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Review Article

A Review of Long-Term Mechanical Circulatory Support as Destination Therapy: *Evolving Paradigms for Treatment of Advanced Heart Failure*

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Left ventricular assist devices as long-term mechanical circulatory support are increasingly utilized as an option for medically refractory advanced heart failure. Rapid advances in this field, from pulsatile paracorporeal flow pumps to now more advanced intracorporeal continuous flow devices, have led to more wide spread use of device therapy. Several trials have now confirmed the survival benefits of ventricular assist devices, not only as a method for bridging patients waiting on the transplant list, but also as an evolving paradigm of destination therapy. Significant improvements in quality of life and functional status have been reported in patients receiving these devices. Survival outcomes with this therapy continue to improve, and long term durability of newer generation devices remains yet to be discerned. Comparative data to heart transplantation remains scarce. This paper will focus on the historical development of ventricular assist device therapy for advanced heart failure, review major trials of destination therapy, and look at comparative literature in the modern era to cardiac transplantation.

1. Introduction

Left ventricular assist devices (LVAD) as long term mechanical circulatory support (MCS) therapy are being used with increasing frequency for medically refractory heart failure. Over 4000 patients in the United States have received LVAD implants, and this number continues to grow [1]. Technological advancements have rapidly advanced this field, with the replacement of pulsatile paracorporeal flow pumps with intracorporeal continuous flow devices. Several trials have now confirmed the survival benefits of LVAD therapy, not only as a method for bridging patients waiting on the transplant list, but also as an evolving paradigm of destination therapy (DT) [2]. Significant improvements in quality of life and functional status have now been reported in patients receiving these devices [3]. This review will focus on the historical development of LVADs, review major trials of LVAD use as destination therapy, and look at comparative literature in the modern era to cardiac transplantation.

2. History

The development of MCS support has evolved over time. Work on engineering designs on LVAD therapy as long term support began in the late 1960s, and after several years of trialed designs, the first HeartMate IP LVAS system was approved for use in the United States in 1994. The first generation LVADs produced pulsatile flow and simulated cyclic stroke volume with normal physiologic blood pressure and pulse. Among these devices, the WorldHeart Novacor and Thoratec HeartMate XVE were initially trialed for use as DT. Several complications limited the long-term use of these pulsatile devices, including high rates of thromboembolic events, driveline and bloodstream infections, bleeding, and ultimately device failure [4]. This latter complication limited the longevity of device therapy in patients for use as DT and was thought to be related to the nondurability of mechanical bearings that allowed for pulsatile flow to occur. In fact, device malfunction was noted in up to

35% of patients in study trials, occurring approximately 18–24 months after implant [4]. These limitations led to the conceptual development of continuous flow technology, to minimize bearing wear and improve longevity of device mechanics. A rapid increase in device implants began to occur with the use of continuous flow LVAD technology. The Food and Drug Administration (FDA) granted approval of the first continuous flow LVAD (HeartMate II) in 2008 as a bridge to transplant (BTT), and subsequently as DT in January 2010. The development of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) began documenting LVAD implants within a database since June 23, 2006. Since that time, over 4,000 patients have been entered into the database with a primary device implant [1]. By the mid of year 2011, more than 99% of those LVAD implants were continuous flow devices [1].

3. Destination Therapy Trials

The first DT trial, published in 2001, was the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, which paved the way for future studies in this arena. This multicenter study enrolled 129 patients between May 1998 and July 2001 with end-stage heart failure, who were deemed ineligible for heart transplant, to either implantation of HeartMate VE LVAD (pulsatile flow device) or optimal medical management. Entry criteria included New York Heart Association (NYHA) class IV heart failure, left ventricular ejection fraction <25%, and either peak oxygen consumption <12 mL/kg/min or intravenous inotropic therapy [4]. All patients were estimated to have a life expectancy of less than two years. The trial demonstrated a marked survival benefit. At 1 year, LVAD therapy revealed a superior survival rate compared to optimal medical therapy (52% versus 23%, $P = 0.002$), and this benefit continued at 2 years (23% versus 8%, $P = 0.009$). There was a 48 percent reduction in the risk of all-cause death in the group that received LVAD, as compared with the medical-therapy group (relative risk, 0.52; 95 percent confidence interval, 0.34 to 0.78; $P = 0.001$). Significant improvement in functional NYHA class was noted at 1 year of study followup ($P < 0.001$), and quality of life as assessed by the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36) was also significantly improved at 1 year as compared to medical therapy ($P = 0.01$). However, the frequency of adverse events in the device group was twofold greater than in the medical-therapy group, with a predominance of infection, bleeding, and device malfunction [4].

Several points can be gleaned from this landmark trial. First, survival, as well as quality of life, was improved by the use of LVAD therapy as compared to medical therapy. However, despite optimal care, mortality was still quite dismal in both arms of the study, suggesting the severity of end-stage heart failure at entry into the study, with the majority of patients requiring intravenous inotropic support. The dismal survival of 25% at 2 years in the LVAD arm was still quite alarming, and multiple factors may have contributed to this high mortality. Given the mechanics of first generation devices, the high rate of device malfunction (35%) certainly was a causal factor, along with infection, bleeding, ischemic stroke, and a noted learning curve for device implantation and patient selection [4]. Despite the suboptimal survival in this trial, a new era of device therapy had now been introduced to a cohort of patients with very limited medical options, thus paving the way for future developments in device mechanics.

Looking further at improvements in patient selection, post-REMATCH era implant survival for DT therapy continued to improve. In a study of 280 patients with HeartMate XVE implants for DT subsequent to the REMATCH trial, the 1-year survival after LVAD implantation improved slightly to 56%. However, stratification of DT candidates by risk score assessment revealed that, particularly in the low risk cohort, survival could be as high as 81% at 1 year. The main causes of death appeared to be sepsis, right heart failure, and multiorgan failure, with preoperative worsening end-organ function as a marker for worse outcomes after LVAD implant [5]. This provided further evidence of the importance of careful patient selection for LVAD implantation.

The Clinical Utility Baseline Study (CUBS) trial was the first European study of DT that evaluated the LionHeart-2000 (LionHeart Ventricular Assist System), as a fully implantable LVAD. The device was unique in its ability to be powered by transcutaneous energy transfer, thereby eliminating the need for external drive lines, and decreasing the potential for infection. This was a small, nonrandomized, observational trial, with only 23 patients enrolled in the study between October 1999 and December 2002. All patients were in NYHA class IV heart failure and were deemed ineligible for heart transplantation. As predicted, the LionHeart device caused less infectious complications in comparison to the REMATCH data cohort. However, the survival rates in the patients receiving the device were markedly inferior (1-year survival 39%, 2-year survival 22%) compared to prior REMATCH data. This increased mortality was thought once again to be secondary to enrollment of higher risk patients, who may have had excessive operative risk at the time of implant [6]. The DT strategy once again appeared to be limited by device complications and a high mortality rate in this study population.

The Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent (INTREPID) trial results were revealed in 2007. This multicenter trial looked at the use of the Novacor LVAD device in 55 patients enrolled between 2001 and 2003. 37 patients underwent LVAD implantation and 18 remained on medical management. The LVAD-treated patients had superior survival rates compared to medical treatment at 6 months (46% versus 22%; $P = 0.03$) and 12 months (27% versus 11%; $P = 0.02$). Although overall survival was improved, the Nocavor LVAD outcomes were inferior to those of the HeartMate VE in the REMATCH trial. Again, patient selection may have played a role in the high mortality noted. However, device design and antithrombotic strategies may have also contributed, as 62% of LVAD patients experienced a stroke or transient ischemic attack during the study, contributing to the highest cause of death (34%) during

the trial [7]. Since then, improvements in implant technique and anticoagulation strategies have improved the stroke risk with this particular device [8]. However, the pulsatile devices, as a group, appeared continually to be inferior in device durability and longevity, limiting ultimate long term utility as a DT strategy.

A major shift in paradigm for DT began as continuous flow technology reached the clinical trial arena. The HeartMate II continuous flow LVAD system was designed as a smaller pump for implant feasibility with a solitary rotary component, allowing for axial flow through the device with limited wearing of mechanical parts. This increased the longevity of device mechanics and yet also provided an interesting change in patient physiology, that of pulseless continuous blood flow to the systemic circulation. The HeartMate II investigators published their randomized trial data in 2009, comparing the pulsatile HeartMate XVE versus the continuous flow HeartMate II device. They enrolled 200 patients from March 2005 to May 2007, who met the following criteria: a left ventricular ejection fraction of less than 25%; a peak oxygen consumption of less than 14 mL/kg/min; NYHA class IIIB or IV symptoms for at least 45 of 60 days, or dependence on an intra-aortic balloon pump for 7 days, or inotropes for at least 14 days before enrollment. The results were remarkable in that actuarial survival estimates were substantially improved with the HeartMate II device in comparison to the Heartmate XVE device (68% versus 55% at 1 year, 58% versus 24% at 2 years, $P = 0.008$). Also, significant reductions in the rates of major adverse events were noted with continuous-flow LVAD technology, including a decrease in infection rates, right heart failure, renal failure, and cardiac arrhythmia. There was a 38% relative risk reduction in the rate of rehospitalization among patients with the HeartMate II as compared with the HeartMate XVE device implant [9].

To further this marked advance in survival with new generation technology, the HeartMate II investigators recently published a review of 281 patients, with similar entry criteria, who were implanted from May 2007 to March 2009, and compared these patients with the initial study cohort as noted above. Compared with the early trial group, patients in this cohort had further reduced adverse event rates for bleeding (1.66 versus 1.13 events per patient-year, $P < 0.001$), sepsis (0.38 versus 0.27, $P = 0.025$), device-related infections (0.47 versus 0.27, $P < 0.001$), and hemorrhagic stroke (0.07 versus 0.03, $P = 0.01$). There was a trend towards increased survival at 1 year in the more recent cohort compared to the early trial group (73% versus 68%, $P = 0.21$) [10]. As familiarity and experience continued to advance with the second generation devices, patient outcomes similarly improved.

In the more recent experience of continuous flow devices, actuarial survival at 1 year since implant now approximates 80% within the INTERMACS registry and only marginally diminishes to 69% at 2 years [1]. Survival notably continues to improve within the more recent era of LVAD technology, and improvements in patient selection have noted a decrease in implants particularly in the INTERMACS 1 category of patients, that of critical cardiogenic shock. The strategy of DT continues to evolve in the United States, with a notable shifting paradigm. The percentage of implants with a BTT strategy decreased from 44% in 2006 down to 23% in 2011. Reciprocally, a twofold increase in the proportion of implants for DT has been noted (16% in 2006 versus 34% in 2011). No further pulsatile devices have been implanted since 2010 as a DT strategy [1].

4. Comparison to Heart Transplantation

Given the marked advances within the last decade in MCS, with the noted increase in survival offered by current LVAD technology, what can be said about comparative data to cardiac transplantation? One-year survival for cardiac transplantation approximates 85% in the era of 2002 to 2008, with the highest mortality occurring within the first 6-months. Improved immunosuppression strategies have particularly enhanced this initial 6 month survival. However, the subsequent median survival of 10–13 years after transplant has not substantially changed over the last decade of cardiac transplantation [11]. Long term survival and durability of the continuous flow devices as DT therapy have yet to be born out, with case reports of event-free survival over four years in certain device implants [12–14]. Improvements in peak oxygen consumption occur similarly in both cardiac transplantation and LVAD assist therapy [15]. In a study comparing extended criteria donor heart recipients versus those of LVAD implants as a DT strategy, similar postoperative and 1-year mortality has been noted in both groups, though 3-year survival outcomes were still better with transplantation [16]. Quality of life as assessed by self-reported questionnaires appears also to be slightly improved with cardiac transplantation versus that of LVAD therapy, acknowledging the differences in lifestyles to be had with driveline and battery management versus that of medication adherence to an immunosuppression regimen [17]. In studies of cost effectiveness comparing transplant data with LVAD implants, total actuarial hospital costs for LVADs implanted in the era of pulsatile devices (1996–2000) exceeded that of cardiac transplantation ($197,957 ± 77,291 for LVAD versus $151, 646 ± 53,909 for transplant, $P = 0.005$) [18]. However, continuous flow devices have since markedly diminished the costs of implants, with more recent studies suggesting a 75% reduction in the incremental cost-effectiveness ratio as compared to the pulsatile device era ($198,184 per quality-adjusted life year for continuous flow devices versus $802,700 per quality-adjusted life year for pulsatile devices) [19]. In the current era, it will be difficult to assess overall comparisons, until one has an appropriate matched patient cohort with similar length of followup for both LVAD therapy and heart transplantation. Donor selection will continue to limit the availability of heart transplants, whereas institutional resources, costs of care, and adverse events associated with device therapy in the current era will continue to limit its durability and widespread utility [20].

5. Current Guidelines

Current guidelines among various heart failure societies have now incorporated destination therapy as part of an acknowledged treatment algorithm for patients with advanced heart

failure. The 2009 update to the American College of Cardiology/American Heart Association guidelines for heart failure management recommend consideration of an LVAD as destination therapy as reasonable in highly selected patients with refractory end-stage heart failure and estimated one-year mortality over 50 percent with medical therapy [21]. The 2010 Heart Failure Society of America guidelines recommend destination therapy with a permanent mechanical assist device in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced heart failure center [22]. The 2012 European Society of Cardiology guidelines offer a Class IIA indication for LVAD therapy in patients who are not transplant eligible as a DT strategy but also give credence to the fact that earlier implantation in less severely ill patients, before right ventricular or multiorgan failure develops, may lead to better surgical outcomes [23].

6. Future Directions

LVAD technology continues to rapidly advance, and new investigational devices continue to improve on prior designs. Newer third generation devices continue to be smaller in size and weight, with improved ease of implantation. The Heartware LVAD, as an example, is a smaller size continuous flow pump with centrifugal flow design, with a magnetically levitated impeller to allow for contact-free rotation, which is implanted completely within the pericardial space, minimizing the need for an abdominal pocket. This device has been commercially available in Europe for several years now and is under current FDA review for approval as a DT strategy in the US [24]. Other third generation devices utilizing magnetic based levitation in the horizon include the HeartMate III, the Berlin Heart Incor, and the DuraHeart [25]. Total artificial heart technology is slowly emerging, with a benefit particularly in those patients with biventricular failure who may not be LVAD candidates [26, 27]. Advances in device therapies for right ventricular failure, for indications in both the perioperative setting and for long term destination use, have been developed with newer right ventricular assist devices in the horizon [28]. Ultimately, fully implantable LVAD technology will likely reach clinical trials in the near future and then pave the way for further paradigm shifts in advanced heart failure management.

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