and mechanical failure were the two factors that limited 2-year survival to only 23 % in the LVAD group. Neurologic events occurred 4.35 times more commonly in the LVAD group than the medical group [3].

Many of these complications and limitations were addressed in the 2009 landmark study comparing the continuous flow HeartMate II with the pulsatile flow HeartMate XVE. The primary endpoint investigated was survival free from disabling stroke and reoperation to repair or replace the LVAD at 2 years. Remarkably, the authors found that 46 % of patients achieved this end point in the continuous flow cohort while only 11 % achieved it in the pulsatile flow cohort ($p < 0.001$). Additionally, survival at 2 years was 58 % in the continuous flow group and only 24 % in the pulsatile flow group ($p = 0.008$) [7]. This study confirmed the superiority of continuous flow technology over pulsatile flow technology and has paved the way for the second and third generation continuous flow LVAD.

Devices

LVAD can be classified based on how they function mechanically: pulsatile flow or continuous flow. The first generation LVAD, including the HeartMate XVE and Novacor, rely on pulsatile-flow technology, mimicking the function of the heart. These are also known as volume displacement devices. These pumps have multiple moving parts, including one-way valves and a flexible pumping chamber. Their complexity makes them prone to device breakdown and failure.

The second and third generation LVAD are continuous flow devices. The second generation, including the HeartMate II and Jarvik 2000, relies on axial continuous flow technology. The key mechanical changes in the second generation LVAD include the elimination of valves and chambers and the introduction of an internal rotor, which is suspended by contact bearings. However, this direct contact between the bearings and blood promotes thrombosis.

The third generation LVAD, including the HeartWare and DuraHeart, relies on centrifugal continuous flow. The key technological advancement in the third generation LVAD includes the introduction of noncontact bearings, which utilizes magnetic levitation. Theoretically, the elimination of this contact will lessen the incidence of thrombosis. This, however, has yet to be proven in clinical trials.

Overall, the second and third generation LVAD are smaller in size and require less surgical dissection and time for implantation. In addition, since they have fewer moving parts, these devices have greater durability with an expected lifespan of 5–10 years.

Indications

The indications for LVAD implantation include BTT, bridge to recovery (BTR), DT, and bridge to candidacy (BTC). The INTERMACS registry has developed patient profiles to stratify patients and allow for optimal patient selection for LVAD implantation. These range from Level 1–7. Level 1 includes patients with critical cardiogenic shock requiring circulatory support while Level 2 includes patients who are declining despite inotropic support. Level 3 includes patients who are stable on inotropic support and Level 4 includes patients with resting symptoms. Level 5 patients are exertion intolerant, Level 6 patients can engage in limited exertion, and Level 7 patients have advanced NYHA III heart failure. As illustrated by the levels above, progressing from Level 1 to Level 7 results in patients who are more functional and have less severe symptoms related to their heart failure. The majority of patients (about 80 %) being implanted with LVAD are INTERMACS Levels 2–4 [1].

Bridge to transplantation

The most common indication for LVAD implantation remains BTT. The Seventh INTERMACS report showed that BTT accounted for 51 % of biventricular and

univentricular assist device implantation in 2014 [1]. Multiple studies have shown that LVAD implantation as a BTT improves survival. A 2013 study with 332 patients showed that implantation with the HeartWare LVAD led to a 91 % survival at 180 days and 84 % survival at 1-year [8]. Similarly, a 2016 study utilizing the United Network of Organ Sharing (UNOS) database showed that patients who underwent LVAD implantation prior to being listed for heart transplantation had improved survival compared to those who were medically managed (HR 0.811 for status 1A, $p = 0.034$; HR 0.633 for status 1B, $p < 0.001$). This survival benefit extended to those who were implanted with a LVAD while being listed and awaiting heart transplantation (HR 0.553 for status 1A, $p < 0.001$; HR 0.696 for status 1B, $p < 0.001$) [9].

Implantation of a LVAD as a BTT also allows a patient with end stage heart failure to leave the hospital, have an improved quality of life, and have an improved functional status, while awaiting heart transplantation. A small 2004 study showed that patients who were implanted with the Jarvik 2000 LVAD as a BTT and surveyed with the Minnesota Living with Heart Failure Questionnaire (MLHFQ) before LVAD implantation, 1 month after LVAD implantation, before heart transplantation, and 1 month after heart transplantation had an overall improvement in physical performance and quality of life [10]. Miller et al. conducted a larger study of 133 patients in 2007. In their study, the continuous flow LVAD (HeartMate II) was implanted as a BTT, with the principle outcome being the proportion of patients who underwent transplantation, had cardiac recovery, or required ongoing mechanical support while remaining on the transplantation list at 180 days. Functional status and quality of life were also assessed at baseline and at 3 months. Most patients had at least a two New York Heart Association (NYHA) functional class improvement ($p < 0.001$) and an improvement in the 6-min walk test by more than 200 m ($p < 0.001$). Quality of life measured by the MLHFQ and Kansas City Cardiomyopathy questionnaire also showed a statistically significant improvement [11].

Bridge to recovery

Another indication for LVAD implantation is as a BTR in patients with acute decompensated heart failure. These patients typically have reversible causes of heart failure, such as medication-induced cardiomyopathy, post-partum cardiomyopathy, postcardiotomy syndrome, and viral myocarditis with refractory cardiogenic shock. Atluri et al. performed a retrospective study in 2013 on 24 patients implanted with a ventricular assist device (VAD) for fulminant myocarditis. They showed that patients who had acute fulminant myocarditis that progressed rapidly (median of 7 days from onset of symptoms to VAD implantation) had a greater likelihood of myocardial recovery, function, and VAD explantation than patients who had a more indolent presentation (median of 22 days between onset of symptoms to VAD implantation). This particular study showed that those who did not recover rapidly should be evaluated for heart transplantation [12].

In 2011, Krabatsch et al. conducted a retrospective study with 387 patients implanted with LVAD for idiopathic dilated cardiomyopathy between 1992 and 2009. In the study, 144 patients were implanted with a pulsatile LVAD and 243 patients were implanted with a continuous flow LVAD. They showed that 34 patients had sufficient myocardial recovery to allow for LVAD explantation, with a weaning rate of 8.8 %. Interestingly, younger patients and patients who had a pulsatile flow LVAD had an almost threefold chance of myocardial recovery than the continuous flow group [13]. Although this study found that patients with a pulsatile LVAD had an increased chance of myocardial recovery, it was limited by several factors, including a time bias. It compared two different types of LVAD devices implanted during different time periods, with the pulsatile flow devices implanted in the 1990s and the continuous flow devices implanted after 1998. As LVAD are now implanted in older patients with more medical comorbidities than those placed in the early 1990s, this could explain the differences in myocardial recovery and LVAD explantation between these two groups.

Another study published in 2011 by Kato et al. showed improved myocardial recovery with pulsatile LVAD. In that study, 61 patients were implanted with the LVAD between 2002 and 2009. Of these, 31 patients were implanted with a pulsatile flow LVAD and 30 patients were implanted with the continuous flow LVAD. The pulsatile flow group had an improved postoperative left ventricular ejection fraction than the continuous flow group (33.2 ± 12.6 versus 17.6 ± 8.8 %, $p < 0.0001$) [14]. This study had similar limitations to the study by Krabatsch et al. Since the first generation pulsatile flow LVAD are obsolete and no longer routinely implanted, a prospective study between the pulsatile and continuous flow LVAD cannot be conducted to assess which LVAD type leads to improved myocardial recovery. However, an interesting direction for future study could involve studying the effects of continuous flow speed settings and myocardial recovery in patients implanted with an LVAD as a BTR. By altering the speed settings, the flow patterns can be adjusted to be more pulsatile.

Destination therapy

Given the severe donor organ shortage and improved device durability, increasing numbers of LVAD are

implanted as DT. Typically, these patients do not meet criteria for heart transplantation, secondary to advanced age, frailty, advanced liver or kidney disease, obesity, severe pulmonary hypertension, and malignancy [15]. The criteria enumerated by Slaughter et al. in 2009 for LVAD consideration as DT included the following: left ventricular ejection fraction of less than 25 %, peak oxygen consumption of less than 14 mL/kg/min, NYHA class IIIB or IV, and dependence on an intraaortic balloon pump for 7 days or inotropes for 14 days [7].

In the Seventh INTERMACS annual report, this trend towards greater utilization of the LVAD for DT is clearly evident. While only 28.6 % of all LVAD implantations between 2008 and 2011 were as DT, in 2013 and 2014, the percentage was 43.6 and 45.7 %, respectively [1]. These intentions are subject to change based on the patient's clinical situation. In a 2013 study of 2816 patients in the INTERMACS database, Teuteberg et al. showed that nearly 15 % of patients initially implanted as DT were considered for transplantation at 1-year [16].

Bridge to candidacy

The final group, BTC, is another growing indication for LVAD placement. Studies have shown that LVAD placement in individuals who do not meet transplant criteria may allow them to become eligible for a transplant in the future. One study showed the utility in LVAD implantation as a way to allow for weight loss and eventual transplant in patients with a body mass index (BMI) greater than 30 [17]. Patients with secondary pulmonary hypertension that prohibits them from transplant have also been shown to benefit from LVAD placement to unload the left ventricle which allows them to eventually become transplant candidates [18].

Complications

With the increased prevalence and acceptance of LVAD as treatment for end stage heart failure, we are seeing the lifesaving and life-improving benefits of these devices. These, however, come at a cost. Despite numerous studies supporting improvement of quality of life in LVAD patients, several recent studies have addressed negative impacts on quality of life. A recent study of 15 patients showed that many patients' perceived expectations of what their quality of life would be post-implantation were unmet. Many felt that the LVAD implantation was the only choice available, outside of hospice and death [19]. Other studies have echoed this dissatisfaction with quality of life after surgery. A 2015 study by Merle et al. of 26 LVAD patients showed that many patients were dissatisfied with their sexual lives secondary to fears of disappointing their partners, risk of sudden cardiac arrest, and LVAD failure [20].

Post-implantation complications can be grouped into several major categories, including bleeding complications, thrombotic complications, infectious complications, and stroke. One recent study analyzed 126 patients who were implanted with continuous flow LVAD devices. It was shown that patients were readmitted on average 2.2 times during their 11-month median follow-up time. The most common causes for readmission were gastrointestinal bleeding (19 %), driveline infection (13 %), and stroke (8 %). The median time to readmission was 35 days with the median direct hospital cost of a single readmission being $7546 [21].

A separate large center study showed that 81.8 % of LVAD patients were readmitted for unplanned reasons. The main LVAD associated complications were infection (28.6 %), bleeding (27.1 %), neurologic events (11 %), anticoagulation issues (11 %), and pump and driveline events (9 %) [22]. These studies illustrate the importance of understanding the causes of readmissions. In an era of increasing costs and decreasing reimbursements to hospitals, understanding this can help reduce unplanned readmissions and thereby lower healthcare costs.

Bleeding

The primary site of bleeding complications in LVAD patients is from the gastrointestinal tract. The pathophysiology of gastrointestinal bleeding in LVAD patients is multifactorial. Patients with LVADs require anticoagulation, which predisposes them to bleeding complications. These patients also develop an acquired von Willebrand syndrome, especially if implanted with centrifugal or axial continuous flow devices. Meyer et al. showed that between 2003 and 2010, all 102 patients who underwent implantation with the axial continuous flow HeartMate II or the centrifugal continuous flow HeartWare Ventricular Assist Device developed an acquired von Willebrand syndrome. These patients all had a reduction in the high molecular weight multimers of the von Willebrand Factor (vWF), by 30 ± 14 % in HeartMate II patients and 34 ± 13 % in patients with a HeartWare Ventricular Assist Device [23].

Additional mechanisms that may contribute to bleeding include increased shear stress, increased intraluminal pressure, and a narrowed pulse pressure. Combined, these are thought to play a role in the development of angiodysplasia [24]. Strategies for lowering the incidence and severity of bleeding complications have been proposed, including lowering the international normalized ratio (INR) goals, reducing the use of antiplatelet agents,

altering pump speed to allow for pulsatile flow, and using somatostatin therapy.

Altering pump speeds on continuous flow devices to allow for pulsatile flow is one strategy that holds promise. A study by Wever-Pinzon et al. showed that reduced pulsatility in continuous flow devices led to an increase in bleeding complications. In that study, patients were stratified based on low, intermediate, or high pulsatile index. Those patients in the low pulsatility index had a hazards ratio of 4.06 ($p = 0.04$) when compared to the high pulsatility group [25].

Another strategy for reducing bleeding complications is the injection of somatostatin, an agent that promotes vasoconstriction in the splanchnic bed and suppresses gastric acid production. Loyaga-Rendon et al. investigated somatostatin as a potential medication for managing recurrent gastrointestinal bleeding in patients on continuous flow LVAD. Although this was a limited study with only a trend towards significance, it provides a potential novel approach to managing chronic gastrointestinal bleeds in LVAD patients with continuous flow devices. Further prospective studies are necessary to determine its potential as a treatment option in the LVAD patient [26].

Thrombotic complications

Pump thrombosis is a complication that carries significant morbidity and mortality. In 2011, there was an abrupt increase in pump thrombosis in the HeartMate II. Starling et al. showed that the prevalence of pump thrombosis 3 months after implantation rose from 2.2 to 8.4 %. It was noted that lactate dehydrogenase (LDH) more than doubled in the weeks prior to the diagnosis of pump thrombosis. This complication was managed by heart transplantation in 11 patients and pump replacement in 21 patients. These patients had a mortality rate similar to individuals without pump thrombosis. However, in the 40 patients who suffered from pump thrombosis and did not undergo a heart transplantation or pump replacement, mortality was elevated at 48.2 % in the 6 months after diagnosis of pump thrombosis [27]. This study suggested the utility of LDH as a marker for impending thrombosis, and demonstrated the importance of aggressive early intervention in patients with pump thrombosis.

Identifying those at risk for pump thrombosis has been an area of active research. Cowger et al. investigated the relevance of elevated serum hemolysis markers in patients supported with the LVAD. Two definitions of hemolysis were utilized in this study: LDH levels $\geq$600 IU/L or serum free hemoglobin level >40 mg/dL with signs and symptoms of hemolysis including jaundice and hemoglobinuria. In the 182 patients included, 37 % of patients met the LDH criteria for hemolysis and 18 % of patients met the serum free hemoglobin criteria for hemolysis. Survival was adversely affected by the presence of hemolysis, with 1-year event-free survival being 32 and 16 %, respectively [28]. Once again, the negative prognostic implication of pump thrombosis was highlighted by this study.

Infection

Studies have shown the incidence of driveline infections to be in the 17–30 % range [29]. There is no defined treatment algorithm for managing this complication. Antibiotic therapy combined with local wound care, driveline replacement, LVAD replacement, and heart transplantation have all been studied. Individual case reports describing omentoplasty have also been described in the literature as another strategy to combat driveline infections [30]. After driveline infection, mortality has been shown to be as high as 9.8 % at 6 months and 31 % at 12 months [31].

Such driveline infections are thought to be related to driveline dressing changes. To address this problem, standardized driveline care has been proposed. In a study by Cagliostro et al., an absolute risk reduction of 11 % was noted after the implementation of a standardized kit, including silver gauze and a standard anchoring device, for dressing changes.

Stroke

Strokes remain one of the most dreaded complications of LVAD support. In a retrospective study by Morgan et al., the incidence of stroke was found to be 12 % in the LVAD patient. Multivariate analysis showed that diabetes, aortic cross clamping with cardioplegic arrest, duration of LVAD support, and INR were independent predictors of stroke [32]. Another study by Harvey et al. demonstrated the incidence of strokes to be 17 % post-continuous flow LVAD implantation. During long-term follow up, mortality rates in patients who suffered from strokes were found to be 2.01 times that of stroke-free patients ($p = 0.004$).

The degree of anticoagulation necessary to prevent strokes continues to be investigated. In 2008, John et al. investigated 45 patients implanted with the HeartMate II who were treated with both aspirin and warfarin. Forty-one of these patients had a mean INR less than 2, and 21 had a mean INR less than 1.6 over the follow-up period. In their series, only one patient suffered from a stroke [33]. Although the incidence of strokes in that series was much lower than what has been reported in the literature, this small series did highlight that subtherapeutic INR does not predispose a patient on LVAD support to cerebrovascular accidents. Another recent study by Katz et al. showed that patients who were placed on a reduced anti-thrombotic

therapy regimen (only aspirin, only warfarin, or no agents at all) due to bleeding complications, had a 1 year freedom from ischemic stroke of 93.8 ± 2.5 % [34]. Future prospective studies are required to identify the ideal level of anticoagulation and antiplatelet therapy to minimize both the risk of bleeding and the incidence of thromboembolism in the LVAD patient.

LVAD in noncardiac surgery

As the number of LVAD implanted continues to increase, clinicians will face ever-growing number of LVAD patients with noncardiac surgical needs in both the acute setting and for elective purposes. In the acute setting, some of these patients will require non-cardiac surgical interventions for complications that occur around the time of implantation. In addition, as LVAD patient survival improves and the prevalence of these devices increases, many of these patients will present with elective surgical problems [7, 35]. These patients are often a challenge for physicians not familiar with these devices [36].

Studies have shown that non-cardiac surgeons are often needed in the care of patients with LVADs. With the continuous flow devices in use today, more patients with acute abdominal pathology after LVAD implantation are surviving to discharge and developing chronic surgical problems [37]. Current literature suggests that both acute and elective non-cardiac surgical procedures can be performed without increased mortality in this unique patient population [36, 38, 39]. These outcomes are likely secondary to improved perioperative management and the evolution from pulsatile flow devices to continuous flow devices.

Presently, multidisciplinary teams are utilized where the operating surgeon coordinates and ensures the availability of anesthesiologists, cardiologists, and cardiothoracic surgeons that are familiar in caring for these patients. Arterial cannula placement and position is often left to the anesthesiologist's discretion based on their experience and the complexity of the operation. They were more likely to be placed for more involved procedures such as colon resection, cholecystectomy, and arterial bypass. The surgical approach has tended towards an open technique because of the unknown consequences of establishing pneumoperitoneum in LVAD patients. Studies have shown it decreases venous return potentially leading to compromised right heart filling and hemodynamic instability [40, 41].

Importantly, these patients have higher morbidity most commonly secondary to postoperative bleeding complications. LVAD patients routinely receive anticoagulation and aspirin to prevent device thrombosis and thromboembolic complications. Prior studies have shown that as many as 36 % of patients have bleeding requiring transfusion [36] with some requiring reoperation. Unfortunately, there is no consensus on the perioperative management of anticoagulation and antiplatelet therapy in these patients. Some studies have shown that anticoagulation can be safely lowered or even discontinued prior to surgery while continuing antiplatelet therapy [36, 42].

Surgical considerations

The technical steps for implantation of the LVAD will not be discussed here. Rather, several salient points that need to be considered during LVAD implantation will be reviewed. The LVAD outflow conduit insertion angle plays an important role, as the angle has been shown to be associated with shear stress on the aortic wall in computer simulations. Flow through the LVAD occurs both in series and in parallel to the heart. If most of the blood flows through the LVAD and minimal blood flows through the aortic valve, the system is in series. If blood flows through both the LVAD and aortic valve, the system is in parallel [43]. In a simulated study by May-Newman et al., various angles of insertion of the aortic outflow conduit, from 30° to 90°, were investigated. Shear stress was noted to be the least with the lowest angle studied (30°). In addition, blood flow in series was associated with higher shear stress [44]. Although a simulation, this study highlighted an important area of surgical consideration, which requires further investigation to minimize shear stress on the aorta after LVAD implantation.

Another important aspect to consider during LVAD implantation is post-operative aortic insufficiency (AI), which occurs in as many as 50 % of patients at 18 months [45]. Significant AI can result in a decrease in cardiac output. The etiology for AI after LVAD implantation is multifactorial with changes in aortic blood flow dynamics, aortic wall shear stress, and increased diastolic pressures thought to be contributing [45]. De novo AI has been shown to be associated with worse survival after LVAD implantation [46]. Different therapies have been developed to treat this including placing a coaptation stitch or performing an aortic valve repair or replacement at the time of LVAD implantation or once the AI becomes clinically significant [47]. A novel therapy for treating AI in patients who are poor surgical candidates is via transcatheter aortic valve closure, using the Amplatzer cribriform device (AGA Medical, Plymouth, Minnesota). There are several small studies documenting resolution of AI with this device [47, 48]. However, long-term results are not yet available.

Conclusion

Despite significant advances in the field of heart failure surgery, many questions remain unanswered and challenges unaddressed. The exact timing of implantation is still not known. If patients are implanted with these devices when they have a high INTERMACS level, they run the risk of LVAD complications. Conversely, if they are implanted once their INTERMACS level becomes low, they run the risk of ongoing clinical deterioration and a progression of their heart failure.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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