Title

Risk Stratification in Patients with Advanced Heart Failure Requiring Biventricular Assist Device Support as a Bridge to Cardiac Transplantation

Author

Cheng, Richard Kar-Hang

Publication Date

2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Risk Stratification in Patients with Advanced Heart Failure Requiring Biventricular Assist Device Support as a Bridge to Cardiac Transplantation

A thesis submitted in partial satisfaction of the

requirements for the degree Master of Science

in Clinical Research

by

Richard Kar-Hang Cheng

2012

ABSTRACT OF THE THESIS

Risk Stratification in Patients with Advanced Heart Failure Requiring

Biventricular Assist Device Support as a Bridge to Cardiac Transplantation

by

Richard Kar-Hang Cheng

Master of Science in Clinical Research

University of California, Los Angeles, 2012

Professor Robert M. Elashoff, Chair

Background: Prior studies have identified risk factors for survival in patients with end-stage heart failure (HF) requiring left ventricular assist device (LVAD) support. However, patients with biventricular HF may represent a unique cohort.

Methods: We retrospectively evaluated a consecutive cohort of 113 adult, end-stage HF patients at UCLA Medical Center who required BIVAD support between 2000 and 2009.

Results: Survival to transplant was 66.4%, with 1-year actuarial survival of 62.8%. All patients were INTERMACS level 1 or 2 and received Thoratec paracorporeal BIVAD as bridge-to-transplant. We generated a scoring system for survival to transplant. Our final model with age, gender, dialysis, cholesterol, ventilator, and albumin gave a c-statistic of 0.870. A simplified system preserved a c-statistic of 0.844. Patients were divided into normal or high risk groups (median survival of 367 and 17 days, respectively), with strong discrimination between groups for mortality. In this study, we generate a scoring system that offers high prognostic ability for patients requiring BIVAD support, in hopes that it may assist in clinical decision making. Further studies are needed to prospectively validate our scoring system.

The thesis of Richard Kar-Hang Cheng is approved.

William Robb MacLellan

Janet S. Sinsheimer

Robert M. Elashoff, Committee Chair

University of California, Los Angeles

2012

TABLE OF CONTENTS

Section III. Appendix

LIST OF TABLES AND FIGURES

Section I. Introduction

Section II. BIVAD Scoring Analysis

ACKNOWLEDGEMENTS

Section II is an earlier version of the manuscript entitled “Risk stratification in patients with advanced heart failure requiring biventricular assist device support as a bridge to cardiac transplantation” by Cheng RK, Deng MC, Tseng C, Shemin RJ, Kubak BM, and MacLellan WR that is in press, but not yet in publication, in The Journal of Heart and Lung Transplantation.

Section I. Introduction

Background

Heart failure (HF) is a chronic, progressive disease that affects approximately 5.7 million individuals in the United States (U.S.), with an incidence that approaches 10 per 1,000 individuals after age 65[1]. It is well established that HF has age-dependent prevalence[2-3] and it has been projected that the U.S. population aged ≥ 65 will increase from 12.4% in 2000 to 19.6% in 2030[4]. With the rapidly increasing prevalence, it is imperative to determine optimal treatment strategies to minimize cardiac mortality. Despite this global epidemic there has been limited progress in medical therapies since the introduction of beta-blockade, angiotensin inhibitors/receptor blockers, and aldosterone antagonists. Moreover, there has been an increasing focus over the recent years on the economic implications of medical care and a growing emphasis on appropriate allocation of resources. It is estimated that by 2030, the prevalence of heart failure will increase by approximately 25%, with total direct costs of cardiovascular disease exploding to $818 billion[5].

Cardiac transplantation can offer a significant survival advantage to patients with end-stage HF but is restricted by the number of donor hearts available. Currently, only about 2,200 heart transplants are performed per year in the U.S.[6], which is a small fraction of the actual number of patients with advanced HF. This has resulted in increasing wait times for individuals on the transplant list leading to a growing interest in mechanical circulatory support as a bridge for these very ill patients. In the majority of adult patients with HF, their left ventricle (LV) is predominantly affected. Typically, the right ventricle (RV) remains preserved during the early to intermediate phases. For this reason, most patients can undergo left ventricular assist device (LVAD) support without RV support. For patients with failing left and right ventricles, they

may require biventricular (BIVAD) support. Isolated right sided heart failure is uncommon in adults. Since there is no natural limitation in supply of ventricular assist devices (VAD) and this therapy is very costly, correctly identifying the characteristics of patients most likely to benefit from this therapy is critical.

Improved patient selection and risk stratification is necessary to assist with clinical decision making, provide patients and their families with appropriate expectations, and to optimally guide resource spending to achieve the most benefit.

Patient selection from heart failure perspective

Despite the potential for explosive growth for mechanical circulatory support devices (MCSD) in the near future with the aging population, there are no definitive patient selection criteria for VAD use. Patient selection must take into account (1) the appropriateness for device therapy based on patient condition and (2) the risk of therapy to the patient.

The landmark Randomized Evaluation of Mechanical Assist in the Treatment of Congestive Heart Failure (REMATCH) trial randomized patients with New York Heart Association (NYHA) class IV heart failure on maximal medical therapy for 90 days, left ventricular ejection fraction (LVEF) < 25%, and with peak exercise oxygen consumption ≤ 12 ml/kg/min (later expanded to 14) who were ineligible for cardiac transplantation to LVAD compared to optimal medical management. LVAD implantation significantly improved survival compared to medical therapy (relative risk 0.52 with 95% confidence interval of 0.34-0.78; p = 0.001). Quality of life was also improved in the LVAD group[7].

Given this clear benefit in the selective REMATCH cohort, it could be suggested that this population should be eligible for LVAD. However, this excludes a large majority of patients with advanced heart failure, including those who are functionally better than NYHA class IV,

LVEF better than 25%, or who are not yet excluded from transplant candidacy. Despite this gap, no consensus guidelines for MCSD or VAD candidacy have been established[8]. Rather, patients continue to be evaluated for VAD implantation across most centers in the U.S. on a case-by-case basis without clear guidelines. Typical inclusion criteria include patients unable to be weaned from inotropic support, who develop intolerance to medical therapies, have poor functional capacity, and cannot be restored to a reasonable NYHA class despite maximal medical therapy.

The centers for Medicare and Medicaid services (CMS) have requirements in place for reimbursement. However, criteria for VAD use in the post-cardiotomy setting or as bridge to cardiac transplantation are not well-defined. For destination therapy, current CMS criteria mirrors the inclusion criteria from the REMATCH trial[9]. A recent review by Wilson SR et al. tackles this problem and includes an extensive list of indications, relative contraindications, and absolute contraindications to VAD implantation[8]. The recommendations incorporate a combination of REMATCH inclusion criteria, CMS reimbursement requirements, case series, anecdotal reports, published literature, and experience from general clinical practice (Table 1.1).

INTERMACS staging

The Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) is a national registry for patients receiving MCSD. It was established as a joint collaboration by the National Heart, Lung, and Blood Institute (NHLBI), CMS, and the Food and Drug Administration (FDA). INTERMACS has proposed a staging system with 7 clinical profiles that define sequential severity (Table 1.2)[10]. The benefit of this system is the rapidity of application due to its simplicity. However, an obvious limitation is the lack of more in-depth case by case analysis. It also includes an inherent assumption of uniform outcomes based on overall status at the time of assessment. However, many would argue that a patient who is NYHA stage III, with

clinically stable mild-moderate inotrope dependence can vary across a wide spectrum of clinical illness depending on their right ventricular function, acuity of onset of current disease, and the degree of impairment of renal, hepatic, or pulmonary systems. Along the lines of this argument, some patients in this group may require MCSD within the proposed "next few weeks" while others may recover completely and not ever require MCSD support.

Other cardiovascular considerations

In addition to the overall clinical status of the patient, there are more specific cardiovascular parameters that can affect the decision of VAD implantation. One of the strongest predictors of subsequent poor outcomes after LVAD implantation is right ventricular (RV) failure. It is well documented that patients with right heart failure have a higher early mortality rate compared to those without right heart failure (19.0% vs. 6.2%, $p = 0.039$). Predictors of RV dysfunction including right ventricular dilatation, elevation in right atrial pressure, reduced right ventricular stroke work index, and severe tricuspid regurgitation[11]. A recent analysis by Matthews JC et al. derived a risk score to predict right ventricular failure[12]. They found that vasopressor requirement, aspartate transaminase (AST) $\geq$ 80 IU/L, bilirubin $\geq$ 2.0 mg/dl, and creatinine $\geq$ 2.3 mg/dl (or renal replacement therapy) were predictors of RV failure. For patients with right coronary ischemia, consideration for bypass of the right coronary should be considered at the time of LVAD implantation to avoid right sided heart failure due to ongoing ischemia.

Aortic valve competency should also be considered. For patients with aortic regurgitation, implantation of a LVAD can potentially worsen the degree of regurgitation. LVAD support reduces LV pressure, which can increase the gradient across the aortic valve. Thus, even mild or moderate aortic regurgitation can have a significant impact on the

hemodynamic effects of a LVAD[13]. For patients with prosthetic aortic valves, a potential concern is thrombus formation on the aortic side of the valve since the aortic valve does not open normally after LVAD implantation. Some surgeons have advocated replacing mechanical prostheses with bioprosthetic ones and/or pericardial patch closure of the aortic valve annulus prior to LVAD implantation[14-15].

Intracardiac shunts are not well tolerated with LVAD support. Patients with a patent foramen ovale or atrial septal defect are at risk of right to left shunting after LVAD implantation due to unloading of the LV. As a result, the shunt should be closed at the time of or prior to MCSD implant[8 13].

Arrhythmias are generally well tolerated with LVAD implantation. Atrial arrhythmias are not a problem since the VAD will compensate for the failing native heart. On the other hand, it was previously felt that biventricular assist device (BIVAD) support should be considered in patients with ventricular arrhythmias[15-16]. However, more recent experience suggests that the hemodynamic consequence of ventricular arrhythmias in the absence of pulmonary hypertension is not a contraindication to LVAD only support. In effect, as long as pulmonary arterial pressures are normal, patients with refractory ventricular arrhythmias after LVAD implantation have a Fontan-type circulation[8 13 17].

Non-cardiovascular considerations

Additional considerations for VAD implantation include comorbidities and the functional status of other organ systems. This includes body habitus, since body surface areas of smaller than 1.5 square meters can potentially be too small for abdominal implantation of devices. However, paracorporeal or newer axial flow devices such as the Heartmate II can be considered.

Dysfunction of other organ systems, including hepatic, renal (in particular those requiring dialysis), or pulmonary dysfunction (in particular those on mechanical ventilation) are all associated with worse post-implant outcomes[8 13 15]. Other parameters that lead to worse outcomes include poor nutrition with low serum albumin, cachexia with body mass index of < 21 kg/sq meters in males and < 19 kg/sq meters in females, a history of malignancy, and impaired self care from prior stroke, neuropathy, or musculoskeletal disease.

What is the risk for the patient?

Patient selection is a dynamic work in progress and will likely continue to remain so with constantly evolving devices and increasing experience with MCSD. Shifting from the clinician's perspective of appropriate patient selection, it is equally important to choose patients that will derive the most benefit and not be exposed to excessive risk. There is no shortage of patients that should be considered for VAD implantation and this number continues to grow with the aging population worldwide. However, not all patients may benefit from MCSD and some may not benefit at all. Given the relatively high costs of VAD use (mean Medicare 1-year payment of $178,714 [18]) and the potential lack of benefit, it is important to understand what subsets of patients demonstrate increased survival rates with VAD support. There have been several attempts to date in generating different risk scores to identify which patients are most likely to survive after VAD implantation.

An earlier study based on the European VAD registry from 1986-1993 and contained a heterogenous grouping of VAD devices found a 62% survival rate to transplant with mean support length of 18.3 days (standard deviation 43.2 days, range 2 hours-623 days) [19]. Even though the survival distribution appears skewed, further details regarding survival are not available. Since this study was based on registry data, there was a lack of clinical information on

the patients and associated risk factors with mortality were based on reported conditions and complications in the perioperative period (age, indication for graft failure, neurological impairment, renal insufficiency, infection, bleeding, and "support different than VAD"). This study was also limited by the registry being voluntary and incomplete. In addition, the study may not be applicable to current patients since treatment for advanced HF has changed over the last 16 years.

Another retrospective study based on the Novacor European Registry between 1993-1999 looked at 464 patients who received the Novacor LVAD [20]. Their 1-year survival rate after LVAD (including the posttransplantation period) was 60%. They found the following pre-implantation risk factors to be associated with decreased survival: respiratory failure with septicemia, right heart failure, age > 65 years, acute postcardiotomy, and acute infection. A major limitation is that this study utilized the Novacor LVAD, which is not FDA approved in the United States.

A single institution study by Rao et al. evaluated 130 consecutive patients who received a HeartMate VE LVAD from June 1996-March 2001 as long-term bridge to transplantation and risk factors associated with operative mortality [21]. This group of patients included those undergoing primary bridge to transplant, bridge-to-bridge support (patients with a temporary device prior to LVAD implantation) and postcardiotomy patients. In this high risk group of patients, risk factors found to be associated with operative mortality included pre-operative ventilation, postcardiotomy status, temporary LVAD prior to HeartMate VE implantation, CVP > 16 mmHg, and prothrombin time > 16 seconds. Their assessment of risk was focused predominantly on the peri-operative period and longer term outcomes were not evaluated.

Another retrospective analysis was carried out on 280 patients who underwent HeartMate

XVE LVAD implantation between November 2001 and December 2005 as destination therapy from registry data [22]. In this study, 1-year survival rate was 56%. On multivariate analyses, risk factors associated with 90-day in-hospital mortality were poor nutrition (low albumin), hematologic abnormalities (thrombocytopenia, anemia, elevated INR), RV dysfunction (low mean pulmonary artery pressures, elevated AST, elevated BUN), and lack of inotropic support. This is one of the most commonly referenced scores, known as the Lietz-Miller score, but it has not been as useful in predicting risk when applied to other datasets. One of the major limitations may be that the population consisted of patients ineligible for heart transplantation and were implanted for destination therapy. Applying this score to patients undergoing VAD as bridge to transplant or recovery may not be accurate.

A recent analysis from the INTERMACS database by Holman et al. attempted to identify risk factors for poor outcomes across a wide variety of VAD types [23]. For the subset of patients that were bridge to transplant, 24% were dead at 1 year, 53% received a transplant, and 20% were still waiting for transplant at 1 year. Across all VAD types (AbioCor total artificial heart, HeartMate IP/VE/XVE, MicroMed LVAD, Novacor PC, Cardiowest TAH, and Thoratec IVAD/PVAD), they found that older age, right heart failure (characterized by ascites and elevated bilirubin) and cardiogenic shock were associated with increased mortality. The multi-institutional aspect of this study strengthens external validity. However, the grouping of many different device types including LVAD only with total artificial heart and BIVAD may weaken the overall applicability of their score to each individual subgroup.

Another recently developed score by Klotz et al. focused on death during ICU stay. They retrospectively analyzed all patients who underwent VAD implantation between 1993 and 2009 at a single center, excluding patients who required biventricular support or TAH. Similar to the

INTERMACS analysis, their dataset incorporated a large variety of devices including extracorporeal, paracorporeal, intracorporeal, first-generation, second-generation, and several third generation devices. Mortality rate in the ICU was 32.0% with total in-hospital mortality of 34.4%. The majority of patients were bridge to transplant, although they did not exclude patients undergoing bridge to recovery or destination therapy. After multinomial logistic regression, 13 parameters were identified as significant risk factors, that included age > 50 years, ischemic cardiomyopathy, re-do surgery, extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), prior cardiac surgery, need for ventilation, emergency implant, inotropic support, renal replacement therapy, pre-operative resuscitation, need for transfusions and a variety of laboratory values (elevated BUN, creatinine, lactate, white blood cell, c-reactive protein, lactate dehydrogenase, creatine kinase, troponin; and low platelets, hemoglobin, or hematocrit). A risk score was generated with a point scale of 50, and patients were assigned into low, medium, and high-risk groups corresponding to mortality rates of 15.8%, 48.2%, and 65.2%, respectively, while in the ICU[24]. This analysis carried several limitations. First, their risk score range of 50 consisting of 13 variables including multiple laboratory parameters is very bulky and not easily applicable in the clinical setting. In addition, they only examined ICU mortality, with the argument that the majority of patients die in the ICU setting after VAD implantation. However, a converse argument is that the majority of clinicians and patients are more interested in absolute survival. Similar to the INTERMACS dataset, the incorporation of a wide variety of device types and generations makes the score difficult to interpret since there may be variation across devices.

Even though numerous attempts have been made to better risk stratify patients undergoing VAD implantation, their applicability to patients requiring BIVAD is unknown. In

almost all the studies, patients with biventricular failure were excluded. Further, patients with biventricular failure typically will have a degree of hepatic and renal dysfunction related to RV failure. As most of the prior scores are dependent on these parameters, and some directly on pre-existing right heart failure, they will likely be weakened when applied to a cohort of patients that all have biventricular failure. In addition, as RV dysfunction is associated with increased mortality, theoretically there should be increased mortality in patients requiring BIVAD which may skew the risk prediction in these LVAD-only models.

BIVAD scoring

Given that there is very little literature on BIVAD use and even less on risk stratification in patients with biventricular failure, we felt it would be important to address this gap. At UCLA, there is extensive experience with Thoratec paracorporeal VAD (PVAD) for biventricular support. The Thoratec PVAD is an early generation pulsatile device that provides short-to-intermediate term support[25]. While there are a number of tools to estimate the risk of morbidity and mortality in candidates for LVAD only, they rely on risk factors for right ventricular failure, which may not be suitable to assess patients undergoing BIVAD placement. As well, many of these risk scores were derived in populations with less advanced heart failure than the BIVAD candidate population. Understanding these limitations and the general lack of data on BIVAD use in the literature, we analyzed outcomes in the UCLA BIVAD cohort from 2000-2010. We identified risk factors and derived a prediction model for patients with advanced, refractory, biventricular heart failure requiring BIVAD support. Please refer to section II for the manuscript on the BIVAD cohort analysis.

Timing of Implantation

The practice at most institutions is to implant MCSD only when patients are critically ill. With increased durability and decreased complication rates with modern devices, an emerging question is whether LVAD implantation should be considered earlier in patients who are not as sick. As REMATCH demonstrated, patients with VAD implantation have improved outcomes compared to those with conventional medical therapy. The applicability of this finding to patients who are functionally more compensated than REMATCH cohort remains unknown[7]. An advantage of earlier implantation would be that patients should have fewer comorbidities at that point (i.e. lower incidence of liver and renal failure related to their cardiac disease, fewer arrhythmias, lower hospital-acquired infection rates). Prior studies have shown that patients in severe cardiogenic shock have worse outcomes compared with elective implantations[26]. Hence, survival would theoretically be improved significantly in a cohort with earlier MCSD implantation. The optimal timing of device implantation remains unknown.

Future exploratory direction: Gene leukocyte expression profiling

Circulating peripheral blood leukocytes continuously monitor the body and serve as a systemic organ that senses the functional state of all organ systems in a coordinated manner. It has been shown that serial leukocyte gene expression profiling (GEP) can characterize the systemic inflammatory response in healthy individuals after endotoxin administration[27], in heart transplant patients with rejection[28], and in patients with multiorgan dysfunction after trauma[29]. Preliminary data have also suggested that it may be an accurate predictor of severity of illness in heart failure patients undergoing cardiac surgery, more specifically in those undergoing VAD implantation. There appears to be a distinct up-regulation and down-regulation of different gene profiles in the circulating leukocytes of these patients. Leukocyte GEP may eventually serve as

an additional dimension in a novel systems biology approach that has the potential to improve the prediction of risk with VAD implantation in addition to traditional clinical parameters. This remains an area for future exploration.

Table 1.1. Indications for VAD Implantation (adapted from Wilson SR et al.[8])

- NYHA functional class IV symptoms
- Life expectancy < 2 years
- Not a candidate for heart transplantation
- Failure to respond to optimal medical management for at least 60 of the last 90 days
- Left ventricular ejection fraction ≤ 25%
- Refractory cardiogenic shock or cardiac failure
- Peak oxygen consumption ≤ 12 ml/kg/min with cardiac limitation
- Continued need for intravenous inotropic therapy limited by symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion
- Recurrent symptomatic sustained ventricular tachycardia or ventricular fibrillation in the presence of an untreatable arrhythmogenic substrate
- Body surface area > 1.5 square meters

Table 1.2. INTERMACS clinical profiles (adapted from Stevenson et al)[10]

Profile	Description	Timeframe for intervention
1	Critical cardiogenic shock despite escalating inotropic support	Within hours
2	Progressive decline despite intravenous inotropic support	Within a few days
3	Stable but inotrope dependent with repeated failure to wean from support	Elective over periods of weeks to months
4	Patients with resting symptoms that have recurrent HF, but can be stabilized	Elective over periods of weeks to months
5	Comfortable at rest but are intolerant to exertion and live predominantly within the house	Variable urgency depending on nutrition, organ function, activity
6	Exertion limited and fatigues after few minutes of any meaningful activity	Variable urgency depending on nutrition, organ function, activity
7	Advanced NYHA III patients, without recent episodes of decompensation	MCSD not indicated

References

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119(3):480-6.

2. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;22(4 Suppl A):6A-13A.

3. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 2004;25(18):1614-9.

4. Unverferth DV, Magorien RD, Lewis RP, Leier CV. Long-term benefit of dobutamine in patients with congestive cardiomyopathy. *Am Heart J* 1980;100(5):622-30.

5. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011;123(8):933-44.

6. Taylor DO, Stehlik J, Edwards LB, Aurora P, Christie JD, Dobbels F, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Heart Transplant Report-2009. *J Heart Lung Transplant* 2009;28(10):1007-22.

7. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;345(20):1435-43.

8. Wilson SR, Mudge GH, Jr., Stewart GC, Givertz MM. Evaluation for a ventricular assist device: selecting the appropriate candidate. *Circulation* 2009;119(16):2225-32.

9. http://www.cms.gov/ Accessed February 15, 2012.

10. Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, et al. INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transplant* 2009;28(6):535-41.

11. Dang NC, Topkara VK, Mercando M, Kay J, Kruger KH, Aboodi MS, et al. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. *J Heart Lung Transplant* 2006;25(1):1-6.

12. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. *J Am Coll Cardiol* 2008;51(22):2163-72.

13. Aaronson KD, Patel H, Pagani FD. Patient selection for left ventricular assist device therapy. *Ann Thorac Surg* 2003;75(6 Suppl):S29-35.

14. Rose AG, Park SJ, Bank AJ, Miller LW. Partial aortic valve fusion induced by left ventricular assist device. *Ann Thorac Surg* 2000;70(4):1270-4.

15. Williams MR, Oz MC. Indications and patient selection for mechanical ventricular assistance. *Ann Thorac Surg* 2001;71(3 Suppl):S86-91; discussion S114-5.

16. Farrar DJ, Hill JD, Gray LA, Jr., Galbraith TA, Chow E, Hershon JJ. Successful biventricular circulatory support as a bridge to cardiac transplantation during prolonged ventricular fibrillation and asystole. *Circulation* 1989;80(5 Pt 2):III147-51.

17. Oz MC, Rose EA, Slater J, Kuiper JJ, Catanese KA, Levin HR. Malignant ventricular arrhythmias are well tolerated in patients receiving long-term left ventricular assist devices. *J Am Coll Cardiol* 1994;24(7):1688-91.

18. Hernandez AF, Shea AM, Milano CA, Rogers JG, Hammill BG, O'Connor CM, et al. Long-term outcomes and costs of ventricular assist devices among Medicare beneficiaries. *JAMA* 2008;300(20):2398-406.

19. Quaini E, Pavie A, Chieco S, Mambrito B. The Concerted Action 'Heart' European registry on clinical application of mechanical circulatory support systems: bridge to transplant. The Registry Scientific Committee. *Eur J Cardiothorac Surg* 1997;11(1):182-8.

20. Deng MC, Loebe M, El-Banayosy A, Gronda E, Jansen PG, Vigano M, et al. Mechanical circulatory support for advanced heart failure: effect of patient selection on outcome. *Circulation* 2001;103(2):231-7.

21. Rao V, Oz MC, Flannery MA, Catanese KA, Argenziano M, Naka Y. Revised screening scale to predict survival after insertion of a left ventricular assist device. *J Thorac Cardiovasc Surg* 2003;125(4):855-62.

22. Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 2007;116(5):497-505.

23. Holman WL, Kormos RL, Naftel DC, Miller MA, Pagani FD, Blume E, et al. Predictors of death and transplant in patients with a mechanical circulatory support device: a multi-institutional study. *J Heart Lung Transplant* 2009;28(1):44-50.

24. Klotz S, Vahlhaus C, Riehl C, Reitz C, Sindermann JR, Scheld HH. Pre-operative prediction of post-VAD implant mortality using easily accessible clinical parameters. *J Heart Lung Transplant* 2010;29(1):45-52.

25. Korfer R, El-Banayosy A, Arusoglu L, Minami K, Breymann T, Seifert D, et al. Temporary pulsatile ventricular assist devices and biventricular assist devices. *Ann Thorac Surg* 1999;68(2):678-83.

26. Schmid C, Deng M, Hammel D, Weyand M, Loick HM, Scheld HH. Emergency versus elective/urgent left ventricular assist device implantation. *J Heart Lung Transplant* 1998;17(10):1024-8.

27. Calvano SE, Xiao W, Richards DR, Felciano RM, Baker HV, Cho RJ, et al. A network-based analysis of systemic inflammation in humans. *Nature* 2005;437(7061):1032-7.

28. Deng MC, Eisen HJ, Mehra MR, Billingham M, Marboe CC, Berry G, et al. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant* 2006;6(1):150-60.

29. Laudanski K, Miller-Graziano C, Xiao W, Mindrinos MN, Richards DR, De A, et al. Cell-specific expression and pathway analyses reveal alterations in trauma-related human T cell and monocyte pathways. *Proc Natl Acad Sci U S A* 2006;103(42):15564-9.

Section II. BIVAD Scoring Analysis

Introduction

Heart failure (HF) is a chronic, progressive disease that affects approximately 5.7 million individuals in the United States (U.S.). Despite progress in the medical treatment of HF, prognosis remains poor. Cardiac transplantation can offer a significant survival advantage to Class IV patients but is restricted by the number of donor hearts available. Currently, only about 2,200 heart transplants are performed per year in the U.S.[1], which is a small fraction of the actual number of patients with advanced HF. This has resulted in increasing wait times for individuals on the transplant list leading to a growing interest in mechanical circulatory support as a bridge to transplant.

Although the majority of patients requiring an assist device can be adequately supported by a left ventricular only device, certain patients require biventricular (BIVAD) support due to the presence of pre-existing right ventricular dysfunction or multiorgan failure. At our institution, we primarily used the Thoratec paracorporeal VAD (PVAD) for BIVAD support. The Thoratec PVAD is an early generation pulsatile device that provides short-to-intermediate term support[2]. While there are a number of tools to estimate the risk of morbidity and mortality in candidates for LVAD only, they rely on risk factors for right ventricular failure, which may not be suitable to assess patients undergoing BIVAD placement. As well, many of these risk scores were derived in populations with less advanced heart failure than the BIVAD candidate population.

In this study, we present a single institutional experience with BIVAD use over the last decade. This is one of the largest cohorts of BIVAD patients to date as literature with BIVAD

use remains limited. Further, we identify risk factors and derive a prediction model for patients with advanced, refractory, biventricular heart failure requiring BIVAD support.

Methods

This is a single center, retrospective phase IIA study, evaluating a consecutive cohort of adult (age ≥ 18 years) patients at UCLA Medical Center with advanced biventricular heart failure who required BIVAD support as a bridge-to-cardiac transplantation between January 1, 2000 to December 31, 2009. UCLA maintains a clinical database for mechanical circulatory support, which is prospectively recorded. We used this clinical database with appropriate IRB approval for our current study, filling in additional data via retrospective chart review. Multiple imputation was used to account for residual missing data, making the assumption that data were missing completely at random[3].

The study cohort consisted of 113 patients who received Thoratec paracorporeal BIVAD devices. Of these, 108 patients received BIVAD at the time of initial implantation and 5 received sequential left followed by right ventricular assist device support. Of the entire cohort, only 1 patient demonstrated cardiac recovery and was explanted without the need for heart transplantation.

The percent of missing data for variables in our final model were: 0% age, 0% gender, 0% dialysis use, 0% ventilator use, 1.8% albumin, and 18.5% total cholesterol. The percent of missing data in all variables that were examined include: Baseline characteristics (0% age, 0% VAD support, 0% gender, 1.8% race, 0% etiology, 0% diabetes, 0% ventricular tachycardia, 1.8% LVEF, 12.4% LVEDD); Pre-BIVAD support (0% hemodialysis, 0% intra-aortic balloon pump, 0% ECMO support, 0% antibiotics pre-implant, 0% ventilator pre-implant, 0% inotrope/pressor use); hemodynamics (17.7% PA systolic, 17.7% PA diastolic, 31.9% pulmonary

capillary wedge, 22.1% cardiac output, 33.6% SVR, 16.8% RA pressure); chemistries (0.9% sodium, 0.9% creatinine, 0.9% BUN, albumin, 7.1% INR, 1.8% total bilirubin, 2.7% alkaline phosphatase, 1.8% AST, 2.7% ALT); blood counts (0.9% hematocrit, 0.9% platelet, 2.7% lymphocyte percent); lipids (18.5% total cholesterol, 18.5% % LDL, 18.5% HDL, 18.5% triglycerides), 10.6% TSH and 20.4% troponin-I.

Our primary objective was to develop a scoring model for survival to cardiac transplantation after BIVAD implantation, based on multivariable logistic regression analysis and fit on a ROC curve. Appropriate parametric (independent samples t-test and chi-square) and nonparametric (Wilcoxon Mann-Whitney) analyses were used for comparison of continuous and categorical variables (as listed in Tables 2.1 and 2.2). Characteristics with p-values of < 0.05 in either the mean comparisons or univariate regression analyses were selected. Backward stepwise selection was used in logistic regression models. Although age did not appear to be significant in this cohort, it was forced into the model since it appears most frequently in prior LVAD scoring systems. It may not play a large role in our dataset due to the younger cohort, with only 8.8% of the patients 65 years of age or older. Characteristics that appeared most frequently across the imputed datasets were identified. Variables were tested for their impact on the area under the curve on a receiver operator curve and removed if they had little impact on the c-statistic.

A final model was generated, with discrimination tested on a ROC curve and calibration tested with the Hosmer-Lemeshow statistic[4]. A simplified scoring model was derived based on rounded estimates from beta-coefficients. Classification and regression tree analyses identified the point of highest discrimination for continuous variables and the variables (cholesterol and

albumin) were dichotomized[5]. For validation of our model, we carried out bootstrapping of the original, non-imputed dataset 1000 times to estimate the optimism of our final model.

For exploratory analysis taking into account survival time, patients were divided into normal and high risk groups based on their score. A Kaplan-Meier survival curve was generated with patients censored at time of transplant[6]. For the 1 patient that was bridged to recovery, the patient was censored at the time of recovery.

We evaluated prior LVAD models (Table 2.6) for fit on our BIVAD patient cohort, but most of these models did not apply due to their inclusion of markers for RV failure or due to major differences in underlying characteristics. Since the Lietz-Miller (LM) model[7] is commonly used and contained a population of patients with advanced heart failure, we explored it further. In our dataset, we did not have information regarding IV vasodilator use, but we did have intact data for the rest of the variables.

All statistical analyses except bootstrapping were carried out on SAS version 9.2 and/or IBM SPSS 19. Bootstrapping was done on R software.

Results

The baseline demographics for our BIVAD patient cohort are shown in Table 2.1. The mean age was 46.9 ± 14.5 years. Overall, 76.1% of the patients were male and 18.9% were African-American. The majority of the patients (73.5%) were non-ischemic in etiology. Patients in the cohort were critically ill, with 97.3% on inotropes, 59.3% requiring intra-aortic balloon pump (IABP), and 17.7% requiring extracorporeal membrane oxygenation (ECMO). Cardiac function was severely compromised with mean left ventricular ejection fraction (LVEF) of 19.8 ± 9.3%, and LV end-diastolic diameter of 66.2 ± 13.2 mm. Cardiac hemodynamics were poor with evidence of left and right-sided heart failure, with right atrial pressure of 14.7 ± 6.6 mmHg,

mean pulmonary artery pressure of 34.8 ± 9.4 mmHg, pulmonary capillary wedge pressure of 25.8 ± 8.5 mmHg, and cardiac index of 1.9 ± 0.5 liters per minute per square meter. 39.8% of patients were on a ventilator pre-VAD implantation. Many patients showed evidence of multiorgan involvement based on their laboratory data, with an average total bilirubin of 2.9 mg/dL, AST of 335 U/L, creatinine of 2.0 mg/dL and platelets of 165,000/uL (Table 2.2). As the overall acuity of patients was severe with patients being INTERMACS class 1 or 2, with elevated mean pulmonary artery pressures, and evidence of RV dysfunction with elevated liver enzymes, they were not candidates for LVAD-only support.

In our BIVAD cohort, survival to cardiac transplantation was 66.4% with an overall median survival time of 135.0 days (Figure 2.1). There were 38 deaths prior to transplant, with 27 deaths from multiorgan dysfunction, 6 from progressive cardiogenic shock, 2 from sepsis, 2 from intracranial bleeding, and 1 from massive pulmonary embolism. Actuarial survival, including post-transplant survival, was 78.8% at 30 days, 67.3% at 6 months, and 62.8% at 1 year. Longitudinally, survival appeared to improve in the later years, with survival to transplant of 44.2% during 2000-2004 that increased to 68.4% during 2005-2009.

Regression analyses were carried out to identify predictors of early mortality. On univariate analyses, we identified 15 variables that appeared to be associated with death. Pre-LVAD dialysis, ventilator use, and need for ECMO were associated with increased mortality. The only hemodynamic parameter associated with increased mortality was cardiac output. Paradoxically, higher LVEF and lower LVEDD appeared to be associated with worse outcomes. This was driven by 6 patients with preserved LVEF that all died prior to transplant. Patients in this group had restrictive physiology, were post-cardiotomy, or were post-cardiac arrest, which differs from the majority of the patients who underwent BIVAD placement (Table 2.3). After

removing these 6 patients with preserved LVEF (≥ 40%), there was no significant difference in LVEF in patients who survived to transplant compared to those that died prior to transplant (LVEF 17.9 ± 6.2% vs. 18.9 ± 4.5%, OR = 1.02 (95% CI 0.96 – 1.09), p = 0.48).

Laboratory values associated with worse outcomes included normal-high sodium, low platelet count, lower total cholesterol, lower LDL, lower HDL, low albumin, and elevated AST. Gender, pulmonary artery diastolic and mean pressure, and hematocrit were also strongly predictive of outcomes in mean comparisons and chi-square testing.

Based on multivariate logistic regression models, independent risk factors for increased mortality included female gender, low serum albumin, lower cholesterol quartile (Q), dialysis use, and ventilator use. Initial modeling of this analysis revealed that logit (mortality) = 0.03*Age – 2.12*Gender + 0.89*Albumin + 1.49*Dialysis use + 1.33*Ventilator use – 1.32*Cholesterol (Q2) – 2.07*Cholesterol (Q3) – 1.03*Cholesterol (Q4) – 0.89. In this model, Age = years, Gender = 1 if male, Albumin = 1 if < 3.7 g/dL, dialysis use = 1 if requiring dialysis, ventilator use = 1 if requiring ventilator, cholesterol Q1 = reference, Q2 = quartile 2, Q3 = quartile 3, and Q4 = quartile 4. This initial model provided strong discrimination in predicting mortality with a c-statistic of 0.87 for a binary receiver operating curve. We tested the calibration of the model for survival to transplant with the Hosmer-Lemeshow statistic and found a good fit (Table 2.4), with an overall p-value of 0.90 for survival to transplant, indicating support for the model. In order to validate our model, we carried out bootstrapping of the original, non-imputed data set 1000 times and found an optimism of 4.98%, where optimism is the (observed fit – true fit)/true fit.

Since clinical application of this complex logistic regression is cumbersome, we created a simplified model that can be readily used for clinical decision making (Table 2.5). The

simplified system demonstrated a preserved ability to predict mortality, with a c-statistic of 0.84 (Figure 2.2).

Using this simplified BIVAD scoring system, we risk stratified our patients into normal (score 0-6) or high (score 7-11) risk groups. The Kaplan-Meier survival curve (Figure 2.3) shows good separation between these groups, with median survival time of 367 days in the normal risk group and 29 days in the high risk group. Log rank (Mantel-Cox) test is highly significant with a *P*-value < 0.001.

We next compared the utility of this model versus prior models developed primarily for LVAD patients to predict mortality in our cohort since these models may not be readily applicable to our BIVAD population. Since essentially all the patients in our cohort had right-sided heart failure and received RV support, we expected that markers for RV failure would not be important discriminators of risk. In contrast, in LVAD population markers of RV dysfunction are critically important. Of the previously published models utilized for LVAD that we considered (Table 2.6), most of the models were deemed to not be applicable to our BIVAD cohort due to all our patients being in cardiogenic shock at the time of implant with biventricular failure. The LM model did appear reasonable, giving a c-statistic of 0.71 in predicting survival to transplant.

Discussion

Medical therapeutic options remain limited for advanced, refractory heart failure, and most patients inevitably decline and do not survive. For those patients with progressive, biventricular heart failure, therapies are limited but include heart transplantation and BIVAD or total artificial heart (TAH) for BTT. A recent analysis of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data suggests that patients with

BIVAD do worse than those with LVAD, and poorly overall, with less than 40% survival at 1 year[8]. Our results suggest much better survival with PVAD BIVADs. This finding was not explained by a less sick patient cohort receiving this therapy as all of the patients in our cohort were INTERMACS Class 1 or 2 and had hemodynamic and biochemical profiles that would have made them unsuitable for LVAD only therapy[9]. The higher survival rate may be related to greater experience with BIVAD in both patient selection and care. However, there may also be some limitations in the published registry series from selection bias and the patient population is more likely to be heterogeneous in multi-institutional registries. Although this may increase external validity, it may be difficult to make accurate assessments of outcomes.

Given the high acuity level of the potential candidates for this very expensive therapy, we felt it was imperative to accurately predict which subsets of patients are most likely to benefit from BIVAD placement. We examined prior predictive scores developed in patients receiving LVAD only. These included a score derived from the Novacor European Registry[10], the LM model[7], a model for peri-operative mortality developed at Columbia University[11], and a limited scoring system based on INTERMACS data[8]. Although these scores appear accurate in the LVAD population, they were only weakly correlated with mortality risk in a BIVAD cohort. For instance, when the LM model[7] was applied to our data set it appears to offer a limited degree of discrimination in our BIVAD cohort. The limited fit is likely secondary to several issues. First, the model was derived from a cohort of transplant ineligible patients, which differs from our patients who are candidates for transplant. As well, many of the variables used in the LM model are markers for RV dysfunction, which may weaken prediction power in BIVAD patients.

In this study, patients who died had slightly lower LVEF. This difference appeared to be driven by a subset of patients who required BIVAD for restrictive physiology or in the post-

cardiotomy setting. In total, there were six patients with LVEF ≥ 40% on the most recent echocardiogram prior to BIVAD implantation. Of these, all six died prior to cardiac transplantation. When these patients were removed, there was no significant difference in LVEF between those who survived compared to those that died. Two of them had restrictive physiology, three were post-cardiotomy, and one patient had suffered a cardiac arrest prior to BIVAD. This suggests that patients with restrictive physiology or who are post-cardiotomy do poorly compared to other patients receiving BIVAD regardless of their documented LV function prior to BIVAD implantation.

We also found that female gender appeared to be strongly associated with worse outcomes. This may be attributable to physiological differences between the male and female genders. Conversely, it might be explained by differences in body size between genders. In our cohort, we found that females had similar body mass index to males (23.6 ± 4.3 vs. 23.8 ± 4.1 kg/m^2, $p = 0.82$), but that females had lower body surface area than males (1.7 ± 0.2 vs. 1.9 ± 0.2 m^2, $p < 0.001$). The other variables that were identified were not surprising. Ventilator use, need for dialysis, low albumin, and lower cholesterol are all well-established predictors of poor outcomes in heart failure and transplant. Patients with respiratory or renal failure prior to BIVAD implantation did substantially worse. This trend was not unexpected as patients with multi-system dysfunction do worse across a wide spectrum of diseases. It has been previously demonstrated that lower cholesterol is associated with increased risk of death in patients with advanced heart failure[12]. Although the exact mechanism has not been identified, theories have included a pro-inflammatory state with advanced heart failure, poor nutrition, or impaired liver synthesis. In our group, efforts to develop prognostic scoring parameters based on leukocyte gene expression profiling are therefore underway[13]. Low albumin is also a marker of poor

nutrition and systemic inflammation. It is known to be associated with increased mortality in advanced heart failure[14].

In response to the poor outcomes of BIVAD patients, there has been increasing interest in total artificial hearts as a bridge to transplantation patients with biventricular dysfunction. Overall survival at one year with the TAH was 70%[15], which is higher than one year survival in our total cohort (62.8%). However, during the last 5 years in this study, our survival was increased to 68.4%, likely reflecting increased user experience and approaching similar rates to experiences with TAH. Interestingly, similar to our results, prior analysis with the Cardiowest TAH databases showed that the majority of risk factors in LVAD only patients did not apply to the TAH cohort[16]. In fact, for the TAH cohort, a history of smoking was the only predictor of worse outcomes from the time of implant to transplant[16]. BIVAD patients are more similar to TAH patients than LVAD patients, as both TAH and BIVAD patients tend to be sicker with biventricular dysfunction. It will be interesting to evaluate whether our BIVAD scoring system has predictive ability in the TAH cohort.

Limitations

We recognize that our study has limitations. It is a single center study at a major tertiary care center with extensive experience in BIVAD use and cardiac transplantation. This may limit external validity if patient populations or experience with BIVAD vary between centers. Even though most of the clinical data and outcomes were recorded prospectively, the dataset was originally created for clinical care and may lack the rigorous scrutiny of a dataset created completely for research purposes. Our validation of the scoring system was limited by the relatively small size of the data set preventing division of the cohort into separate derivation and validation cohorts. However, bootstrapping as a method of validation does show that the

optimism of our score is approximately 5%, suggesting high validity. The BIVAD score has not been externally validated because BIVAD or TAH use has been limited at most centers.

Conclusion

In this study, we generate a scoring system that offers high prognostic ability for patients requiring BIVAD support, in hopes that it may assist in clinical decision making. Further studies are needed to prospectively validate our scoring system.

Figure Legend

Figure 2.1. Kaplan-Meier survival curve for BIVAD implant to cardiac transplantation. In our BIVAD cohort, survival to cardiac transplant was 66.4% with overall median survival of 135 days.

Figure 2.2. Receiver operating curve for predicting survival to cardiac transplantation. Based on multivariate modeling, we derived a risk prediction model for mortality in patients receiving BIVAD as a bridge to cardiac transplantation. Here, the blue line represents the original model, giving an AUC of 0.87, which is highly predictive of mortality. Subsequently, we simplified this model further by dichotomizing all variables. This is shown by the green line, still highly predictive with an AUC of 0.84.

Figure 2.3. Kaplan-Meier survival curve for normal vs. high risk groups stratified based on the BIVAD score. Patients were divided into normal and high risk groups based on their BIVAD score (normal risk group = 0-6, high risk group ≥ 7). Survival-over-time was plotted on a Kaplan-Meier curve. There was clear separation, with median survival of 367 days in the normal risk group and median survival of 29 days in the high risk group. Log-rank test was highly significant ($p < 0.001$).

Table 2.1. Baseline characteristics, pre-VAD Support, and hemodynamics

Variable	Total Cohort (n = 113)	Death Prior to Tx (n = 38)	Survival to Tx (n = 75)	p-value
Age (Years)	46.9 ± 14.5	48.5 ± 14.0	46.1 ± 14.7	0.409
VAD Support (Days)	66.0 ± 60.8	48.2 ± 70.1	75.1 ± 53.7	0.655
Gender (Male)	76.1%	60.5%	84.0%	0.006
Race (Black)	18.9%	21.6%	17.6%	0.607
Etiology (Ischemic)	26.5%	23.7%	28.0%	0.624
Diabetes mellitus	23.0%	15.8%	26.7%	0.194
Ventricular tachycardia	52.2%	52.6%	52.0%	0.949
Echocardiography data				
LVEF (%)	19.8 ± 9.3	23.8 ± 12.7	17.9 ± 6.2	0.015
LVEDD (mm)	66.2 ± 13.2	60.7 ± 10.9	69.1 ± 13.5	0.003
Pre-BIVAD Support				
Hemodialysis	19.5%	31.0%	12.7%	0.018
Intra-aortic balloon pump	59.3%	60.5%	58.7%	0.849
ECMO support	17.7%	36.8%	8.0%	< 0.001
Antibiotics pre-implant	19.5%	5.3%	26.7%	0.007
Ventilator pre-implant	39.8%	63.2%	28.0%	< 0.001
IV Inotrope/Pressor use	97.3%	94.7%	98.7%	0.220
Dopamine	71.0%	75.7%	68.6%	0.441
Dobutamine	58.9%	54.1%	61.4%	0.461
Milrinone	54.2%	45.9%	58.6%	0.212
Epinephrine	23.9%	32.4%	21.4%	0.213
Levophed	8.4%	10.8%	7.1%	0.516
Hemodynamics				
PA Systolic (mmHg)	50.1 ± 14.0	47.3 ± 13.1	51.4 ± 14.4	0.187
PA Diastolic (mmHg)	27.0 ± 8.1	24.5 ± 6.8	28.2 ± 8.4	0.024
PA Mean (mmHg)	34.8 ± 9.4	32.1 ± 8.0	36.1 ± 9.7	0.043
PCW (mmHg)	25.8 ± 8.5	23.7 ± 8.7	26.7 ± 8.3	0.180
Cardiac index (L/min/m^2)	1.9 ± 0.5	1.7 ± 0.4	2.0 ± 0.6	0.054
Cardiac output (L/min)	3.7 ± 1.3	3.2 ± 0.8	3.9 ± 1.4	0.008
SVR (dyn*s/cm^5)	1475.5 ± 714.7	1625.4 ± 738.6	1424.7 ± 705.9	0.309
RAP (mmHg)	14.7 ± 6.6	15.5 ± 5.9	14.3 ± 6.9	0.386

Tx = transplant, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter, ECMO = extracorporeal membrane oxygenation, PA = pulmonary artery, PCW = pulmonary capillary wedge pressure, SVR = systemic vascular resistance, RAP = right atrial pressure

Table 2.2. Pre-VAD laboratory data

Laboratory Data	Total Cohort (n = 113)	Death Prior to Tx (n = 38)	Survival to Tx (n = 75)	p-value
Chemistries				
Sodium (mmol/L)	133.5 ± 6.7	136.3 ± 5.9	132.1 ± 6.7	0.001
Creatinine (mg/dL)	2.0 ± 1.1	2.2 ± 1.3	1.9 ± 0.9	0.236
BUN (mg/dL)	39.6 ± 27.0	42.2 ± 33.5	38.2 ± 23.1	0.509
Albumin (g/dL)	3.4 ± 0.6	3.2 ± 0.6	3.5 ± 0.6	0.023
INR	1.5 ± 0.7	1.6 ± 1.0	1.5 ± 0.5	0.414
Total bilirubin (mg/dL)	2.9 ± 3.2	3.5 ± 4.1	2.5 ± 2.5	0.169
AP (U/L)	87.4 ± 57.8	98.8 ± 69.4	84.7 ± 51.2	0.528
AST (U/L)	335.0 ± 1249.6	389.5 ± 1356.0	306.6 ± 1199.3	0.003
ALT (U/L)	247.3 ± 762.5	241.8 ± 763.8	250.1 ± 767.1	0.336
Blood counts				
Hematocrit (g/dL)	33.0 ± 6.1	30.8 ± 5.1	34.2 ± 6.2	0.003
Platelet (1000/uL)	165.2 ± 101.9	125.4 ± 85.1	185.6 ± 104.3	0.002
Lymphocyte (%)	11.0 ± 6.7	10.0 ± 6.6	11.5 ± 6.8	0.257
Lipids				
Total cholesterol (mg/dL)	109.1 ± 40.1	97.7 ± 49.5	115.0 ± 33.3	0.004
LDL (mg/dL)	62.2 ± 31.2	53.2 ± 36.8	67.0 ± 26.9	0.005
HDL (mg/dL)	28.4 ± 13.6	24.7 ± 15.8	30.4 ± 12.1	0.012
Triglycerides (mg/dL)	98.0 ± 71.0	96.3 ± 59.8	98.9 ± 76.5	0.970
Other				
TSH (mcIU/mL)	3.5 ± 7.8	4.5 ± 12.5	3.0 ± 3.7	0.509
Troponin-I (ng/mL)	7.9 ± 27.5	8.8 ± 21.5	7.4 ± 30.3	0.052

BUN = blood urea nitrogen, INR = international normalized ratio, AP = alkaline phosphatase, AST = aspartate transaminase, ALT = alanine transaminase, LDL = low-density lipoprotein, HDL = high-density lipoprotein, TSH = thyroid stimulating hormone

Table 2.3. Details on patients with preserved LV function

Patient	Brief history leading to BIVAD
A	The patient is status-post heart transplant who had a cardiac arrest during ICD placement. He was placed on ECMO during the arrest and subsequently BIVAD was placed.
B	The patient has a history of lupus with both constrictive and restrictive physiology. She underwent pericardial window but subsequently developed biventricular failure, requiring ECMO and subsequent BIVAD.
C	The patient had aortic valve endocarditis status-post aortic valve replacement and coronary artery bypass. Post-operatively, he required ECMO and eventual BIVAD.
D	He had longstanding mitral regurgitation requiring mitral valve replacement. The post-operative course was complicated by cardiogenic shock requiring ECMO and eventual BIVAD.
E	She had severe tricuspid regurgitation and severe RV failure. She underwent tricuspid valve replacement but had post-operative cardiogenic shock and eventual BIVAD placement.
F	The patient had severe heart failure secondary to restrictive cardiomyopathy with a low output state requiring intravenous inotropes and eventual BIVAD support.

Patient	Age	Gender	Support Days	LVEF	LVEDD	Cause of Death
A	38	Male	13	50	49	Sepsis/Multiorgan failure
B	48	Female	128	55	45	Multiorgan failure
C	53	Male	10	50	54	Multiorgan failure
D	70	Male	62	50	56	Multiorgan failure
E	37	Female	19	60	---	Multiorgan failure
F	50	Male	5	45	43	Subarachnoid hemorrhage

LVEF = Left ventricular ejection fraction (percent), LVEDD = LV end-diastolic diameter (mm)

Table 2.4. Hosmer-Lemeshow goodness of fit test

Group	Predicted Death	Death pre-OHT	Death at 90 days	Death at 6 months	Death at 1 year
1	0.5	0	0	0	0
2	0.9	1	0	1	1
3	1.3	1	1	1	1
4	2.1	1	0	2	3
5	2.9	2	1	1	2
6	4.1	1	1	1	1
7	5.0	5	4	5	5
8	6.4	4	4	4	5
9	7.5	7	7	7	7
10	8.4	9	8	9	9
Chi-square	n/a	4.8	8.4	5.2	4.0

Table 2.5. Final simplified BIVAD score

Variables	Beta-Coefficient	Rounded Score
Age ≥ 65 Years	0.5	1
Female Gender	1.9	4
Need For Dialysis	1.4	3
Ventilator Support	1.4	3
Cholesterol < 95 mg/dL	1.1	2
Albumin < 3.7 g/dL	0.5	1

Table 2.6. Current scoring systems for LVAD

Model	Variables in Model	Comment
Novacor European Registry[10] (based on the Novacor LVAD)	• Respiratory failure and septicemia • Preexisting right heart failure • Age at implant > 65 years • Acute postcardiotomy • Acute infarction	All patients in our cohort had preexisting right heart failure, which was one of the strongest predictors of mortality in this model.
Columbia Model for Operative Mortality[11] (based on patients receiving Heartmate VE LVAD as BTT)	• Ventilator use • Postcardiotomy support • Pre-LVAD (bridge-to-bridge support) • CVP > 16 mmHg • PT > 16 seconds	Did not apply as the model was derived to estimate operative mortality rather than intermediate or long-term mortality.
INTERMACS scoring system[8]	• INTERMACS level 1 • Age (older) • Ascites • Bilirubin (higher) • BiVAD implant • Total artificial heart	Difficult to apply to our cohort since all patients had a BiVAD, majority of patients were INTERMACS level 1, and ascites and bilirubin are markers of RV dysfunction.
Lietz-Miller model[7] (based on Heartmate XVE LVAD as DT for patients ineligible for transplant)	• Platelet count ≤ 148 x 10^3/ul • Serum albumin ≤ 3.3 g/dL • INR > 1.1 • Vasodilator therapy • Mean PAP ≤ 25 mmHg • AST > 45 U/mL • Hematocrit ≤ 34% • BUN > 51 U/dL • No intravenous inotropes	PAP, AST, BUN, vasodilator therapy may be surrogates for right ventricular dysfunction. Derived on population ineligible for transplant. Model was tested on our cohort given a c-statistic of 0.713.

Figure 2.1

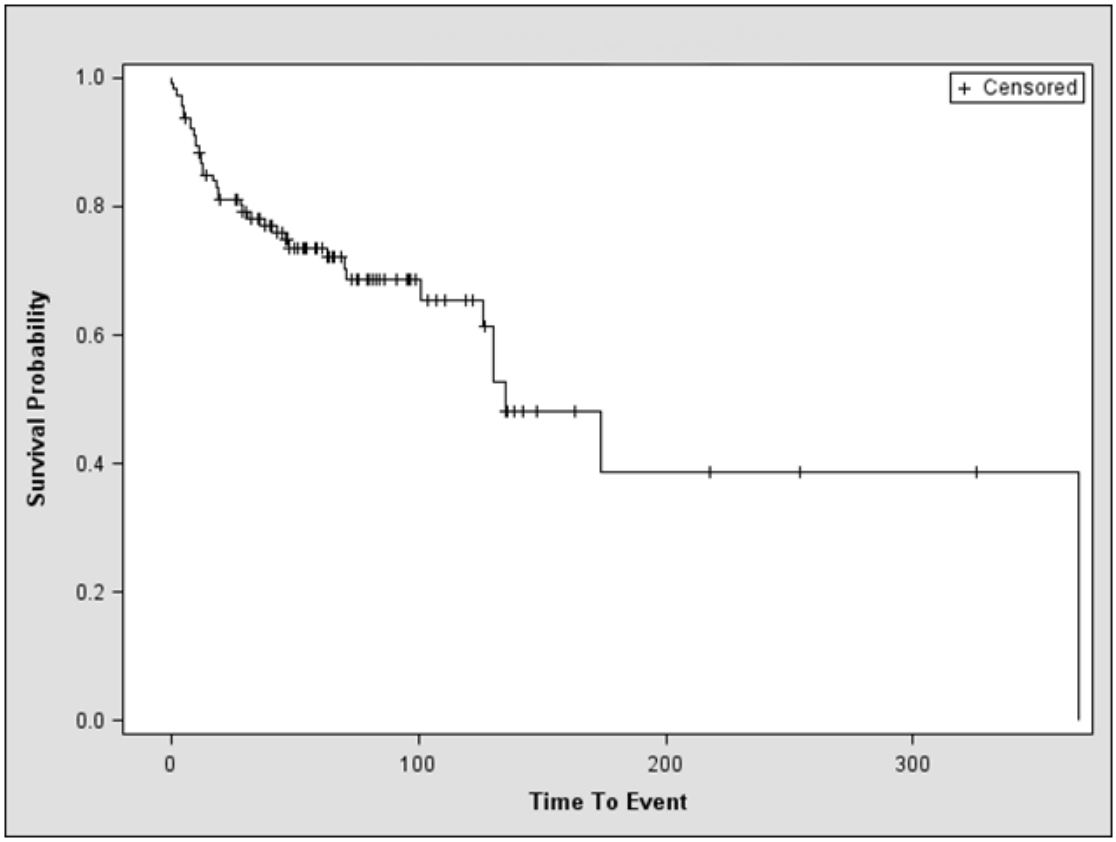

+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
Time To Event

Figure 2.2

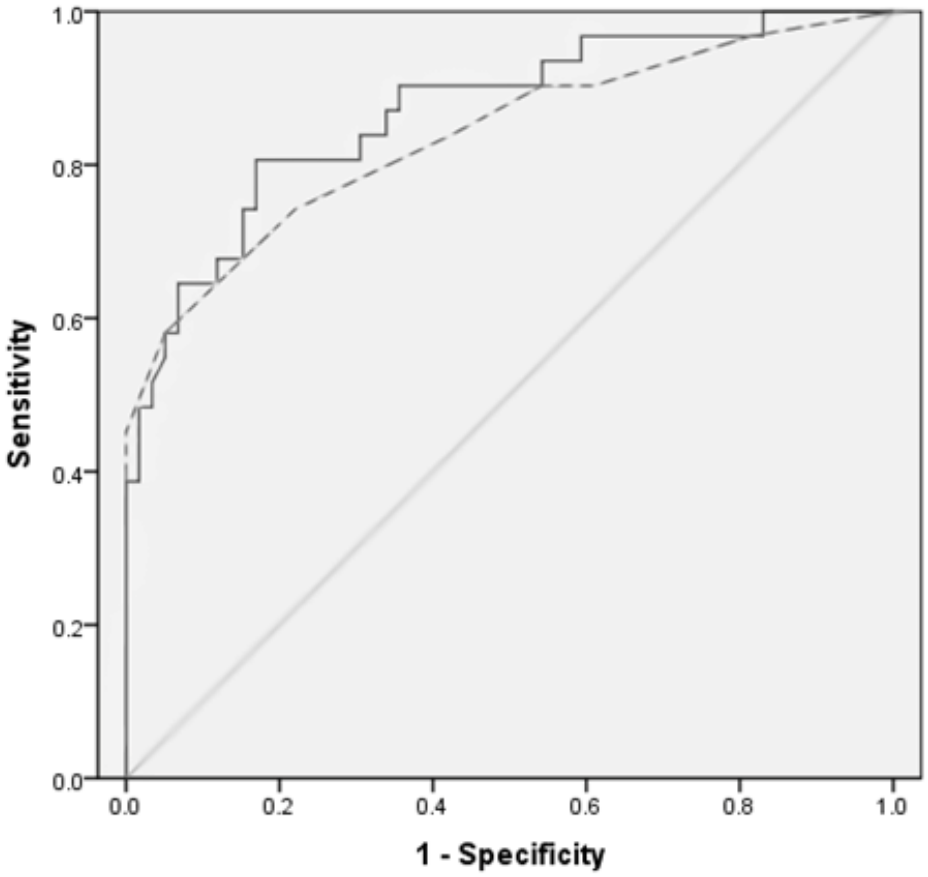
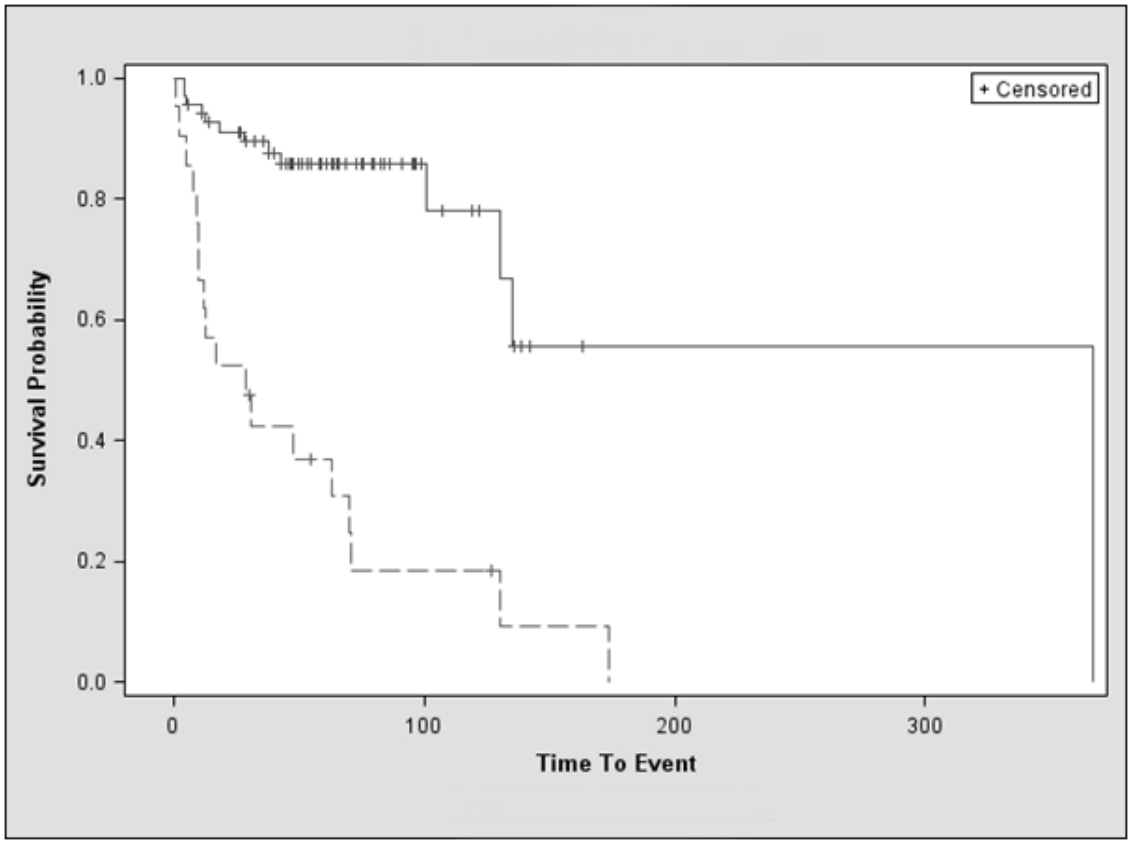


Figure 2.3


+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
Time To Event

References

1. Taylor DO, Stehlik J, Edwards LB, Aurora P, Christie JD, Dobbels F, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Heart Transplant Report-2009. *J Heart Lung Transplant* 2009;28(10):1007-22.

2. Korfer R, El-Banayosy A, Arusoglu L, Minami K, Breymann T, Seifert D, et al. Temporary pulsatile ventricular assist devices and biventricular assist devices. *Ann Thorac Surg* 1999;68(2):678-83.

3. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8(1):3-15.

4. Hosmer D. *Applied Logistic Regression*. New York: Wiley, 2000.

5. Lemon SC, Roy J, Clark MA, Friedmann PD, Rakowski W. Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. *Ann Behav Med* 2003;26(3):172-81.

6. Piantadosi S. *Clinical Trials: A Methodologic Perspective, Second Edition*. Hoboken, New Jersey: John Wiley & Sons Inc., 2005.

7. Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 2007;116(5):497-505.

8. Holman WL, Pae WE, Teutenberg JJ, Acker MA, Naftel DC, Sun BC, et al. INTERMACS: interval analysis of registry data. *J Am Coll Surg* 2009;208(5):755-61; discussion 61-2.

9. Fitzpatrick JR, 3rd, Frederick JR, Hsu VM, Kozin ED, O'Hara ML, Howell E, et al. Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. *J Heart Lung Transplant* 2008;27(12):1286-92.

10. Deng MC, Loebe M, El-Banayosy A, Gronda E, Jansen PG, Vigano M, et al. Mechanical circulatory support for advanced heart failure: effect of patient selection on outcome. *Circulation* 2001;103(2):231-7.

11. Rao V, Oz MC, Flannery MA, Catanese KA, Argenziano M, Naka Y. Revised screening scale to predict survival after insertion of a left ventricular assist device. *J Thorac Cardiovasc Surg* 2003;125(4):855-62.

12. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002;8(4):216-24.

13. Sinha A, Shahzad K, Latif F, Cadeiras M, Von Bayern MP, Oz S, et al. Peripheral blood mononuclear cell transcriptome profiles suggest T-cell immunosuppression after uncomplicated mechanical circulatory support device surgery. *Hum Immunol* 2010;71(2):164-9.

14. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J* 2008;155(5):883-9.

15. Copeland JG, Smith RG, Arabia FA, Nolan PE, Sethi GK, Tsau PH, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. *N Engl J Med* 2004;351(9):859-67.

16. Copeland JG, Smith RG, Bose RK, Tsau PH, Nolan PE, Slepian MJ. Risk factor analysis for bridge to transplantation with the CardioWest total artificial heart. *Ann Thorac Surg* 2008;85(5):1639-44.

Section III. Appendix (Handling Missing Data)

Missing data in our dataset

The dataset that was utilized in our study was originally created for clinical management of patients undergoing BIVAD implantation. Even though data were collected prospectively, the dataset is not as stringent as those used in randomized clinical trials. We retrospectively analyzed patient records, filled in most of the missing parameters in the dataset and verified the legitimacy of outliers. However, some datapoints were not available either because they were not well-documented in the medical records, certain laboratory testing was not obtained, or in cases where patient care immediately prior to BIVAD implantation occurred at an outside institute.

Types of missing data

The majority of datasets are not complete and will have missing values. It is paramount to try to understand the reason why the data are missing, as it can affect the way missing data are handled and can impact the final analysis[1-2]. Data can be missing completely at random (MCAR) if the probability for missingness is the same for all units. Data can be missing at random (MAR), which is more common than MCAR in clinical research. For MAR, the probability that a value is missing depends only on the available information in the dataset; hence, it would not be dependent on the measurements that would have been observed. In the majority of cases, it is very difficult to assure that missing data are MAR or MCAR. Since unobserved predictors or patterns of related missingness by definition cannot be observed if they exist, they cannot be definitively ruled out[1-2].

Conversely, missing data that depends on unobserved predictors must be explicitly modeled or else there will be bias in the analyses[1-2]. A difficult situation arises for data that are

missing dependent on the missing value itself. For related missing data, the values can be modeled by including other predictors to bring it closer to MAR.

Methods of handling missing data

There are several potential methods in handling missing data[1-2]. One method is to discard variables with missing values. One may argue that this is the best strategy if there is a large proportion of missing data for that variable. The major limitation is loss of information and this can be particularly undesirable if the discarded variable is an important one.

Another method is to remove the patients with the missing covariates from the analysis, which may work best when there are select individuals with a large amount of missing data[1-2]. This complete-case method may be preferred when there are only a few individuals to be removed as it would still preserve most subjects in the dataset. If there are too few complete cases, then this method is not reasonable. Problems can also arise if the units with missing values systematically differ from those with completely observed cases by biasing the complete-case analysis. This can be partially corrected with nonresponse weighting[1]. A related method to minimize case dropout is to carry out an available-case analysis, where different aspects of the analyses are studied with different subsets of patients[1-2]. However, each subset may not necessarily be consistent with each other and this can lead to its own problems.

A third strategy to deal with missing data is to estimate the missing observations[1-2]. There are different methods for this. A simple method would be mean imputation, where each missing value is replaced with the average of observed values for that variable. This can lead to distortion of the distribution for the variable and is not preferred. Subgroup means can be used instead, but may run into similar problems. Another method is least value carried forward, where the last value for a given variable is carried forward longitudinally[1-2]. This only applies if

multiple timepoints for a given variable are available and makes the assumption that the value is the same as the last observed value. It can become biased in cases of differential rates of missing data between comparator groups. A single regression estimate can also be attempted, but this would require that the regression fit appropriately. Further, these methods of estimating a single value will underestimate standard errors and overestimate test statistics as they do not address the fact that there is uncertainty in the missing values.

Another strategy is iterative regression imputation[1]. With this method, univariate methods of imputation are applied iteratively to variables with missingness. For example, if the variables with missingness are a matrix Y with columns Y(1)… Y(k) and the observed predictors are X, the missing Y values are imputed initially with a crude approach. Subsequently, the method is repeated with imputation of Y(1) given Y(2)… Y(k) and X; then Y(2) given Y(1), Y(3)… Y(k) and X, with looping until there is approximate convergence. Iterative regression has the benefit over standard multivariate imputation since each set of separate regression models can be evaluated. It is easier to allow for interactions given the separate models. The major problem with iterative regression is that each model must be consistent with each other and the final results will not correspond to any joint probability model across all the variables being imputed.

Rather than replacing each missing value with a single randomly imputed value, multiple imputation replaces each missing value with several imputed values that reflects uncertainty about the model[1-2]. This permits inclusion of sampling variability and uncertainty about regression coefficients in the model. Multiple imputation creates several imputed values for each missing value, each predicted from a slightly different model. Each set of imputed values are

used to form a completed dataset. A standard analysis is run on each dataset and then the inferences are combined across all datasets.

Missing data in our BIVAD study

In our study, most of the missing data were probably MCAR. Given the thorough nature of the datasets and controlled nature of clinical course (since the patients remained in the hospital), unobserved predictors are unlikely. Further, there is no reason to suspect related missing data since the variables were all demographic, clinical, or laboratory characteristics that can be obtained from medical charts and tests. However, given that some of the patients with incomplete data were from outside institutions referred to UCLA for a higher level of care, there may be a degree of nonrandomness, with a higher likelihood of missing data from these transferred patients. The proportion of patients that fell into this category were minimal and typically included patients who became unstable rapidly after transfer, since most patients have an extensive work-up after arrival and most of the datapoints would be available.

Given the relatively small sample size of our dataset, complete case analysis would not be ideal. In particular, with multivariate modeling, we did not want to eliminate any subjects. In our dataset, the missing data were not localized to certain individuals, so a complete case analysis would eliminate a large number of subjects.

We opted to use multiple imputation, with 10 imputed datasets. Each of the 10 completed datasets were analyzed sequentially, and the inferences were combined across all datasets to reach our final results.

References

1. Gelman A, Hill J. *Data Analysis Using Regression and Multilevel/Hierarchical Models* New York, NY: Cambridge University Press, 2006.

2. Piantadosi S. *Clinical Trials: A Methodologic Perspective, Second Edition*. Hoboken, New Jersey: John Wiley & Sons Inc., 2005.