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Heart Transplantation in the Era of the Left Ventricular Assist Devices

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Abstract

Orthotopic heart transplant is recognized as the gold standard for the treatment of end-stage heart disease. However, there is a perennial shortage of donor organs. Left ventricular assist devices (LVAD) represent a revolutionary tool for temporizing heart failure that is refractory to medical management until a suitable organ becomes available. This review highlights the LVAD as a tool for bridging to transplant. The history of the LVAD and its use in heart transplantation is described, as well as the current indications for use in the general heart transplant candidate as well as for selected subpopulations. It also highlights the major complications of LVAD use, advancements in the field, and selected current controversies related to the LVAD as bridge-to-transplant therapy.

Keywords: heart transplantation, ventricular assist devices, LVAD, mechanical circulatory support, bridge to transplant

1. Introduction

End-stage heart disease represents a worldwide epidemic, with over 6.6 million people affected in the United States alone. The prevalence of end-stage heart disease is increasing due to the aging population in the US and Europe, as well as improved management and therefore increased survival of other cardiac diseases. It is estimated that upwards of 600,000 new cases are diagnosed each year. Furthermore, the incidence of end-stage heart disease is estimated to increase at a rate of 25% by the year 2030 [1]. The disease is associated with significant morbidity and mortality; 50% of patients in this population will die within 4 years; in the subset of patients hospitalized with acute heart failure, 40% will be readmitted or die within 1 year. In

suitable candidates, heart transplantation is the gold standard therapy for this disease, providing the best opportunity for long-term survival and improved quality of life. However, organs that are suitable for transplantation are a scarce resource. This approach is limited for many years by availability of donor hearts as only approximately 2300 orthotopic heart transplants are performed each year; the pool of patients who are candidates for heart transplantation continues to increase, with no evidence that this trend will reverse any time soon. As a result, the management of end-stage heart failure with cardiac transplantation must increasingly rely on an armamentarium of medical and mechanical tools for bridging patients to transplant.

In particular, the introduction of the left ventricular assist devices (LVAD) has become instrumental in the management of the heart failure patient who is refractory to medical therapy; in their current iteration their use has been associated with a decrease in mortality and an improvement in the quality of life among suitable patients awaiting transplantation. In this review, we will discuss a brief history of the LVAD as it relates to heart transplantation, in particular the evolution of available devices, and the current indications for use. It bears highlighting that LVAD implantation is associated with significant device-related complications and these are described in detail. Lastly, we will discuss several topics of current controversy and areas of evolution within the field of mechanical device support of the heart transplant candidate.

2. History

2.1. Early LVAD devices

A timeline of advances in LVAD technology and in heart transplantation is included in **Figure 1**. In the early 1950s, open-heart surgery was associated with high mortality as a result of the frequent complication of postcardiotomy shock, a problem for which there was little answer at the time. In order to combat this problem, cardiopulmonary bypass as a means of bridging to recovery became a major experimental target. Initial clinical use of a cardiopulmonary bypass system for temporary circulatory support may be attributed to the work of Gibbon in 1953. This work into circulatory support would pave the way for future innovation in development of intracorporeal left ventricular assist devices.

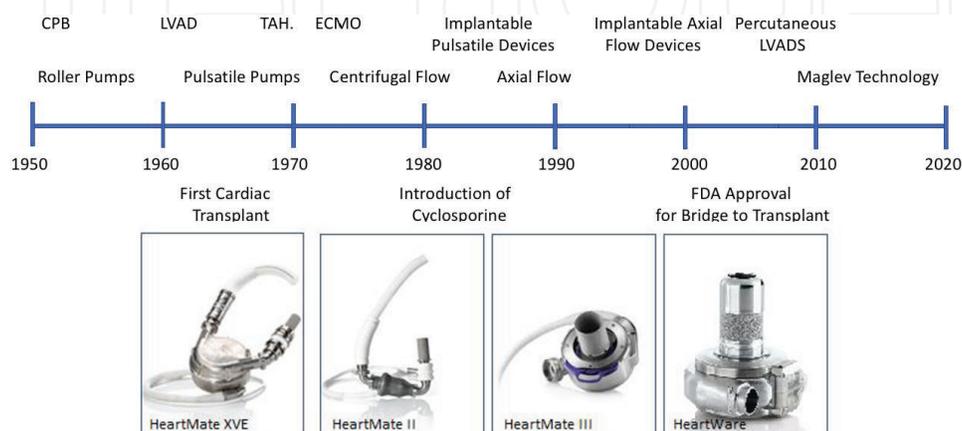


Figure 1. Timeline of advances in mechanical cardiac support and heart transplantation.

In 1964, the National Heart, Lung, and Blood Institute established the Artificial Heart Program with the express goal of developing therapies that would allow for the bridging of patients with postcardiotomy shock to recovery. Liotta and Crawford at the Texas Heart Institute are identified as performing the first LVAD implantation in 1963. The index patient was successfully weaned from the device from a cardiopulmonary standpoint; however, he ultimately succumbed to neurologic complications. Further modifications by Liotta and DeBakey led to first use of a paracorporeal LVAD for bridge to recovery after double valve replacement in a 37-year old female patient in 1966. After 10 days of support, the patient recovered and the LVAD was explanted without complication; the patient ultimately survived another 6 years prior to death due to a motor vehicle accident.

Concurrent with these initial models for mechanical circulatory support for bridge to recovery, the innovative concept of orthotopic heart transplant was also undergoing experimentation. This therapy was first demonstrated in animal models by Lower and Shumway in 1966, and subsequently the first human-to-human heart transplant performed by Barnard in 1967. With the advent of this new therapy, an alternative use for the LVAD besides bridge to recovery was identified. In 1969, Cooley implanted the first temporary total artificial heart into a patient as a bridge to cardiac donor availability for heart transplantation; his patient survived with total artificial heart support for over two and a half days prior to transplantation but died in the early postoperative period due to pneumonia. Mechanical complications associated with the total artificial heart led to a greater focus on the LVAD as preferred mechanical support after open heart surgery; in 1975 the first clinical trials of LVADs as temporary support after open-heart surgery were initiated, and in 1978, the first LVAD as bridge to transplant was used by Dr. Frazier.

Advances in technology and better understanding of cardiac flow dynamics have contributed to the evolution of the rapid VAD as a mechanical device. Early VADs made use of implanted pneumatic pump-driven volume displacement technology to drive forward flow. These first generation LVADs, mimic the function of the heart. The first generation of volume displacement pumps had multiple complex moving parts, with one-way valves and a flexible pumping chamber. Because of this, the devices were susceptible to breakdown and failure, among other complications.

The Pierce-Donachy VAD was a displacement device that was developed at Penn State University in 1970; it would serve as the prototype for Thoratec pulsatile-low VADs utilizing a pusher-plate system which could be implanted either paracorporeally (Thoratec pVAD) or intracorporeally (iVAD). This membrane-displacement technology was also used in the development of the 1978 Model 7 LVAD, later modified to the Heartmate implantable pneumatic and first used in clinical trials in 1986 [2]. A further evolution would lead to a variation known as the HeartMate VE (vented electric), and subsequently the HeartMate XVE (extended vented electric). By 1990, the FDA had given approval of LVAD as a bridge to heart transplant therapy, and a 1999 single-institution retrospective review of the use of the HeartMate XVE in bridge to transplant identified 75% of candidates as undergoing successful transplantation after a mean LVAD use of 106 days [3].

The success of LVAD as a bridge to led to clinical trials exploring the use of the LVAD as durable therapy. Perhaps the most well-known of the major clinical trial assessing the functionality of a LVADs for long-term use was the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial of 2001 [4]. Here, patients

with end-stage heart failure who were not candidates for heart transplantation underwent either LVAD implantation using the HeartMate VE or received maximal medical therapy; these two groups were compared for long-term complication and mortality outcomes. In this landmark study, survival among the VAD placement group was found to be 52% compared to 25% in the medical management group at 1 year, with a further 48% relative risk reduction in mortality over the 2-year study period. Additionally, the LVAD cohort was also highlighted as having improved quality of life.

However, we highlight the REMATCH study here primarily because it also identified a number of serious complications and limitations related to the use of LVAD support as durable therapy. The pulsatile flow HeartMate VE first-generation LVAD used in this study was found to have a rate of serious complications 2.35 times greater than in medical therapy group. Indeed, this group carried a relative risk of stroke 4.35 times that of the medical group. Intraperitoneal placement of the large LVAD device was associated with early satiety, and the extensive surgical dissection required for implantation was associated with a significant bleeding and infection risk. Over 21% of patients ultimately required device replacement. As a result, and primarily due to the long-term risk of infection and mechanical failure, the-year survival in the LVAD group was limited to 23% [4].

2.2. The modern era of LVAD

Continuous-flow devices making use of either an axial flow model (second-generation LVADs) or a centrifugal flow model (third-generation) were the next innovation in LVAD performance. The second generation has key mechanical advantages compared prior, including elimination of valves and chambers and the introduction of an internal rotor suspended by contact bearings. These alterations were theorized to lead to a decreased rate of complications, due in part to their fewer moving parts. However, analysis of outcomes has also shown that the direct contact between the bearings and blood in second generation LVADs serves as an area of thrombosis formation.

The second generation of LVADs were implemented into clinical practice in the late 1990's and demonstrated an acceptable safety profile for bridge to transplant when compared to existing pulsatile-flow devices despite the aforementioned higher-than-expected incidence of pump thrombosis. Approval of these later-generation LVAD's was primarily derived from three landmark clinical trials either directly comparing the pulsatile HeartMate XVE with the continuous flow HeartMate II [5], or with the use of historical controls to compare their outcomes [6, 7]. The earliest of these studies was a prospective multicenter trial of 133 patients with end-stage heart failure who underwent VAD therapy as a bridge to transplant [6]. Among these participants, a total of 100 (75%) survived to the principal aggregate outcome of either heart transplant, cardiac recovery, or survival to the end of the study; of note, of those patients on persistent mechanical support through the study, there was a 1-year survival of 67%. There was no control group in this study, but survival was compared favorably with a historical control of 53% 1-year survival among patients using the pulsatile-flow HeartMate XVE as a bridge to transplant. A follow-up study identified further improvements in survival among those using these devices, with that improvement being attributed to increased device experience [7]. Another major study evaluating the morbidity benefit of continuous over pulsatile-flow VADS identified an 1-year

endpoint of stroke, reoperation, or mortality-free VAD use of 46% in the continuous flow cohort compared to 11% in the pulsatile flow cohort [5]. Further multi-center reporting of adverse events between the two groups also demonstrated a statistically significant reduction in infection, neurologic dysfunction, renal and respiratory dysfunction, and need for device replacement resulting from mechanical failure among those patients with continuous-flow LVADs.

The third generation of LVADs relies on centrifugal continuous flow. The key technological advancement in the third generation LVAD is the implementation of noncontact bearings, which utilize magnetic levitation and decrease the incidence of thrombosis due to the lack of contact. In recent years, much of the data regarding the comparative effectiveness of LVADs stems from the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) organization, which serves as a multi-center registry data registry. From this, we identify >20,000 patients that have been implanted with an LVAD nationwide [8]. A 2011 multicenter trial by Strueber et al. [9] identified survival rates during support in patients bridged to transplant at being 84 and 79% at 1 and 2 years post-transplant, respectively. The ADVANCE multicenter clinical trial identified greater than 86% survival at 1 year among those patients using a third generation VAD, with improved functional capacity, quality of life, and a decreased complication profile. Under a continued access protocol of the latter study, the use of third generation VADs as a bridge to transplant continues to demonstrate a high preoperative survival rate despite a low rate of transplant. Although frequent hospitalizations due to device-related issues and other complications are noted, rates of adverse event rates are similar to or improved from those observed in historical bridge-to-transplant trials, despite longer exposure times due to longer survival and lower transplant rates.

Recent advances include the approval of the HeartMate III as a bridge to transplantation. This is an intrapericardial centrifugal-flow pump making use of pump rotor that is levitated and completely suspended by magnetic forces. This is designed to minimize shear stress, stasis, and platelet activation compared to earlier LVAD models. Its unique design allows for functioning in the absence of any friction or heat generation; furthermore, it holds the capacity for device-initiated pulsatility of flow. The burgeoning evidence from clinical trials have been encouraging; results of the Conformité Européene Mark study evaluating the HeartMate III demonstrated a mortality rate of 18% with low rates of embolic events and no cases of pump thrombosis [10] the concurrent MOMENTUM 3 trial further supports a significantly reduced rate of bleeding or thrombotic complications among HeartMate III users, with 69% achieving complication freedom compared to 55% of HeartMate II users at 1 year [11].

3. Indications for LVAD bridge-to-transplant

3.1. Current outcomes

While left ventricular assist devices are increasingly used in the role of bridge to transplant, conflicting data exists regarding outcomes compared to the patients who proceed directly to transplant. Outcomes are improving both as a result of greater use of the continuous flow device, and as a result of more sophisticated algorithms for dealing with LVAD complications. Currently, current survival to transplant and post-transplant outcomes appear to be

essentially equal between groups, especially in the absence of LVAD-related complications. Graft rejection also appears to be similar in patients who are bridged with LVADs compared to those without LVADs.

3.2. General indications

Currently, the European Society of Cardiology guidelines for treatment of end stage heart failure include the use of left ventricular assist devices as a Class IB recommendation in patient's refractory to medical therapy while waiting for a heart transplant. In addition, the American Heart Association has also issued a guidance document describing the use of mechanical circulatory support in the setting of bridge to transplant as a Class IB recommendation [12]. There is data to suggest that patients bridged to heart transplant with LVAD have higher post-transplant mortality compared to those without LVADs. However, much of this data stems from old risk calculations based on outcomes after implantation of pulsatile flow LVADs. As identified above, complication rates improved markedly as these devices have largely given way to continuous flow VADs with a more acceptable side-effect profile.

The current indications for heart transplantation include hemodynamically compromised patients with New York Heart Association class III-IV, as well as patients with stage D heart failure who are in refractory cardiogenic shock and dependent on intravenous inotropic support to maintain adequate organ perfusion. Further indications include severe angina that limits routine activity and is not amenable to revascularization, and recurrent symptomatic ventricular arrhythmias refractory to all other therapeutic modalities. Once listed, the current United Network for Organ Sharing (UNOS) organ-allocation system gives its highest transplant priority status (Status 1A) to those hospitalized patients who dependent on either inotropic medical therapy, or mechanical circulatory support such as LVAD support. UNOS designates an intermediate priority status (Status 1B) to those patients who are receiving inotropic or mechanical support at home. Patients who have infectious, bleeding, or thromboembolic complications while on VAD support may be advanced to 1A status until the time of transplantation; there is an additional discretionary option where patients with LVAD support may be advanced to Status 1A based on the decision of their transplant team and lasting for 1 month before downgrade back to 1B. Most other patients are given standard priority on the waitlist (Status 2).

In order to assist with optimal patient selection for placement of an LVAD, the INTERMACS registry has developed seven clinical profiles to identify patients. (1) Level 1 includes patients who are in critical cardiogenic shock requiring mechanical support. (2) Level 2 includes patients who are declining despite inotropic support. (3) Level 3 includes patients who are stable on inotropic support. (4) Level 4 includes patients with resting symptoms. (5) Level 5 includes patients who are intolerant to exertion. (6) Level 6 includes patients who are able to engage in limited exertion. (7) Level 7 includes patients who have advanced NYHA III heart failure. In the early years of LVAD implementation, the first two profiles (Level 1 and 2) comprised 60–80% of the LVAD candidates who were considered to be candidates for bridge to transplant. More recently, a shift has occurred in response to improved patient selection and risk stratification such that that the majority of patients implanted are now INTERMACS 3 and 4 profiles. Currently, 80% of patients who are being implanted with LVAD fall within INTERMACS Levels 2–4 [13].

A number of additional risk stratification and preoperative predictive factors have been developed to help select LVAD candidates and predict in-hospital mortality. For example, a multivariable risk score has been generated from preoperative factors of destination-therapy patients, and this highlights risk factors such as low albumin, low platelet count, abnormal liver function test or evidence of right ventricular dysfunction [14]. More recently, a risk score for LVAD patients was developed which showed that age and center experience were determinants of long-term survival [15]. While conventionally, LVAD placement is increasingly likely with increasing severity of INTERMACS profile, the ROADMAP clinical trial has shown that early implantation in lower INTERMACS profiles (4–7) outcomes are as favorable as earlier trials with improvements in quality of life [16]. Survival patterns from the UNOS database suggest that with the current LVAD technology, patients supported with LVAD support as a bridge to therapy demonstrate an improved survival while listed for heart transplantation, and the use of LVADs as a bridging strategy could potentially improve patient survival while waiting for transplantation, in turn allowing for better allocation of donor hearts [17]. Similarly, a 2016 study utilizing the United Network of Organ Sharing (UNOS) database showed those patients who underwent LVAD implantation prior to being listed for heart transplantation had improved survival compared to those who were medically managed; this survival benefit extended to those who were implanted with a LVAD while awaiting heart transplantation [18].

In general, the implementation of the VAD has led to a number of significant effects upon heart transplantation and the donor population. (1) There are now a significant number of patients with end stage heart failure who would otherwise have died while awaiting emergency transplantation, who are now surviving to have heart transplants performed under non-emergent circumstances. This has a profound effect on the pool of available donors as well as the acuity of transplant. (2) Cardiogenic shock with multi-organ dysfunction, previously an indication for emergency transplantation, is increasingly becoming a contraindication to transplantation due to the relatively poor likelihood of successful transplantation. With the option for temporization and recover without risking the high perioperative mortality and loss of scarce allografts associated with transplantation, the procedure is now being supplanted by mechanical support and then transplantation when the patients are recovered and shock is reversed. (3) The overpopulation of waitlists by patients with LVADs with acuity Status 1A who receive priority over ambulatory patients will make heart transplantation increasingly unlikely as a therapy for the treatment of ambulatory heart failure. (4) The LVAD as a bridge to transplant has allowed end stage heart failure to be treated in certain patients as an ambulatory disease in an outpatient fashion, rather than a disease requiring continued ICU management [6].

4. Selected subpopulations

In addition to the patient indications listed above, there are a number of unique subpopulations with a need for heart transplantation that would potentially benefit from LVAD as a bridging therapy. For one, mechanical circulatory support is an acceptable bridge to transplantation in pediatric patients suffering from heart failure due to structural defects. The feasibility of mechanical support as a bridge to transplantation in this subgroup has been demonstrated in single- and multi-institutional [19] case reports. For example, a small retrospective case series in 2017 of five patients who underwent VAD placement for congenital

heart defects with single ventricle physiology (mean age 12), had a 60% success rate in cardiac transplantation without long-standing end organ dysfunction [20]. The factors which play into the use of mechanical support in this population are the anatomy of the initial pathology and subsequent repairs, as well as pediatric patient size, which may predispose toward the use of smaller pumps over others. This relative safety of VAD support in pediatric patients has been confirmed in retrospective review of pediatric outcomes in the United Network for Organ Sharing database [21]. In general, it is agreed that pediatric patients should be analyzed on a case-by-case basis; although the rate of postoperative complications is high, the initiation of mechanical circulatory support can allow for resolution of end-organ dysfunction and allow for aggressive pre-transplant rehabilitation.

With improved management of congenital disease, more pediatric patients are surviving into adulthood prior to transplantation; this represents a growing patient subpopulation in whom LVAD support may confer a benefit. The American Heart Association opinion paper on LVAD in adult congenital disease highlights the challenges of supporting these patients; the typical history of many prior surgical and nonsurgical interventions, as well as the complex anatomy and physiology of these patients poses a challenge in LVAD implementation. Additionally, the use of the LVAD in this population is hampered by a lack of multi-institutional data regarding selection criteria and surgical technique. It is reinforced that the ultimate goal for these patients is cardiac transplant, an intervention after which most appropriately-selected adults with congenital heart disease will have survival rivaling that of recipients [22].

One unique group that greatly benefits from LVAD placement are those individuals who do not initially meet transplant criteria. In this group, entitled, "bridge to candidacy", the LVAD may provide an opportunity to alleviate relative contraindications to transplantation, such as active smoking, poor social support, undiagnosed tumors, obesity, and advanced lung disease, whereas they would otherwise automatically exclude patients from transplantation. Several months of LVAD support can be enough time for this group to rehabilitate and become eligible for a transplant in the future. For example, one study showed the utility of LVAD implantation in patients with a body mass index (BMI) greater than 30 during the process of losing weight loss in order to become a candidate for eventual transplant [23]. Recently, laparoscopic sleeve gastrectomy has been highlighted as an option for patients who want to have cardiac transplantation after LVAD implant [24].

Additionally, patients with secondary pulmonary hypertension that is prohibitive of transplant have been shown to benefit from LVAD placement. Very high pulmonary vascular resistances fall over the course of months as the left ventricle is unloaded, allowing for future transplant candidacy.

5. Complications

5.1. Readmission

Unfortunately, although LVADs is an effective adjunct in bridging candidates to transplant, they are associated with several challenging complications. Mortality and morbidity on the heart transplant waiting list has decreased owing to the advancement of VAD technology;

candidates supported with contemporary continuous-flow LVADs have favorable waiting list outcomes. However, outcomes worsen significantly once a serious LVAD-related complication occurs. In the current era, the annual rate of readmission for LVAD patients is 65% with most occurring in the first 6 months post-implant. The causes for readmission are multifactorial, are commonly due to gastrointestinal bleeding, cardiac causes, infections, and thrombosis (Figure 2).

Hasin et al. reported the findings of a single-institution analysis of readmissions due to complication after the implantation of ventricular assist devices over 2 years. The major primary causes in the first 6 months were bleeding (30%, primarily gastrointestinal), cardiac (30%, with

(extrapolated from INTERMACS data)

	Pulsatile Flow		Continuous Flow, Era 1		Continuous Flow, Era 2		Ratio Pulsatile: Era 1	Ratio Pulsatile: Era 2	Ratio Era 1 : Era 2
	2006 - 2012	17.2 8	2,6 43	10.5 7	2011-2013	7.79			
Bleeding	630	17.2 8	2,6 43	10.5 7	3,867	7.79	1.63	2.22	1.36
Right heart failure	90	2.47	497	1.99	1,268	2.55	1.24	0.97	0.78
Myocardial infarction	2	0.05	21	0.08	34	0.07	0.63	0.71	1.14
Cardiac arrhythmia	254	6.96	1,3 55	5.41	2,056	4.14	1.29	1.68	1.31
Pericardial drainage	64	1.75	185	0.74	271	0.55	2.36	3.18	1.35
Hypertension	118	3.24	197	0.79	367	0.74	4.1	4.38	1.07
Arterial non-CNS thrombosis	14	0.38	39	0.16	93	0.19	2.38	2	0.84
Venous thrombotic event	59	1.62	191	0.76	303	0.61	2.13	2.66	1.25
Hemolysis	23	0.63	143	0.53	588	1.18	1.19	0.53	0.45
Infection	832	22.8 1	2,4 92	9.96	3,933	7.92	2.29	2.88	1.26
Neurologic dysfunction	139	3.81	469	1.88	1,086	2.19	2.03	1.74	0.86
Renal dysfunction	108	2.96	364	1.46	756	1.52	2.03	1.95	0.96
Hepatic dysfunction	48	1.32	150	0.6	324	0.65	2.2	2.03	0.92
Respiratory failure	206	5.65	689	2.75	1,338	2.69	2.05	2.1	1.02
Wound dehiscence	18	0.49	54	0.22	83	0.17	2.23	2.88	1.29
Psychiatric episode	87	2.39	297	1.19	521	1.05	2.01	2.28	1.13
Total burden	281 1	77.0 7	9,7 86	39.1 3	16,88 8	34.0 2	1.97	2.27	1.15

Figure 2. Complications rates, pulsatile versus two eras of continuous flow (extrapolated from INTERMACS Annual reports: Kirklin et. al., 2011, 2012, 2013, and 2014).

50% from heart failure and 50% from arrhythmias), infections (22%), and thrombosis (14%). During the second 6 months, readmissions decrease but after 2 years, bleeding admissions were more frequent [25]. A similar retrospective single institution review of VAD complications demonstrated that progression of the underlying cardiac disease accounted for >50% of the rehospitalizations. For LVAD factors, device infection was overwhelmingly the reason for admission (57%) [26]. As unplanned hospitalizations are common after VAD implantation, and increase as one spends more time on mechanical support, avoiding complications requires a multidisciplinary team of specialists, close postoperative follow-up, a stable home support system, and a well-educated patient population. Here we highlight a number of common complications after LVAD placement in the patient bridging to heart transplantation.

The INTERMACS annual report describes complication rates.

5.2. Gastrointestinal bleeding

One of the most common causes of admission to the hospital post-implant is gastrointestinal bleeding. In the bridge-to-transplant population, large-scale studies have estimated its overall prevalence at 22% with an event rate of 0.3 per patient-year [27]. Similar studies of complications in the bridge-to-transplant population have highlighted major bleeding episodes as occurring in 25% of the cohort, with an estimated 70% due to GI sources. Continuous flow devices have been implicated, with reduced pulsatility having been found associated with a 4-fold risk of bleeding compared to those with high pulsatility. Although the mechanisms are not fully clear, it is hypothesized that axial flow devices may predispose to increased intraluminal vessel pressure, narrowed pulse pressure, and arteriovenous dilation leading to formation of angiodysplasia. Patients on LVAD have been identified as having higher mucosal vascularity as well as abnormal vascular architecture in the intestinal submucosa. Additional risk factors of angiodysplasia formation and bleeding including older age, female sex and ischemic etiology of heart failure [27]. Lesions are primarily located in the upper GI tract, although they can be located anywhere along the length of the entire GI tract.

In this setting, initial approaches to mitigate bleeding or prevent further episodes include the reduction or discontinuation of antiplatelet agents and anticoagulants and decreases in pump speed to allow for aortic valve opening and closure. In the setting of bleeding, treatment may involve injecting or clipping of the angiodysplastic area; surgical resection of a bowel segment is reserved for emergent or refractory cases. Identifying the bleeding site may pose a challenge; in the setting of failure to reveal a bleeding source after colonoscopy and esophagogastroduodenoscopy, capsule endoscopy has been found to provide little additional diagnostic yield [28]); balloon enteroscopy appears to be more effective. Somatostatin may be an effective analogue to vasoconstrict the splanchnic bed, suppress gastric acid production and overall reduce the frequency of bleeding, and may attenuate the risk of rebleeding when administered in the outpatient setting after a bleeding event [29]. In refractory cases, heart transplantation may be the only way to restore cardiovascular physiology and ameliorate the bleeding risk.

Of note, there is a significant body of research which shows that LVAD patients develop an acquired von Willebrand factor abnormality, which results in subsequent impaired anticoagulation [30]; a recent study demonstrated a reduction in the high molecular weight multimers

of the von Willebrand Factor by 30% in patients with a continuous flow LVAD [6]. In a study of patients with LVAD placement, Crow and colleagues identified that patients with bleeding had significant reductions in von Willebrand factor, ristocetin cofactor, and collagen-binding capacity compared to prior to implant, suggesting that bleeding complications after continuous flow LVAD are function of coagulopathy on a larger scale than just von Willebrand factor consumption [31].

5.3. Stroke

While the improved flow dynamics of newer-generation LVAD technology has reduced the relative risk of stroke events associated with LVAD usage, the rate per year remains quite high. The rate varies between 4 and 10% in most studies, with some modern series highlighting an incidence to be as high as 17%. Stroke after LVAD implantation has found to be associated with a mortality that is double those of patients who stroke-free [32].

The risk of stroke remains difficult to predict in this population. A number of factors, including the type of LVAD used, differences in anticoagulation practice, and the baseline risk of the patient population appear contributory. The degree of anticoagulation necessary to prevent strokes is not fully clear. Retrospective reviews of patients on both aspirin and warfarin have not found subtherapeutic INR to be associated with a stroke, nor has reduced anti platelet been highly correlated [13]. In contrast, other studies such as the ADVANCE trial have identified non-strict adherence to anticoagulation guidelines, including INR <2 and aspirin dose of ≤ 81 mg, as significant risk factors. Future prospective studies will be necessary to identify the correct levels of anticoagulation and antiplatelet therapy in the LVAD patient.

The results from initial bridge-to-transplant trials identified a difference in event rates between second- and third generation VADs [34]. This is supported by more recent INTERMACS annual report notes which note that there has been a decline in the rate of thromboembolic events in recent years compared to earlier [33]. The duration of LVAD usage is correlated with increasing rate of strokes and mortality; additional contributory factors included a higher rate of stroke among patients with mean arterial pressure > 90 mmHg, a history of previous strokes, malnutrition, concomitant infection and inflammation, severity of heart failure, and prior hematological conditions [34, 35]. A recent study has identified those patients with a CHA₂DS₂-VASc scores greater than or equal to three at the time of implant to be associated with an 18% risk of stroke compared to 4% in the population with a score less than 3 [36]. Ultimately, although the rate rates have decreased, stroke still represents a significant cause of morbidity in the VAD patient.

Current International Society for Heart and Lung Transplant guidelines recommend evaluation of pump parameters as well as CT angiography of the head and neck for diagnosis of stroke. In the setting of hemorrhagic stroke, discontinuation or reversal of anticoagulation is advised; interventional radiology or selective thrombolytic agents may be indicated in strokes without intracranial hemorrhage [37]. In a small case series of LVAD patients with acute ischemic stroke, thrombectomy with or without thrombolytics was not associated with intracerebral hemorrhage as a complication. Therapeutic anticoagulation on an LVAD should not contraindicate thrombectomy [38].

5.4. Infection

Infection represents a major limiting factor in the LVAD patient. Post-implantation device related infection is associated with significant morbidity, raising costs and length of stay. Modern clinical trials of LVAD efficacy for bridge-to-transplant therapy reported incidence of sepsis between 20 and 44% patients-year and driveline infection of 10.7–21%, although in some cases this may be as high as 30% [39]. Recent retrospective analysis identifies a 1- and 3-year freedom from LVAD infection to be 60 and 32%, respectively. High body mass index, diabetes, malnutrition, trauma to the exit site, surgical factors, and low lymphocyte count have all been found to increase the incidence of infection. Length of implantation of the device is also implicated with longer periods of implantation being associated with increasing risk [40]. While early infection tends to present as driveline infections, late infections tend to present as bacteremia. Predictors of death in those with sepsis include presence of right ventricular failure and non-Gram-positive cocci infection. Persistent bacteremia has been found to be a predictor for further events, including strokes.

Recent retrospective analysis of the UNOS database has identified increased mortality among LVAD patients with infection. One single-institution study reported a 1-year mortality of 30% in those with driveline infections (with 50% of the patients dying from sepsis) [40]. In contrast, other small non-matched studies of the bridge-to-transplant population do not identify a statistically significant reduction in the presence of controlled infection. A retrospective analysis reported that pre-transplant driveline infections predicted post-transplant infection at former sites and led to longer length of stay without affecting survival [41]. Another retrospective analysis demonstrated that the presence of infection during the period of LVAD support did not affect post-transplant survival when compared to patients transplanted without prior use of an LVAD. We may surmise that while infection does have a negative effect on outcomes and may reduce the likelihood of transplantation, especially when refractory to treatment, it appears that selected patients with controlled LVAD infection have comparable rates of transplantation as well as early and late post-transplant survival.

Even if infection does not directly lead to morbidity at the time of transplant, there may be long-term implications; for example; the surgery may be more challenging, and there may be increased allosensitization as Class I and II panel reactive antibodies levels are higher in the device infection group. Prevention and control are therefore of paramount importance. The proper maintenance of sterility at the driveline exit site is critical; small trials have identified an absolute risk reduction of 11% after the implementation of a standardized dressing kit with silver-impregnated gauze and a standard anchoring device [42]. When infection does manifest, there is no defined treatment algorithm; treatment is often multimodal and consists of antibiotic therapy combined with local wound care, driveline replacement, and device replacement. Omentoplasty has been reported as a surgical option.

Unfortunately, conservative treatment of the infected LVAD with antibiotics therapy and local incision and drainage is not associated with clearance on infection in the majority of cases, as this approach leaves behind infected hardware; infections on prosthetic surfaces are highly resistant to antibiotic treatment due to the reduced penetration of antibiotics into biofilms. In many cases, cardiac transplantation may represent the best option for long-term survival in patients who are bridge to transplant as it represents the only procedure where all infected hardware can be removed.

5.5. Pump thrombosis

Recent INTERMACS reports and retrospective analyses note that the incidence of pump thrombosis has actually increased in the modern era, with current yearly estimates at 2.2–8.4% [43]. In 2011, there was an abrupt increase in pump thrombosis associated with the use of the HeartMate II [44]. Pump thrombosis may initially be identified by the presence of hemolysis with an increasing lactate dehydrogenase (LDH) as well as other hemolysis markers such as serum free hemoglobin and bilirubin. While the greatest risk for pump thrombosis occurs in the first 3 months after LVAD implantation, that risk continues to increase after 6 months. The risk of thrombotic device malfunction, device exchange, and mortality is greater if hemolysis occurs within 6 months post-implantation [33].

Modifiable risk factors for thrombus formation have been identified to be poor control of hypertension, suboptimal anticoagulation with a mean INR less than 2, and a lack of full-strength aspirin therapy. In modern series the pump thrombosis is associated with higher rates of tamponade, ventricular arrhythmias, hemolysis, venous thromboembolism [34], stroke, worsening renal function and poor survival. This is a lethal condition in many cases if it is not appropriately treated. Patients with pump thrombosis have a 1-year survival rate of 69% compared to 85% for patients who do not experience this complication [34]. Identification of high-risk patients remains a priority, with serial X-rays to evaluate cannula position, regular monitoring of LDH, and potentially the use of echocardiographic ramp test to detect device malfunction [45]. Additionally, pump thrombosis may be diagnosed by laboratory signs of hemolysis, evaluation of LVAD waveforms, and acoustic analysis of the pump noise.

Aggressive early intervention in patients with pump thrombosis is necessary. In a subset of patients with evidence of worsening hemolysis, heparin or bivalirudin infusion may be attempted until LDH shows a decline to normal levels and symptoms such as impaired renal function resolve. A 50–75% success rate of thrombosis resolution has been reported with this method in modern series, although bleeding events (including fatal hemorrhagic strokes) were a significant side effect [34]. A recent meta-analysis of medical management of pump thrombosis demonstrated thrombolytic therapy to be the most effective therapy at 66% salvage, but with a 20% mortality rate—albeit this was only identified when thrombolytics were used in conjunction with other anticoagulants. The use of a combination of heparin and IIB/IIIA antagonists/direct thrombin inhibitors was associated with high rates of major bleeding (35%) and intracerebral hemorrhage (18%). Death was most commonly reported after thrombolytics (20%), and the rate of intracerebral hemorrhage was 17%, but only when thrombolytics were used in combination with IIB/IIIA antagonists/direct thrombin inhibitors [46].

Often, LVAD replacement or ideally heart transplantation are appropriate management options [44]; patients that undergo pump exchange for thrombosis have a 44% mortality rate at 2 years compared to 31% after primary implant. In those with pump thrombosis who do not undergo transplantation or pump replacement, mortality may be as high as 48% [44]. A recent study found a 90-day event-free survival of 89% after device exchange compared to 60.7% after thrombolytic therapy [47].

5.6. Right heart failure

Unfortunately, the use of LVAD can be associated with concomitant worsening of right heart failure. This is defined as the need of inotropic therapy in order to support right heart function or use of right sided ventricular assist device (RVAD). Overall, right heart failure in the LVAD bridge-to-transplant population can be as high as 10–30%. This condition is associated with significant morbidity and mortality, with 71% of patients surviving to 6 months in the presence of right heart failure compared to 89% without. Furthermore, a single-institution retrospective review has identified 5-year post-transplant survival to be dramatically worse in patients who developed late right heart failure during LVAD support compared with survival in patients who do not (26% survival with right heart failure versus 87% without). Significantly worse post-transplant outcomes and increased mortality among patients with a need for both LVAD and RVAD, especially in the setting of long term outcomes, has been confirmed in large-scale retrospective database studies [48].

Identifying patients at risk for right heart failure can significantly impact candidate selection for LVAD, and has implications regarding timely and appropriate treatment, resource utilization and quality of life. Multiple pre-operative risk scores have been developed to estimate the risk of right heart failure post-implantation. Identifiers include an elevated central venous pressure/pulmonary capillary wedge pressure ratio, increased creatinine blood urea nitrogen, INR, need for and number of preoperative vasopressors, transaminitis and hyperbilirubinaemia [49]. However, low sample sizes and a retrospective study design have typically limited the generalizability of these risk scores; recent validation studies of multiple right heart failure prediction models demonstrated a predictive value that was suboptimal at best [50].

5.7. Allosensitization

One issue with particular significance in the bridge-to-transplant population is that of increasing panel-reactive antibody (PRA) levels after placement of a left ventricular assist device. These devices have been shown to induce sensitization in that they are associated with the development of circulating anti-HLA antibodies with potential donor reactivity [51]. In the era of first generation LVAD support, reports indicated that these elevated levels of antibodies were linked to poorer outcomes, notably graft rejection. This association is less clear in modern studies; while some have indicated that this difference may not be significant, other studies have noted an increased level of antibody-mediated rejection in the setting of increased sensitization [52]. This remains an issue of considerable controversy.

6. Selected issues in bridge-to-transplant

6.1. Cost-effectiveness

With the changing landscape of healthcare in the United States, and a push for single-payer healthcare systems similar to that of other industrialized nations such as the United Kingdom and Canada, the clinical and cost effectiveness of bridging to transplant using LVAD bears some mention. The cost-effectiveness of LVAD support as compared to medical management with inotropic support in the bridge-to-transplant candidate has been evaluated in a number of studies.

The argument can be made against LVAD as a cost-effective treatment strategy for bridge-to-transplant. While LVAD implantation significantly increases survival compared with medical management, the survival of heart transplant candidates treated conventionally while on the waiting list has significantly improved in recent years. Therefore, the relative mortality benefit of LVAD over medical therapy has become less dramatic. Coupled with the high acquisition cost of the device, estimated in some studies to be upwards of \$150,000, LVAD does not necessarily provide good value for the money spent according to established thresholds of cost-effectiveness in many single-payer systems [53].

Initial analyses based on first-generation pulsatile VADs identified LVAD support at the time as being more expensive than medical management while appearing less clinically beneficial. However, with the widespread adaptation of second and third-generation LVAD support, more recent models of cost effectiveness have identified LVAD support as delivering greater clinical benefits but at a higher cost. It remains unclear whether LVADs are clearly cost-effective from a policy standpoint, but as changes in VAD technology allow for cheaper implementation, it is hoped that cost-effectiveness benefits will become more apparent [54].

6.2. Donor allocation in the modern LVAD era

The proportion of new candidates with VADS in the heart transplant waiting list grew from 3 to 22% from 2007 to 2013 [55]. With the initiation of third-generation LVADs with continuous flow, which have fewer complications, improved durability, and smaller size, a significant improvement in survival to transplant has been realized [2]. There has been an increasing use of VADs for heart transplant over the past decade as a result of these improvements [56], and this in turn has had direct implications for the allocation of these scarce organs.

First, there is the issue of transplantation of marginal heart in the LVAD-supported candidate. The shortage of donor hearts relative to has led to the increasing use of marginal donor hearts for cardiac transplantation in an effort to increase the donor pool, as well as the increased use of left ventricular assist devices as bridge-to-transplant. Initially, propensity-matched studies of outcomes LVAD versus marginal heart transplantation have favored transplantation for better outcomes [57]. However, with the increasing validation of LVAD for extended use, the best treatment option and long-term survival outcomes remain unclear. Comparison of these populations within the UNOS database demonstrate no significant difference between waiting list survival for patients with LVAD support as a bridge-to-transplant versus survival of recipients with marginal donor hearts. Currently, this decision remains within the discretion of the transplant team and the patient, but evidence at this time suggests that there could be clinical benefits to using LVAD support in order to allow time for better allocation of optimal donor hearts as opposed to transplantation with a marginal donor heart [58].

The selectivity afforded to LVAD transplant candidates may be exposing inefficiency within the organ allocation system, which does not appear to take into account the increased survival gains made by patients bridging to transplant with LVAD. A recent study calculated a hypothetical Cardiac Allocation Score based on a number of heart failure severity stratification systems in VAD and non-VAD patients awaiting transplantation. In non-VAD patients, the majority of heart failure severity stratification scores provided accurate risk stratification; however, none of the tested scores could predict mortality among VAD-supported patients. This is in contrast to earlier evaluations that suggested that at least the INTERMACS score can

provide an accurate representation of waiting list mortality in patients receiving continuous-flow LVAD support. Because the cause of death of LVAD patients is usually unrelated to heart failure; heart failure score models may either under- or overestimate the risk of mortality in these patients. This, in turn, leads to inaccurate organ allocation, and may come at the cost of detrimentally affecting the transplant chances of those patients without LVADs.

The current organ procurement protocol for patients with an LVAD is based on outcome studies performed in the era in which pulsatile flow devices were used. Based on these outcomes, patients implanted with an LVAD awaiting orthotopic heart transplant are status 1B on the waiting list, with the option of a 30-day upgrade to status 1A at the discretion of the transplant center. In addition, patients with an LVAD can be upgraded to status 1A in the event of a device complication or malfunction. However, it is not clear that patients on LVAD support necessarily merit this degree of prioritization. For example, a retrospective review of UNOS data revealed that despite being older, less favorable recipients, modern LVAD patients spend more time in Status 1A and have greater waitlist survival, which allows LVAD patients to receive preferred donor hearts and could allow for better post-transplant survival [59]. In particular, a 30-day upgrade of relatively stable LVAD patients to the highest priority level (compared with other critically ill patients at Status 1A) may allow for competition between patients with different risks of death. With this in mind, there is a concern that LVAD is perceived as a not a bridge to transplant, but a necessary gateway to transplant that is at risk of being over utilized. Furthermore, simulations have failed to demonstrate improvements in waiting list survival or post-transplant mortality with the Status 1A time allotment [60].

There is still an argument to be made, however, that the risk of VAD complications, including thrombosis, infection and sensitization that compromise post-transplant outcomes and abrogate any potential benefit that may have been realized by having the VAD; furthermore, the aforementioned allocation simulations do not demonstrate increased waiting list mortality for other candidates who did not have VADs in lieu of other mechanical support. What is perhaps the most likely reason for all of these findings is that the allocation system is already saturated with candidates at Status 1A and adding more Status 1A time for VAD patients would do little to solve the problem—instead, a more efficient method would involve risk stratification prioritization of those VAD patients at higher risk for mortality in contrast to those stable VAD patients who are at relatively lower risk.

6.3. The future of LVAD support

Studies are ongoing to develop strategies to make smaller and more durable devices, to diminish thrombosis, and to minimize surgical complication rates. A miniaturized LVAD could reduce the extent of surgical intervention, and would potentially extend the use of the LVAD for support of earlier stages of heart failure. Revolutionary future devices currently under trial will not require sternotomy or cardiopulmonary bypass; instead they will be placed through a minithoracotomy incision into a subclavicular subcutaneous pocket similar to a pacemaker. Future technology will ideally allow for completely implantable devices, as well as for devices that can provide variable flow in the LVAD, with automated modulation of flow in the setting of increased demand such as during exercise.

A return of pulsatile LVAD is also to be expected. There is recent research to suggest that pulse pressure causes vascular responses such as the endothelial production of nitric oxide and vasodilation

and improved circulation in the capillary beds of end organs. Comparison of older pulsatile flow models suggest a significant hemodynamic to pulsatile flow, with increases in total cardiac output, lower pulmonary pressures, improved coronary flow, and superior left sided unloading compared to continuous flow LVADs. Based on these observations, there is now an interest in developing algorithms to generate a pulse pressure in an attempt to reduce adverse events associated with continuous flow LVADs. The HeartMate III represents an exciting disruptive technology in this regard because it holds the capacity to generate device-induced pulsatility of blood flows.

7. Conclusion

Left ventricular assist devices represent a useful adjunct in the setting of bridge to orthotopic heart transplant. There are still a number of unanswered questions regarding their efficient use; most of these questions have come about secondary to the incredible speed innovation surrounding these tools as well as their rapid and widespread adoption. There is a critical need for continued high quality studies such as large, well conducted, randomized controlled trials, particularly addressing the issues of justice in donor organ allocation, patient selection, complication avoidance, and needs of high-risk patient groups. Although this technology, and the field of heart transplantation in general, is associated with multiple remaining challenges and complications remain, it is clear that the LVAD is a powerful tool for augmenting the failing heart and stabilizing the transplant candidate while a donor organ becomes available. It represents an important facet in the holistic care of this challenging patient population.

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