Ventricular Assist Device as Bridge-to-Transplant

6

Vidang Nguyen and Song Li

Contents

Abstract

Due to the limited donor supply and long wait times for heart transplantation, the use of a ventricular assist device as a bridge to heart transplantation is increasing. With the development of the continuous flow device, there has been improved mechanical durability with a resultant decrease in waitlist mortality for patient who are waiting for heart transplantation. When selecting patients for potential assist device therapy, it is important to consider heart failure severity for timing of device implantation, right ventricular function, and ability to tolerate anticoagulation.

Keywords

Bridge-to-transplantation · heart transplantation · left ventricular assist device

Introduction

Heart transplantation has long been considered the ultimate long-term therapy for refractory (American College of Cardiology/American Heart Association (ACC/AHA)) stage D heart

V. Nguyen (✉)
Cardiology, Cedars-Sinai Heart Institute, Los Angeles, CA, USA
e-mail: vidangnguyen@gmail.com

S. Li
Cardiology, University of Washington, Seattle, WA, USA
e-mail: lisong@uw.edu

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failure (HF). However, since transplant wait time can be long and unpredictable, ventricular assist devices (VADs) have been widely used to help appropriate patients stay alive and active on the transplant list until a suitable donor heart can be identified. This strategy has commonly been termed bridge-to-transplant (BTT). VADs can also be implanted in patients with temporary and potentially reversible contraindications to transplant with intention of eventual listing, a strategy termed bridge-to-candidacy (BTC).

Despite a slight increase in the number of heart transplants in recent years (2015 to 2017), the number of suitable donor hearts remains inadequate to meet the demand. New active listings for heart transplant have increased 49% between 2006 and 2017 and the number of candidates on the waiting list has increased by 119% (Colvin et al. 2019). The median waiting time for heart transplant, as a result, has nearly doubled from 4.0 months in 2006–2007 to 7.9 months in 2016–2017. With lengthening transplant wait time, VAD implantation as BTT has become increasingly necessary. The proportion of patients on the transplant waiting list with a VAD has increased from 9.1% in 2006 to 32.6% in 2017, and among those transplanted in 2017, 49.4% had a VAD prior to transplant (Colvin et al. 2019).

The Ventricular Assist Device

The VAD field has progressed tremendously in recent years so that VAD therapy on its own significantly improves end stage HF patients' survival and quality of life. In addition, patients on the transplant waiting list with VADs are less likely to be delisted for being too ill compared to those without durable devices (Cogswell et al. 2018). The implantation of VADs significantly increased after the commercialization of the continuous flow (CF) HeartMate II (Thoratec Corp, Pleasanton, CA) VAD with much improved mechanical durability compared to earlier pulsatile devices. With the third generation centrifugal flow VADs, the HeartWare HVAD (Medtronic, Framingham, MA) and the HeartMate 3 (Abbott, Chicago, IL), mechanical durability and VAD thrombosis risk have further improved (Rogers et al. 2017; Mehra et al. 2019). According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the 1-year survival rate for CF-VAD is now 81% and patients' perception of health, as measured by EQ. 5D visual analog scale, on average improves from 35 out of 100 before VAD to 71 1 year after VAD implantation (Kirklin et al. 2017). Furthermore, patient satisfaction rate with VAD is high and steady at around 81% from 3 months to 2 years after VAD implantation (Kirklin et al. 2017).

Outcomes of VAD as BTT

The strategy of VAD as BTT has become more successful with iterative improvement in VAD technology and medical management. Waitlist mortality for patients with VADs have declined significantly from 47.8 to 11.8 deaths per 100 waitlist-years, nearly identical to patients without VADs (Colvin et al. 2019). Among BTT VAD patients in the INTERMACS registry from 2015 to 2016, 88% were alive and 34% were transplanted at 1 year (Kirklin et al. 2017). A recent clinical trial of BTT/BTC patients implanted with the HVAD showed similar results with a 20% transplant rate at 6 months and an impressively high 87% Kaplan-Meier survival rate at 2 years with very low rates of complications such as stroke (Fig. 1) (McGee et al. 2019; Khush et al. 2018). These results show that with appropriate patient selection and post implantation care, VAD as BTT can achieve very favorable outcomes even with extended transplant wait time. However, with implantation of VAD as BTT, lower waitlist mortality has occurred at the expense of reducing the likelihood of transplantation. Therefore, the circumstances of the individual patients and regional elements must be taken

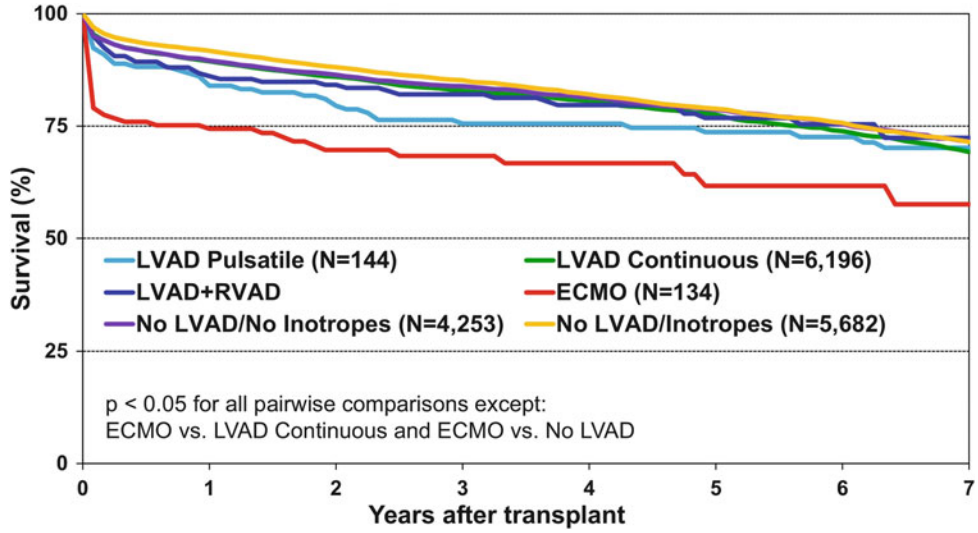

Fig. 1 Kaplan-Meier curve showing posttransplant survival by type of pretransplant mechanical circulatory support. Data includes adult heart transplantation between January 2009 and June 2016. *ECMO* extracorporeal membrane oxygenation, *LVAD* left ventricular assist device, *RVAD* right ventricular assist device. Previously published by Khush et al. (2018). (Reprinted from The Journal of Heart and LUng Transplantation, Vol 37/Issue 10, Khush et al., The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report—2018; Focus Theme: Multiorgan Transplantation, Pages 1155–1168., Copyright (2018), with permission from Elsevier)

into consideration when deciding to implant a patient with VAD (Truby et al. 2018; Nguyen et al. 2016).

Predictors of Outcomes after BTT VAD

Few studies have examined the predictors of short- and long-term outcomes after VAD implantation in the current continuous flow device era. A review of patients implanted with HeartMate II and HVAD as BTT showed that the only independent predictors for 90-day mortality were elevated central venous pressure $>$ 18 mmHg and age $>$ 45 years old (Sabashnikov et al. 2014). Another retrospective analysis of both BTT and destination therapy (DT) VAD patients showed that 1-year survival could be predicted using a model including age, creatinine, total bilirubin, body mass index, and severity of RV dysfunction and aortic insufficiency on echocardiogram (Birati et al. 2018). However, when applied to an external validation cohort, the model's discriminative power was only modest.

Management of Patients on BTT VAD

While careful patient selection and optimizing clinical status prior to VAD implantation might improve post-VAD survival, there is a rapidly expanding evidence basis that meticulous medical management of VAD patients after implantation can improve outcomes. For example, stroke is the number one cause of death in VAD patients and frequently a barrier to future heart transplantation (Kirklin et al. 2017). The ENDURANCE Supplemental trial showed that a blood pressure management protocol targeting a mean arterial pressure (MAP) of less than 85 mmHg significantly reduced stroke, especially hemorrhagic stroke, rates (Milano et al. 2018). It has also been shown in CF-VAD patients that Doppler opening pressure is a highly accurate estimate of MAP and should be used as the default noninvasive BP

measurement method (Li et al. 2019). In addition, in the course of the HeartWare ADVANCE BTT + CAP trial, a protocol change requiring high-dose aspirin 325 mg daily and an INR goal range of 2.0–3.0 reduced ischemic stroke rate without increasing hemorrhagic stroke rate (Slaughter et al. 2013). Therefore, discovering and implementing beneficial medical management strategies post VAD implantation is crucial to improving survival to transplant rate in BTT VAD patients.

Patient Selection

Patient selection is key to a successful transplant outcome after BTT VAD implantation. VADs are most commonly used in men and those with blood group O due to a longer wait time for heart transplantation (Ciarka et al. 2017). On the flipside, CF-VADs remain clinically underutilized in women, who experience a higher waitlist mortality and lower transplant rate (DeFilippis et al. 2019). Additionally, unique anatomies and hemodynamics in congenital heart disease patients have limited the benefits of VAD as BTT with significantly increased waitlist mortality in those with a VAD (Krishnamurthy et al. 2016; Blume et al. 2018; Gelow et al. 2013). The key to successful VAD utilization in this unique patient population is early implementation and thoughtful patient selection (Serfas et al. 2018; VanderPluym et al. 2018). In addition to meeting common requirements for heart transplant listing, below we review the unique considerations for VAD implantation as BTT.

HF Disease Severity

Traditionally, end-stage HF patients on the heart transplant list who are "too sick" to continue waiting for an available donor heart are considered for VAD implantation as BTT. These patients are generally of INTERMACS profile 1–3 at time of VAD implantation (Kirklin et al. 2017). However, several factors favor BTT VAD decision in patients with less severe disease. First, significant advancement in VAD design and VAD management has continually improved patient survival to the point that short-and mid-term survival post VAD is nearly equal to post heart transplantation (Mehra et al. 2019; McGee et al. 2019). Second, it has been shown that heart transplant outcomes in patients bridged with VAD are equivalent to patients not bridged with VAD, possibly due to improved end-organ function and functional status, and longer duration of support does not adversely affect transplant outcome (John et al. 2010; Seco et al. 2017; Williams et al. 2011). On the other hand, INTERMACS registry data clearly show that patients who are sicker at the time of VAD implantation have worse outcomes. Patients with INTERMACS profile 1, 2/3, and 4–7 have 1-year survival of 74%, 82%, and 84%, respectively (Kirklin et al. 2017). Furthermore, post-transplant outcomes in VAD patients are superior when compared to other forms of mechanical support such as extracorporeal membrane oxygenation (ECMO). In fact, VAD remains an effective bridging strategy when implemented after ECMO with a similar survival to those who were implanted with VAD without ECMO (Pagani et al. 2000). From 2008 to 2016, there has been a steady decrease in the proportion of VAD implantation in INTERMACS profile 2 patients (41–34%) and a steady increase in profile 3 patients (25–38%) (Kirklin et al. 2017). Whether it would be beneficial to consider BTT VAD even earlier in INTERMACS profile 4 (resting symptoms) patients remains to be seen. Given the above considerations and the lengthening transplant wait time, it is not surprising that we have seen a trend towards a greater proportion of patients transplanted with VAD bridging and a shift towards implanting VAD in less sick patients.

Another key issue of utilizing the LVAD as a bridge to transplantation is to get to the heart transplant prior to the onset of device-related complications, such as infection, bleeding, or thromboembolic events as described (Steffen et al. 2017; Wever-Pinzon et al. 2013; Dardas 2018). With the newly implemented heart allocation system in October of 2018, patients with durable LVADs are experiencing longer wait times,

which therefore increases the risk of developing a complication. The longer the wait time for transplantation, the more likely the patient is to be upgraded to a higher listing status due to device complication (Uriel et al. 2013). Wait times for LVAD patients vary significantly depending on the center transplant rate, regional donor availability, patient blood type, and body size, and thus, it is important to take these factors into consideration when deciding to pursue LVAD implantation as a bridge to transplant (Nguyen et al. 2016). Although device-related complications significantly increase waitlist mortality, there is no impact of posttransplant survival (Chauhan et al. 2017a; Healy et al. 2013).

Right Ventricular Function

It is important to carefully evaluate the right ventricular function when considering a patient for left ventricular assist device (LVAD). LVADs do not support the right heart circulation and in some cases may actually precipitate right ventricular failure (RVF) by (Colvin et al. 2019) altering the contractility of the intraventricular septum which contributes ~30% of RV stroke volume, (Cogswell et al. 2018) increasing venous return to the right ventricle, and (Rogers et al. 2017) arterial-ventricular uncoupling between the RV and pulmonary vasculature. Depending on its definition, RVF complicates 5–35% of LVAD implantations and may be more frequent in nonischemic cardiomyopathy and in patients with longer history of HF (Kormos et al. 2010; Bellavia et al. 2017). Compared to LVAD patients without RVF, those with RVF have significantly higher mortality, longer length of stay, higher risk of bleeding, diuretic resistance, renal failure, and worsening nutritional status in part due to congestive hepatopathy and nephropathy (Patlolla et al. 2013; Lampert and Teuteberg 2015). The evidence that use of pulmonary vasodilators in RV failure is beneficial remains sparse and few therapies have been found to be effective in RVF (Sparrow et al. 2018; Kalogeropoulos et al. 2011). In the consideration for BTT therapy, it is important to note that RVF is one of the greatest risk factors for mortality after transplant. Patient who required a right ventricular assist device prior to transplant have an increased posttransplant mortality (Taghavi et al. 2016). Even in the absence of RV dysfunction at the time of implantation, late RV failure development still correlates with poor posttransplant outcomes (Takeda et al. 2015).

To estimate potential candidates' risk of developing RVF post LVAD implantation, a large number of studies have attempted to identify clinical predictors and develop risk models. These predictors and risk models are summarized in two recent review articles and a meta-analysis (Bellavia et al. 2017; Lampert and Teuteberg 2015; Turner 2019). However, the clinical application of these risk models has been limited for several reasons. First, many studies are small single-center cohorts with different definitions of RVH. Second, most early studies were done in patients with pulsatile LVADs that are no longer applicable to the current era of continuous flow VADs. Third, the predictive power of the published models remains very modest. Six RVF risk models were systemically evaluated in an external validation cohort of CF LVADs using two representative sets of RVF definitions and the models' c-statistics ranged from 0.50 to 0.62, barely better than random guessing (Kalogeropoulos et al. 2015). Routine echocardiographic assessment is important for ongoing surveillance of the RV function during the time of LVAD support, including strain and RV to left ventricular diameter ratio (Grant et al. 2012; Vivo et al. 2013). However, a recent meta-analysis has concluded that, at present, while a number of clinical, hemodynamic, and echocardiographic variables are statistically associated with RVF after LVAD, no single variable is able to predict RVF with clinically acceptable accuracy (Bellavia et al. 2017). Thus, patient selection to avoid RVF post LVAD continues to be challenging.

Anticoagulation

Early LVAD models were designed to mimic the human heart with pulsatile blood flow, but due to a high rate of mechanical failures, newer VADs provide continuous flow with fewer possible

points of failure and greater durability. However, the continuous flow comes at a cost of the ongoing loss of von Willebrand Factor (vWF), which is thought to be due to excessive cleavage of the large vWF multimers by ADAMTS-13 in the CF-VAD circulation (Nascimbene et al. 2016; Meyer et al. 2010). Elevated tumor necrosis factor-α levels in CF-VAD patients have also been shown to induce pericyte apoptosis, tissue factor expression, and vascular instability (Tabit et al. 2018). These patients are therefore prone to hemostatic complications, most notably gastrointestinal bleeding from arteriovenous malformations (Kirklin et al. 2017). Contributing factors to high incident of bleeding in LVAD patients include concurrent hemolysis, abnormal platelet activation, and decreased pulsatility (Shah et al. 2017). Therapeutic anticoagulation can exacerbate the coagulopathy caused by VADs but is necessary to prevent VAD thrombosis and thromboembolic complications. Other pharmacotherapies are being used in attempt to minimize risk of bleeding, however the supporting data remains sparse (Sieg et al. 2017). It is therefore important to ensure that potential candidates of VAD therapy are capable of adhering to warfarin treatment and maintaining International Normalized Ratio in the therapeutic range. VAD patients who develop a thromboembolic event have a significantly elevated mortality, especially when managed conservatively without pump exchange (Wever-Pinzon et al. 2016).

Other Factors for Consideration

VADs can increase the risk of allo-sensitization, which occurs in more than one fifth of VAD patients who are waiting for heart transplantation (Grosman-Rimon et al. 2019). This observation may account for the finding that duration of CF-VAD therapy correlates with the incidence of acute rejection prior to discharge (Chauhan et al. 2017b). Although allo-sensitization raises the risk of both cellular- and antibody-mediated rejection after transplant, several studies suggest that clinical outcomes are not affected (Ko et al. 2016; Shankar et al. 2013; Joyce et al. 2005; Fraser et al. 2019). In severe cases of rejection, plasmapheresis and intravenous immunoglobulin can be considered (Massad et al. 1997; Dowling et al. 1998). VAD therapy as BTT may be indicated prior to heart transplant in candidates with prohibitive pulmonary hypertension due to long-standing left heart failure (Atluri et al. 2013; Mikus et al. 2011). Left ventricular unloading can potentially reverse some degree of fixed pulmonary hypertension with comparable post-transplant outcomes as those without pulmonary hypertension; however, only third of patients with elevated pulmonary vascular resistance (PVR) actually normalize their PVR prior to transplant (Al-Kindi et al. 2017; Moayedifar et al. 2018). RVF as a result of pulmonary hypertension has a significantly elevated posttransplant mortality (Schumer et al. 2018).

Conclusion

The use of VADs as BTT has increased over time since its introduction over 15 years ago with favorable outcomes and a concurrent decrease in waitlist mortality. It should be considered for patients who are expected to have a prolonged waiting time for heart transplantation and in candidates who are becoming too sick to continue waiting. However, sicker patients tend to do worse after VAD implantation so potential candidates should be considered prior to the decline of end-organ dysfunction. RVF is one of the leading causes of mortality both after LVAD implantation and after heart transplantation, so the right heart function should be thoroughly assessed when selecting patients for LVAD as BTT. Potential downsides to the use of VADs include the requirement for therapeutic anticoagulation and the risk of strokes, gastrointestinal bleeding, and infections.

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