Updates on management of advanced heart failure

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Abstract

Advanced heart failure defines a subset of patients with heart failure with reduced ejection fraction having severe symptoms despite usual recommended therapy. These patients require frequent hospitalizations and specialized interventions, such as cardiac transplantation, implantation of mechanical circulatory support devices, continuous intravenous inotropic therapy to palliate symptoms, or continued terminal care. This review summarizes the management of advanced heart failure with updates in medical therapy and recent advances in surgical therapy, particularly left ventricular assist device therapy.

Keywords: Advanced heart failure, left ventricular assist devices

Introduction

Heart failure (HF) is defined as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood"[1]. Heart failure has been classified into two groups according to left ventricular ejection fraction (EF): HF with preserved EF (HF*p*EF) and HF with reduced EF (HF*r*EF).[1] Approximately 50% of the HF population has HFrEF, and 10% of these patients have advanced HF, which will be the focus of this review which summarizes the management of advanced heart failure with updates in medical therapy and recent advances in surgical therapy, particularly left ventricular assist device (LVADs) therapy.

Definition of advanced HF

Advanced HF defines a subset of chronic HFrEF patients with severe symptoms that limit daily life (functional class III or IV of New York Heart Association [NYHA]) despite maximum guideline-directed medical therapy. According to the latest classification proposed by the ACC/AHA[1], this corresponds to Stage D HF, which refers to refractory HF requiring frequent hospitalizations and specialized interventions, such as cardiac transplantation, implantation of mechanical circulatory support devices (MCSDs), continuous intravenous inotropic therapy to palliate symptoms, or continued terminal care. A suggested algorithm for advanced heart failure care is shown in Figure 1.

Advanced HF patients have high mortality rates with frequent and prolonged hospitalizations. Advanced HF seems more 'malignant' and has worse survival than many common types of cancer.[2]

There are clinical clues that may help clinicians identify patients who are progressing toward advanced HF. These symptoms include progressive debilitating dyspnea or fatigue with decreasing level of activity (NYHA Class IIIB or IV), recurrent hospitalizations for volume overload, progressive declines in renal function, weight loss without other cause, intolerance to ACE inhibitors due to hypotension and/or worsening renal function, intolerance to beta blockers due to worsening HF or hypotension, and a recent

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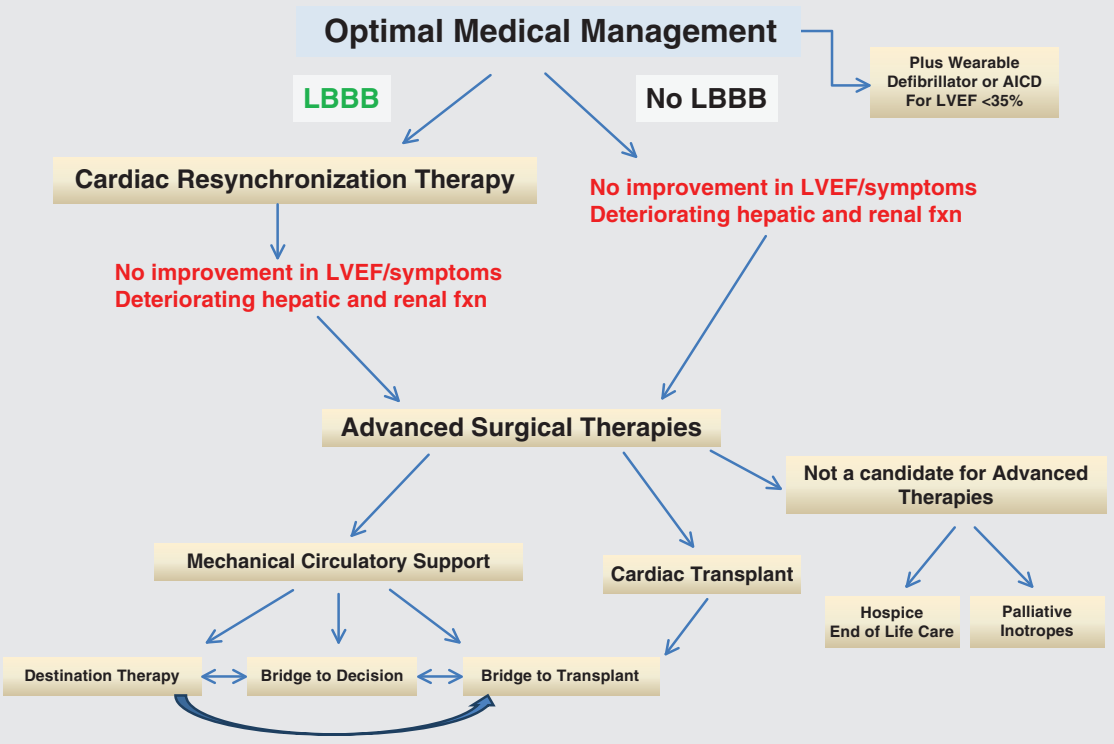

Figure 1.

need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d and/or use of supplemental metolazone therapy.[1]

Recent updates in medical therapy

The major step in medical management of HFrEF was the discovery of neurohormonal antagonists. Both survival and quality of life have improved with the use of β-adrenoreceptor blockers and renin-angiotensin-aldosterone system antagonists in patients with HFrEF.[1] There have been several recent advances in the medical management of HFrEF. The Food and Drug Administration (FDA) has approved two new medications for the treatment of HFrEF: angiotensin receptor-neprilysin inhibitor (ARNI) and ivabradine.

Valsartan/sacubitril is the first FDA approved ARNI. In PARADIGM-HF (the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial), Valsartan/sacubitril was found to be superior over enalapril in reducing the composite endpoint of cardiovascular death or HF hospitalization in symptomatic patients with HF*r*EF.[3] According to recent guidelines, in patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (Class I recommendation, Level B-R).[4] Simultaneous use of valsartan/sacubitril and an ACE inhibitor should be avoided, and a washout period is recommended during the transitioning from an ACE inhibitor to this combination. Angiotensin receptor-neprilysin inhibitors should not be used in patients with a previous history of angioedema with ACE inhibitor or ARB and in patients receiving aliskiren for diabetes.

Ivabradine reduces the heart rate via selective inhibition of the *If* current in the sinoatrial node, and it reduces hospital admissions for worsening HF.[5] According to latest ACC/AHA guidelines on New

Pharmacological Therapy for Heart Failure 2016, ivabradine may help reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving guideline directed evaluation and management, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 beats per minute or greater at rest (Class of recommendation II, Level of evidence B-R).[4]

Surgical therapies in advanced HFrEF

Major advances in the management of HFrEF have been made with surgical approaches over the last decade.

Cardiac transplantation

Cardiac transplantation is considered the gold standard for the treatment of advanced HFrEF.[1] Survival rates and functional status following cardiac transplantation are excellent, particularly if it is compared with the natural course of end-stage HF. Advances in immunosuppressive therapy have vastly improved the long-term survival and quality of life of transplant recipients. The most recent data from the registry of the International Society of Heart and Lung Transplantation show one year survival of 84.5% and a five year survival of 72.5%.[6] The major limitation in the growth of cardiac transplantation has been persistent donor organ shortage. Despite the increasing number of patients with advanced HF, the donor supply has remained flat and much lower than demand. Thus, cardiac transplantation remains an option only for a limited number of patients.

Mechanical circulatory support devices

As a consequence of a persistent donor organ shortage and an increasing advanced HF population, there has been more interest in alternative strategies, in particular MCSDs. This review focuses on long term implantable MCSDs. The primary focus in this field was to provide ventricular support and extend life. A number of pulsatile and continuous flow devices have evolved over the decades with increasing levels of sophistication.

A) Pulsatile devices

Biventricular support with total artificial heart

The first total artificial heart (TAH) was implanted in 1969. Its use has been limited due to several issues, including the risk of sudden device interruption and death, an excessive complication rate, limited durability, and elimination of the possibility of native cardiac recovery. Currently TAH is approved only for use in end-stage biventricular heart failure as a bridge to heart transplantation.

Pulsatile left ventricular assist devices

The start of the modern LVAD era began with the introduction of the HeartMate XVE (Thoratec Inc.; Pleasanton, Calif, US) in 1998. The first generation implantable LVADs, such as HeartMate XVE, were pulsatile, volume displacement pumps using a diaphragm and unidirectional valves to replicate the pulsatile cardiac cycle. The FDA approved the use of HeartMate XVE in patients with advanced HF in 2002 after the results of Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial.[7] In the REMATCH trial, the use of HeartMate XVE resulted in a clinically meaningful survival benefit and an improved quality of life compared to medical treatment in patients with advanced HF who were ineligible for cardiac transplantation.[7] However, the survival in the LVAD group after 2 years was 28%, compared to only 8% in the medically treated patients. This trial also showed the substantial risk of mechanical failure and device-related complications inherent in the first-generation pulsatile devices.[7] Despite the survival benefit, first generation LVADs were not used widely due to their numerous limitations, such as their large size requiring excessive surgical dissection for device implantation, large volume requirement, presence of a large diameter driveline, noisy pump operation, and limited durability.

During the last decade, significant technological advances in pump design resulted in continuous flow-left ventricular assist devices (CF-LVADs), which are

smaller and more durable. These devices provide better patient outcomes with improved survival and less major adverse events compared to pulsatile LVADs.[8,9]

B) Continuous flow-left ventricular assist devices

The discovery of CF-LVADs is a technical milestone in LVAD technology. The success of CF-LVADs has led to the growing acceptance of these devices as a viable therapeutic option for advanced heart failure patients who are not responsive to current pharmacological and electrophysiological therapy.

Continuous flow (CF) rotary pumps consist of blood inlet and outlet ports and a single rotating element that imparts energy to the blood to increase arterial blood flow and pressure. There are a number of benefits of CF-LVADs over pulsatile LVAD technology.[10] CF rotary blood pump designs eliminate the need for blood pumping chamber and volume compensation, which significantly reduce LVAD size and weight. Because of their simpler design (no mechanical bearings, no mechanical or biological valves), these devices have longer durability. Continuous-flow LVADs are also silent in operation and create minimal vibration.[10,11] (Figure 2)

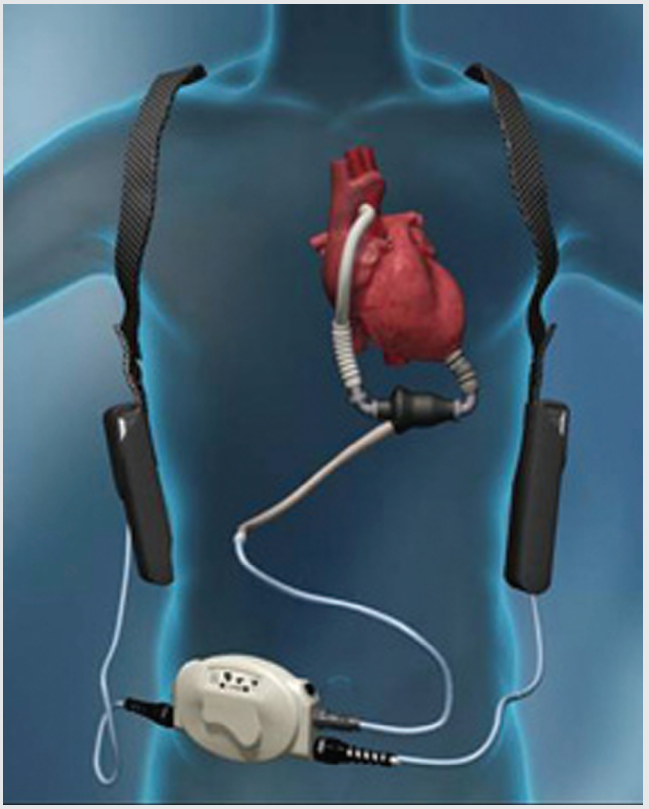

Figure 2. Schematic representation of HeartMate II continuous-flow left ventricular assist device. The pump is connected with a driveline to an external system controller and batteries worn by the patient. From TTUHSC Library OPENi (beta) at https://openi.nlm.nih.gov/. Accessed 6-10-2017.[27]

There are two types of CF pump: axial-flow (e.g., HeartMate II) and centrifugal-flow (e.g., HeartWare) pumps. The primary difference between them lies in the design of their rotating elements. The rotating elements of centrifugal CF pumps operate as a spinning disk with blades that can be described as a "thrower," meaning that the fluid is captured and thrown tangentially off the blade tips. In contrast, axial CF pump rotating elements act like a propeller in a pipe and can be described as a "pusher."[12] In general, the pump blood flow is directly proportional to rotor speed and inversely proportional to the pressure differential between the left ventricle and aorta in CF-LVADs. However, given their different inherent mechanics, the axial and centrifugal pumps differ in their hydrodynamic performances. The most important feature of centrifugal pump differing from the axial flow pump is to generate larger changes in flow with the same change in pressure. As compared to axial flow pumps, the centrifugal pumps have: 1) a more pulsatile waveform; 2) a more accurate flow estimation; and 3) a lower risk of suction events in a setting of dehydration, arrhythmias, or right ventricular failure; but also 4) more dependency of device flow on loading conditions.[13,14]

Continued concerns about device complications, particularly pump thrombosis requiring device replacement have resulted in an evolution of new third-generation CF-LVADs. Third-generation centrifugal pumps are contact free, with no mechanical bearings and an impeller suspended using magnetic and/or hydrodynamic systems. Recently, the trials comparing third-generation CF-LVADs with

HeartMate II in measures of survival free from disabling stroke or need for device replacement have been published.[15,16] In the MOMENTUM 3 trial, HeartMate III, which is a magnetically levitated centrifugal continuous-flow pump engineered to avert thrombosis, was compared with HeartMate II.[15] In the ENDURANCE trial, the HeartMate II was compared with the HeartWare LVAD, which is a smaller intrapericardial centrifugal-flow device.[16] In both trials, stroke risk was not reduced with new third generation CF-LVADs as compared to HeartMate II; the overall stroke risk was higher with the HeartWare pump and was not significantly lower with the HeartMate III.[15,16] However, suspected or confirmed pump thrombosis occurred in more patients assigned to the HeartMate II, and more patients in the HeartMate II groups underwent reoperation to replace the pump in both trials. There was no benefit with either of the third generation CF-LVADs in reducing the risk of bleeding or sepsis. The risk of right heart failure was not lower with the HeartMate III than with the HeartMate II and was actually higher with the HeartWare device.[15,16] Ongoing research is needed to develop newer and improved devices to decrease adverse events related to device therapy.

Clinical use of LVADs

LVADs have been traditionally used as bridges to transplantation (BTT) in transplant candidates who are developing end-organ damage despite maximal medical therapy including inotropic support or who are inotrope-dependent with an anticipated long waitlist time (i.e., large body size and/or blood type O recipients).[13]

Destination therapy (DT) is considered for patients with advanced HF who are ineligible for cardiac transplantation and for whom an LVAD is the only effective treatment option. The trend using LVADs as destination therapy (DT) has begun to evolve since LVADs became more durable, portable, and user friendly. Other factors that contribute to increasing number of LVADs implantations as DT are donor organ shortage and an increasing number of elderly patients with advanced HF who are ineligible for transplantation.

The intention of treatment with BTT versus DT is a dynamic process in most cases as the patient's characteristics may change over time. Some patients assigned to DT can become a transplant candidate during the LVAD support since previous relative contraindications may have resolved or improved after a period of LVAD support (for example, renal dysfunction, pulmonary hypertension, or reduction in body mass index). Additionally, changes in patients' nutritional status, functional status, end-organ function, and compliance after LVAD can affect transplant candidacy. Therefore, many patients may be categorized as "bridge to decision", and the implantation strategy and indication (BTT *vs.* DT) should be continually reevaluated.[17]

LVAD outcomes for destination therapy

The survival benefit of LVAD implantation was first demonstrated in the REMATCH trial in 2001.[7] Subsequent studies using CF-LVADs demonstrated improved survival rates.[8,18-20] Besides improvements in LVAD technology, increased medical expertise in LVADs management has also improved survival rates in post-approval studies over the years.[21] The major clinical trials assessing survival with long-term LVADs are summarized in Table 1.

According to the recent Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data, 1-year survival of the 3,931 patients who underwent LVAD implantation as DT from June 2006 to 2014 was approximately 76%.[22]

Patient selection and timing for destination LVADs

The accepted criteria for LVAD implantation for DT are based on the patient inclusion criteria from the REMATCH trial[7,13] and are as follows:

- Patients with NYHA functional class IV symptoms who have failed to respond to optimal medical management, including angiotensin-converting enzyme inhibitors or beta-blockers, for at least 45 of the past 60 days, or have been intra-aortic

Table 1. Clinical trials with LVADs

Study, Year, Reference #	Indication	n	Device tested	Design	Outcomes
REMATCH, 2001 (7)	DT	129	HeartMate XVE	1:1 HeartMate XVE vs. medical therapy	1- and 2-yr HeartMate XVE survival of 52% and 23% vs. 25% and 8% on medical therapy
HeartMate II, 2009 (8)	DT	192	HeartMate II	Prospective randomized 2:1 HeartMate II vs. HeartMate XVE	1- and 2-yr HeartMate II survival of 68% and 58% vs. 55% and 24% with HeartMate XVE
HeartMate II post-approval, 2014(21)	DT	247	HeartMate II	Prospective nonrandomized	1- and 2-yr survival of 74% and 61%
HeartMate II, 2007 (18)	BTT	133	HeartMate II	Prospective nonrandomized	75% survival to transplant, recovery, or ongoing support although remaining eligible for transplant at 6 months
HeartMate II post-approval, 2011 (20)	BTT	169	HeartMate II	Prospective nonrandomized	90% survival to transplant, recovery, or ongoing support at 6 months
ADVANCE, 2012 (19)	BTT	137	HVAD	Prospective nonrandomized HVAD compared with 499 patients who had FDA-approved LVADs in INTERMACS	90.7% survival to transplant, recovery, or ongoing support on the original device vs. 90.1% in control group at 6 months
MOMENTUM 3, 2017 (15)	BTT or DT	294	HeartMate III	Prospective randomized 1:1 HeartMate III vs HeartMate II	86.2% survival from either disabling stroke or reoperation for device malfunction in HeartMate III group vs 76.8% in HeartMate II group at 6 months
ENDURANCE, 2017 (16)	DT	446	HeartWare	Prospective randomized 2:1 HeartWare vs HeartMate II	59.1% survival free from disabling stroke or device removal for malfunction or failure in HeartWare group vs 55.4% in HeartMate II group at 2 years

ADVANCE, Evaluation of HeartWare ventricular Assist Device for the Treatment of Advanced Heart Failure; BTT, bridge to transplant; DT, destination therapy; ENDURANCE, FDA, Food and Drug Administration; HVAD, HeartWare Ventricular Assist Device; INTERMACS, Interagency Registry for Mechanical Assisted Circulatory Support; n, number of patients, MOMENTUM 3, Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3; REMATCH, Randomized Evaluation of Mechanical Assistance for Treatment of Heart Failure.

balloon pump-dependent for 7 days or IV inotrope- dependent for 14 days;

- Left ventricular ejection fraction <25%; and
- Functional limitation with a peak oxygen consumption <14 ml/kg/min, unless on an intra-aortic balloon pump, IV inotropes, or physically unable to perform the exercise test.

According to the 2013 International Society of Heart Lung Transplant guidelines for the use of MCSDs23, reversible causes of heart failure should be addressed prior to consideration for long term MCSDs, and all patients referred for MCSDs should have their transplant candidacy assessed prior to implantation. The patients selected for DT generally have contraindications for heart transplantation, such as age greater than 70 years, malignancy within 5 years, elevated pulmonary vascular resistance, and end-organ damage.[9]

Appropriate selection of the candidates and the timing of LVAD implantation are critical for improved outcomes.[10] Data from Interagency Registry for Mechanically Assisted Circulatory Support, a North American registry that has collected clinical data since 2006m in patients receiving MCSDs therapy to treat advanced HF, provide valuable information on risk factors and outcomes for patients undergoing MCSDs implantation. The INTERMACS scale assigns advanced HF patients to seven levels according to their hemodynamic profiles and functional capacities. INTERMACS level 1 is used to describe the most critically ill patients with cardiogenic shock, level 2 for patients progressively declining despite inotropic support, level 3 for patients who are stable but inotrope dependent, level 4 for patients who have resting symptoms on oral therapy, level 5 for patients who have exertion intolerance (“housebound”), level 6 for patients who have limited exertion tolerance (“walking wounded”), and level 7 for patients who have NYHA class III functional capacity.

The INTERMACS scale is particularly helpful to identify risks associated with the timing of an LVAD implantation.[10] It is well documented that most patients who are stable on inotropes in INTERMACS level 3 would likely benefit from LVAD therapy.[10,22] However, patients in INTERMACS level 1, cardiogenic shock, have the lowest survival after LVAD implantation.[10,22] These data indicate that patients with cardiogenic shock may need immediate stabilization with extracorporeal membrane oxygenation or short-term single or biventricular assist devices to optimize their condition before permanent LVAD implantation.[10] According to recent INTERMACS report, 15% of patients were in level 1, 65 % in level 2 or 3, and 20% in level 4-7 at the time of an LVAD implantation.[22]

There has been a trend regarding earlier use of an LVAD before major complications of heart failure develop. This approach is supported by the INTERMACS data showing better outcomes in patients with high INTERMACS levels. However, the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management (ROADMAP) study, a prospective, multicenter study investigating the benefits of HeartMate II LVAD implantation in less-advanced HF patients with INTERMACS levels 4-7, showed higher incidence of adverse events, including bleeding, stroke, hospitalization, pump thrombosis, and driveline infection, in the LVAD arm versus the medical arm.[24] In the same study, the mortality rate was similar in both LVAD and medical arms, despite improved functional capacity and quality of life found in the LVAD arm at 1 year.[24] Due to these results, the decision has to be made between LVAD implantation at a later time at a lower INTERMACS level with the risk of rapidly worsening heart failure or earlier LVAD implantation at a higher INTERMACS level with the benefit of improved functional capacity and quality of life but with the associated risk of adverse events related to LVAD therapy.

Exclusion criteria for destination LVAD therapy include intolerance to anticoagulation, as life-long warfarin therapy is required to prevent thrombotic events related with LVAD therapy, severe right ventricular failure, inadequate social support, and noncompliance with care.[10,13] The need for adequate family/caregiver support is imperative for long-term

success of LVAD implantation. Patients with multiple or severe non-cardiac conditions that significantly limit quality or duration of life may not be suitable candidates for LVAD implantation.

The optimization of the comorbid conditions before LVAD implantation is very important to minimize the incidence and severity of post-operative adverse events and to improve survival. The most important steps involve improving nutritional status, managing volume status to minimize right ventricular workload and hepatic congestion, optimizing coagulation, renal, hepatic, pulmonary, and neurologic function, and treating any infection.[10]

Complications of LVADs therapy

Despite improved survival rates, long-term complications of LVAD therapy are frequent. The most common complications are device-related problems, such as coagulation disorders, gastrointestinal bleeding, device related infection, pump thrombosis or cerebrovascular accidents, and right heart failure (RHF).

Technical advances in LVAD design and increased medical expertise with LVAD therapy have resulted in a lower incidence of overall adverse events related with LVAD therapy.[22] However, these complications still contribute to the morbidity and mortality of these patients. The post-approval HeartMate II DT study showed a high probability of device related adverse events at 2 years: driveline infections (19%), sepsis (19%), strokes (11.7%), thrombus formation (3.6%), bleeding (54%), and mechanical failures requiring replacement (4%).[21] Additionally, acquired von Willebrand's disease develops in all patients with long-term CF-LVADs due to the loss of high-molecular-weight von Willebrand factor multimers.[13] Aortic insufficiency is also a common problem with the incidence of more than 30 % at 3 years.[25]

Gastrointestinal bleeding is one of the major adverse events after CF-LVAD implantation. The main causes of the GI bleeding in these patients include the use of anticoagulant medications, the formation of arteriovenous malformations, loss of von Willebrand factor activity, and mucosal ischemia.[26]

Pump thrombosis has been one of the common indications for pump exchange. Given the decrease in survival after each subsequent pump exchange, the prevention of pump thrombosis and pump malfunction are critical.[10] An increase in pump thrombosis for the HeartMate II device has been observed since 2011; the reasons behind this observation are still unclear, but possible explanations may include less frequent use of perioperative heparin, lower target INR ranges due to the high incidence of bleeding, inadequate antiplatelet therapy, overestimation of effective anticoagulation by the partial prothrombin time, infections, or abnormal angulation of inflow or outflow cannulas.[13]

Right heart failure (RHF) is a frequent complication following LVAD implantation with an incidence of up to 50%. It is the leading cause of postoperative morbidity and mortality. RHF is defined as the inability to pump blood through the pulmonary circuit to adequately fill the left heart after LVAD implantation. No approved chronic right ventricular support is currently available. Surgical implantation of a right ventricular (RV) assist device may provide temporary mechanical RV support; however, biventricular support is associated with 50% mortality at 1 year.[22] Thus, screening for potential RHF before LVAD implantation is important, and patients with severe RHF may not qualify for LVAD implantation. Although prediction models, hemodynamic parameters, and echocardiographic measurements are used to assess RV functions before LVAD implantation, there are no absolute predictive criteria for the development of intractable RHF while on LVAD support.[13]

Conclusions

The evolution of mechanical circulatory support has brought about a revolution in extending life. Life expectancies and survival status have improved for those on the waitlist for transplant. We postulate that a combination of identification of CHF in the early stages and improvements in medical and surgical therapy will extend life in this population.

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