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Outcomes Following Heart Transplantation among Those Bridged with VAD

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1. Introduction

Clinical assessment of outcome for post heart transplant recipients who were bridged with ventricular assist device is essential for service evaluation, device evaluation and audit. This chapter will provide a summary assessment of clinical studies and reviews. While most of the data available is retrospective, important aspects of this assessment relies on the quality of assessment and timely re-evaluation of strategy used in the assessment.

We will review the clinical outcomes measured so far in the field of heart transplant recipients who were bridged with VAD. In this chapter we will review the ongoing methods of assessment of outcomes for transplant recipients bridged by VAD and discuss the potential challenges facing the clinicians. We will finalize with brief conclusions and future directions.

2. Survival following heart transplantation: Does VAD Type matter?

There have been many clinical studies comparing outcomes following heart transplantation. Only one has been done in a multicenter fashion with clinically relevant as well as a robust risk-adjustment.

In 2006 we asked the question- does survival differ between those who did and did not receive the left ventricular assist device (LVAD) following heart transplantation?

And in summary we found that survival following heart transplantation for patients who received an LVAD prior to transplantation was comparable to those who did not receive an LVAD. The results of this study were published as lead research article in the British Medical Journal earlier this year (Shuhaiber).

We reviewed all patients above 18 years of age who received heart transplants registered in the United Network for Organ Sharing (UNOS) Registry from 1996 to 2004. The study included 2786 status 1/1A/1B heart transplant patients. We used the entry data for all patients who received LVAD pulsatile device. Our study design included a prospective cohort study in which post-transplant survival between patients who received an LVAD and those who did not receive an LVAD was compared.

Patients were assigned to one of five strata based on the propensity score analysis where the first stratum consists of patients most similar to those that had a heart transplant with no prior bridging of an LVAD and the last stratum consists of patients most similar to those patients that had an LVAD device prior to heart transplantation. As a sensitivity analysis, a
1:1 propensity score matching analysis was also performed. Comparisons of survival distributions were made using the Kaplan-Meier method and the risk ratios were estimated using Cox proportional model.

Our primary outcomes as well as risks and exposures included survival following heart transplantation in heart transplant recipients who did or did not receive ventricular assist device.

The strength of the study was in adopting a robust statistical methodology that can adequately control for confounding variables. A stratified propensity score analysis of data revealed that the risk of death following heart transplantation in an LVAD patient was not significantly different from those who did not have an LVAD within each stratum (see table for estimated hazard ratios and their 95% confidence intervals). A 1:1 propensity score matching analysis also revealed no significant difference in post heart transplant survival between the two groups (hazard ratio = 1.18, 95% CIs=0.75 to 1.86).

The propensity score matching was performed in order to control potential selection biases that can lead to a false association (or false lack of association) between LVAD and survival. Although we attempted to minimize bias through propensity score matching, hidden bias could potentially remain because of other relevant known as well as unknown covariates not available in the UNOS database. Nonetheless, the work provided an application of robust statistical methodology and provided a good signal to noise ratio, that VAD support is safe and is not detrimental to outcomes following heart transplantation.

The other studies published in specialized surgical journals, reflected mainly single center experiences. Nonetheless, they supplement the growing interest in the areas of post heart transplant outcomes in patients with VAD insertion.

In a study from Utah (Bull), patients with idiopathic dilated cardiomyopathy (IDC) that had placement of a Heart mate I (Thoratec Corp, Pleasanton, Calif) ventricular assist device as a bridge to a cardiac transplant were reviewed. The authors studied both alloimmunization as well as survival. They found that the VAD group was associated with elevation in pretransplantation panel reactive antibody sensitization and a decrease in 1- and 5 year survivals after cardiac transplantation. Over the time period from 1993 to 2009, a total of 525 cardiac transplants were performed. VADs were placed as a bridge to transplant in 110 patients. The focus of the study was IDC (n=201) and coronary artery disease (n=213). The authors used variables including gender, age, date of transplant, cause of heart failure, prior heart transplant, placement of a ventricular assist device, type of ventricular assist device, and panel-reactive antibody sensitization. Analysis was performed by Kaplan-Meier survival probabilities and multivariable Cox regression models.

Interestingly, the authors found that the patients who had idiopathic dilated cardiomyopathy - VAD group had a decreased survival at 1 year (P=0.008) and 5 years (P=.019) but not at 10 years post transplant. The number of patients was small and it was not adjusted according to other important donor variables and use of other life support measures such as ventilation or use of intra-aortic balloon pump. The extrapolation to and extension of the results to more than 1 year becomes both conceptually and clinically difficult to comprehend. Moreover, the hazard related death is more early at the time of transplantation due to re-entry and cardiac injury, or VAD related injury mainly at the inflow or outflow conduits.

In a separate multicenter study of post transplant survival after support with a continuous – flow left ventricular assist device, the authors followed 468 patients that underwent heart
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transplantation (John 2010). 53% underwent cardiac transplant after a median duration of LVAD support of 151 days (longest:3.2 years ) of which 23% died, 2.6% recovered ventricular function and the device was removed successfully. 21% were still receiving LVAD support. The overall 30-day and 1 year post-transplant survival was 97% and 87%. Patients requiring more than 2 units of packed red blood cells in 24 hours during LVAD support had a statistically significant inferior 1- year survival than those who did not.

Implantation of the VAD with its associated risk factors both perioperatively and postoperatively is important to appreciate as long as the device is in place. After heart transplantation, the device is removed and the patient continues to survive based on the context of graft function, immune suppression and overall patient management assuming that no serious transplant-surgery related events occurred.

A list of contemporary studies reviewing post VAD heart transplant outcomes is detailed in table 1. While there are studies that demonstrate superior survival among those who received VADs, other studies did not show that. The single most robust study from our group showed that VAD placement really does not have any influence on post-heart transplant outcomes.

Finally, optimal timing of cardiac transplantation after ventricular device implantation is an important variable that can directly or indirectly influence outcome. Although intuitively the transplantation around the time of VAD placement has been associated with far worse outcomes due to patient illness as well as VAD related complications. In a study based on the UNOS registry of 2692 heart transplantations performed between 1999 and 2001, 17% received a VAD (Gammie). Almost half of patients with VAD undergoing transplantation were upgraded to status 1 A as a result of VAD related complications. Creatinine and total bilirubin levels were less in patients undergoing transplantation after 2-4 weeks of mechanical support. One-year survival was higher in the non-ventricular assist device than in the VAD group. Within the VAD, survival was lowest for patients who received a heart within 2 weeks of VAD implantation. Multivariate analysis demonstrated a significant effect of time interval from VAD implantation to transplantation on post heart transplantation mortality. The plausible explanation underlying this finding is when a patient requires a VAD usually they are in decompensated state of heart failure. In this state, there often maintain a similar degree of other end-organ injury mainly renal dysfunction. Weeks of hemodynamic support are required to achieve normalization of end-organ function and are concordant with prior reports that have demonstrated improvement of both hepatic and renal function during long-term VAD support (Gammie). Therefore the general rule is to wait a few weeks between time of VAD insertion and before heart transplantation.

3. VAD induced alloimmunization and post heart transplant rejection

Insertion of VAD is associated with relatively increased risk for blood transfusion. Blood contains a large number of antigen load for which the body mounts selective and non-selective antibodies. These antibodies are naturally formed and can be measured by a test called panel reactive assay. A high PRA has been shown to reduce cardiac graft survival because it increases the absolute risk for rejection both in early and late post transplant stages. We review contemporary studies regarding the role of alloimmunization and post-transplant outcomes.

Also a device such as VAD is placed in circulation, the textured surface of the device results in the formation of pseudointima that contains an abundance of T cells, macrophages, and
<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>LVAD number</th>
<th>Median/Mean Age</th>
<th>1 year survival</th>
<th>Post Transplant Survival Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shuhaiber 2010</td>
<td>Thoratec</td>
<td>1354 LVAD</td>
<td>50.6</td>
<td>No significant difference in survival between the two groups</td>
<td>No difference VAD or no VAD</td>
</tr>
<tr>
<td>John 2010</td>
<td>Heart Mate II</td>
<td>468</td>
<td>54</td>
<td>87%</td>
<td>No difference VAD or no VAD</td>
</tr>
<tr>
<td>Bull 2010</td>
<td>Heartmate I</td>
<td>110</td>
<td>54 CAD 42 IDC</td>
<td>90% 77%</td>
<td>VAD Bridge to TX</td>
</tr>
<tr>
<td>Russo 2009</td>
<td>Implantable Para- &amp; extracorporeal</td>
<td>Intra-1680 Para-514 Extra-128</td>
<td>Intra-50 Para-46 Extra-49</td>
<td>1 year Intra-87% Para-81% Extra-57% 84% 1 yr 72% 5 yr</td>
<td>No difference</td>
</tr>
<tr>
<td>Pal 2009</td>
<td>Authors did not specify type of implantable device</td>
<td>Intra-50 Para-46 Extra-49</td>
<td>49</td>
<td>1 year Intra-87% Para-81% Extra-57% 84% 1 yr 72% 5 yr</td>
<td>No difference</td>
</tr>
<tr>
<td>Paltolla 2009</td>
<td>Authors did not specify type of implantable or extracorporeal device</td>
<td>1433 Intracorporeal 448 extracorporeal</td>
<td>IntraCorp 85% 1 yr 70% 5 yr Extracorp 75% 1 yr 66% 5 yr</td>
<td>Higher with extracorporeal</td>
<td>No difference</td>
</tr>
<tr>
<td>Klotz 2006</td>
<td>Micromed DeBakey</td>
<td>50</td>
<td>44</td>
<td>68%</td>
<td>No difference</td>
</tr>
</tbody>
</table>
monocytes as a result of the continuous dynamic interaction of the blood with the device. Aberrant T Cell proliferation and polyclonal B cell hyper-reactivity with CD 40 ligand interaction has all been reported in association with the use of the Hearmate I device. The interaction between the blood constituents and biomaterials of the VAD, specifically the textured chamber surface found in the Heartmate I, may be the responsible for the increased immunologic and inflammatory response seen in this group of patients.

A study from Utah (Drakos 2007), showed that patients with IDC receiving VADs as a bridge to transplant were more likely to have a PRA greater than 10% than the precardiac transplant population without VADs. In a study by Bull et al, patients who received a VAD as a bridge to transplant, the pretransplant PRA was elevated to 35% versus only 5% in the patients without VADs. Interestingly, the incidence and severity of acute cellular and humoral rejection, immunosuppressive agents, immnosuppression protocols, and cardiac allograft vasculopathy did not differ between those with and without VADs in the IDC and CAD groups.

HLA antibodies are present around 3 months following VAD insertion (Kumpati). PRA greater than 10% is considered positive for anti-HLA antibodies. Sensitisation has been found to be more prevalent with increasing length of support. Patient factors determine the temporal pattern of sensitisation and while some argue that the type of device influences allosensitization, others do not (Kumpati). Table 2 reviews the level of sensitization following VAD.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>LVAD number</th>
<th>Allosensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>George 2008</td>
<td>Heartmate I v.s. Heartmate II (1999-2006)</td>
<td>24 36</td>
<td>Heartmate II and DeBakey device produced less sensitization Heartmate I. There were fewer rejection episodes but did not reach Statistical significance.</td>
</tr>
<tr>
<td>Drakos 2007</td>
<td>Heart Mate I</td>
<td>71</td>
<td>Leuokfiltration in 54 patients and fresh frozen plasma in 17 patients. There were significant trends for less sensitization and lower peak PA with greater blood transfusion.</td>
</tr>
</tbody>
</table>

Table 2. Contemporary studies

The type of VAD as a bridge to transplant does not seem to influence the incidence of posttransplant rejection or survival at 1 year post transplant, but can at 5 years post transplant. In addition, the rate and severity of posttransplant rejection has been noted to be higher in LVAD recipients with continous flow devices than in patients with pulsatile devices. However, further studies need to be conducted to determine if these observations are consistent.

For example, in a recent study by Bull et al, implantation of the Heartmate II device was not associated with an increase in the PRA (Bull). We also reviewed the UNOS registry from October 1991 and June 1994 to determine the influence of the type of left ventricular assisted device as predictor of hospitalizations due to rejection following heart transplantation to delineate any further predictors of such outcome. Patients who received a left ventricular assist device (HeartMate [Thoratec Corp.,
Pleasanton, CA, USA] or Novacor [World Heart Corporation, Ottawa, Canada]) prior to heart transplantation were evaluated. Rejection rates between the two devices were analyzed using multivariable logistic regression model. We reviewed 1255 patients with HeartMate I and 154 patients with Novacor. All-time posttransplant hospitalizations due to rejection were similar between HeartMate and Novacor recipients after adjusting for patient case mix. Interestingly, although the PRA was higher in the HeartMate than the Novacor, this did not reach statistical difference.

While there have been several attempts in reducing PRA levels prior to transplantation, none have shown consistent benefit in reducing absolute rejection episodes post transplantation. Even when leukofiltration has been shown to in reducing sensitization, there is no consistent evidence that it would reduce the burden of acute rejection. Further plasmapheresis can reduce the antibody burden, however the process and hospital-dependent protocols in which it has been developed varies from one to the other. This variation of practice and protocols provides some uncertainty as to what is the best method for managing allosensitization.

4. Infections and infection-related complications following heart VAD support in heart transplant recipients.

Infection is one of the leading causes of mortality during ventricular assist device (VAD) observed during the randomized evaluation of mechanical assistance in chronic heart failure (i.e., REMATCH) Trial (Rose 2001). While the REMATCH was not directed towards heart transplantation, its findings are relevant. Bloodstream infection (BSI) during VAD support is a unique clinical problem whose management is one of three options 1) local remedy of the infected VAD directly affecting the pocket or infected VAD valves 2) explant the VAD 3) replace the VAD 4) cardiac transplantation. In a sub-set of patients with VADs, the BSI clears after appropriately treating the source. In others, the BSI persists without an identifiable extra-device source, strongly implicating device-related infection. A conservative approach to these patients, using long-term suppressive antibiotics, leads to 40% to 50% mortality. Further, two reports have demonstrated infection rate of 50% after heart transplants in patients who had a LVAD. The reasons for this increased infection rate was likely due to many factors including the presence of foreign objects in the blood circulation, in addition to patient comorbidities and immune suppression (Omoto, Messner).

In a study by the Pittsburgh group VAD patients who underwent heart transplantation from 1987 to 2001 and who had BSI during VAD support, and who had positive cultures at VAD explant (device-related BSI, $n = 10$) were compared with those with negative cultures at explant (non-device-related BSI, $n = 11$) (Poston). Of the 123 patients who underwent VAD implantation at the University of Pittsburgh Medical Center from 1987 to 2001, a total of 65 (53%) remained free of infection for the entire duration of support. The length of time that patients received VAD support was nearly 3 times longer in those with infection compared with those with no infection during VAD support ($132 \text{ vs } 48 \text{ days, } p < 0.0001$). The variables that were significant predictors of infection in univariate analysis (age, BMI, length of hospitalization pre- and post-VAD implantation, length of ICU stay, and history of alcohol abuse) all lost their significance when controlling for the length of VAD support. Only young age showed a trend for predicting infection ($p = 0.06$). Of the patients with devices who underwent heart transplantation during this time (88/123), infection of any type
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(i.e., BSI or non-BSI) during VAD support was associated with significantly decreased survival after heart transplantation \((p = 0.01)\). In the multivariate analysis, the only significant predictors of post-transplant mortality were any infection during device support \((p < 0.01)\) and device-related BSI \((p < 0.02)\).

In this study, device-related BSI was a significant risk factor for pre-transplant mortality and showed a strong trend for adverse effects on post-transplant survival. Compared with those with no previous history of VAD support, 1-year post-transplant mortality in those with a history of device-related BSI nearly tripled \((10\% \text{ to } 26\%)\). After transplantation, these patients had significantly longer intubation requirements and worse renal function. Combined with heightened concerns of sepsis, a greater forced reduction in nephrotoxic immunosuppression was seen in those with former device-related BSI. Some of the limitations in this study, were that inability to prospectively differentiate BSI as originating from a device vs a non-device source. A history of re-operation after initial VAD implantation and of prolonged ICU stay were also significant predictors in multivariate analysis that highlight the need for meticulous attention to hemostasis and the broad benefit of aprotinin. The latter unfortunately no longer exists given its side effects.

Further in a similar study published in the Journal of Cardiac Surgery, we reviewed 1255 patients with HeartMate I and 154 patients with Novacor. All-time posttransplant hospitalizations due to infection were similar between HeartMate and Novacor recipients after adjusting for patient case mix (Shuhaiber 2008).

Overall, while infections have decreased in general due to several quality improvement initiatives both during surgery as well as postoperatively, an episode of infection during VAD can have direct implications on the post-transplant patient. Our group documented a case of pseudoaneurysm of the ascending aorta in a patient who had biventricular assist device for refractory ventricular fibrillation. Aortic aneurysms after heart transplantation are rare. Although this condition is associated with a history of infection, causality remains to be fully explained. The marked difference in compliance between donor and recipient aorta has been presented as a potential mechanism of pseudoaneurysm formation. However, other causes, such as suture dehiscence or aortic wall tissue necrosis, cannot be excluded. Resection of residual aortic tissue harboring pathogenic organisms associated with the aortic cannulation site of the VAD should be considered to avoid future aortic complications in this immunosuppressed group (Shuhaiber 2008).

5. Neurocognitive following VAD insertion

With more than 5 million people sustaining heart failure and more than 550000 newly diagnosed each year. The number of VAD placements will only increase. While this occurs, there has been more interest in understanding quality of life for VAD patients. One aspect regarding this involves neurocognitive changes (NC) in heart failure patients receiving left ventricular assist devices. While concerns have been raised about functional and neurobehavioural changes during mechanical support, there are few studies objectively assessing this.

One interesting study details neurocognitive function in heart failure patients receiving left ventricular assist devices. While the study did not review NC outcomes following heart transplantation, the findings are relevant in this review. A protocol designed to evaluate patient performance at 1, 3, 6 months after LVAD implantation at 11 centers was carried out.
A total of 239 sessions were complete in 93 patients including paired evaluations in 51 to 57 patients from 1 to 3 months, and in 20 to 28 patients with results from 1, 3 and 6 months. Five NC domains were assessed, including visual spatial perception, auditory and visual memory, executive functions, language and processing speed. The devices included continuous-flow HeartMate II LVAD as a bridge to transplant.

Overall there were no statistical significant differences but limited improvements between 1, 3 and 6 months in NC domain performances as seen in visual memory, executive functions and visual spatial perception and processing speed. Interestingly, there were no significant declines in any neurocognitive test in any domain over these time periods.

The cognitive performance of advanced heart failure patients remained stable or showed slight improvements from month 1 to Month 6 of continuous-blood flow support with the HeartMate II LVAD.

Patients who received a VAD and survived heart transplantation will have a recollection of the events surrounding both the time to VAD implantation, explantation and heart transplantation. Such recollections can have an effect on their cognition, psychological feelings and thoughts. There has been much interest in the role of psychology, as well as behavioural responses following cardiac surgery in the adult population. For example, a proportion of patients with depression following heart surgery are associated with poor outcomes. Patients following transplantation particularly with prior VAD implantation may have different psychological profile that is different from those with heart transplantation only. Further studies in understanding these differences may help in changing the outlook of such patients.

Finally, when a VAD is implanted, there is subclinical thromboemboli formed systemically. This may surface clinically with direct injury to vital organs. The burden of thromboembolic disease can present with worsening end-organ function following heart transplantation. For example, if the kidney injury fails later, renal failure ensues and the survival of heart transplant recipient decreases. Or if there are unwitnessed decline in mental status from silent thromboemboli to the brain, neurocognitive impairment ensues. To provide some more quantitative numbers regarding thromboemboli complications following VAD, we reviewed autopsy findings of patients who had a temporary mechanical device placed (Levitronix). Although we clinically witnessed 3 patients with cerebrovascular infarcts, autopsy revealed far more thromboembolic events (Shuhaiber 2009). Among the 18 patients who did not survive after Levitronix implantation, autopsy was obtained in 11 and the results show that 6 (54%) had evidence of thromboembolism, including pulmonary thromboembolism, and 3 had cerebrovascular infarcts. The autopsy findings of the non-survivors demonstrated a bedside underestimation of the thromboembolic burden of VADs. The underlying etiology for thromboembolism was complex and related to cerebrovascular disease, calcification of the aorta, repeat operative procedures, recent myocardial infarction and mural thrombosis, as well as terminal low flow states with secondary venous and arterial thrombosis. Furthermore, 2 patients developed retroperitoneal hemorrhage from unknown causes contributing to significant blood loss, which were not clinically apparent.

The next decade will begin to appreciate these intricate areas further as the methods of diagnosis and assessment of bleeding as well thromboembolic disease during VAD support become more sophisticated and reliable.
6. Future directions and follow up of patients following VAD bridged to heart transplantation

The future has been rewarding since the introduction of VADs into surgery. Its role in prolonging the lives of patients who would not otherwise be candidates or live long enough for heart transplantation has been astounding. The current state of affairs in VAD technology is continuous evolution of myriad of devices for various diagnostic cardiomyopathy patients. Quality outcome research and assessment of small series for different patient cohorts different patient cohort is not the best way to study the device at hand especially since not all patients survive VAD implantation and or heart transplantation. Standardized clinical assessment and management protocols for designated safe VAD in qualified institutions is essential before we can fully appreciate the impact of VAD on post heart transplant outcomes. While certain devices may suit some patients, others may not benefit from this. The next challenge is to begin stratifying those patients who will benefit them the most.

7. References


The assist devices will continue adding a large number of years of life to humans globally and empower the medical society to optimize heart failure therapy. While expensive and cumbersome task, the foundation provided in this book reflects a contemporary product of original research from a multitude of different experts in the field. We hope this cumulative international effort provides the necessary tools for both the novice as well as the active practitioner aiming to change the outcome of these complex patients.

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