Published in final edited form as:

J Card Surg. 2015 February ; 30(2): 194–200. doi:10.1111/jocs.12474.

Ventricular Assist Devices and Increased Blood Product Utilization for Cardiac Transplantation

Matthew L. Stone, M.D.^{*}, Damien J. LaPar, M.D., MSc.^{*}, Ehsan Benrashid, M.D.[†], David C. Scalzo, M.D.[§], Gorav Ailawadi, M.D.^{*}, Irving L. Kron, M.D.^{*}, James D. Bergin, M.D.[‡], Randal S. Blank, M.D. PhD.[§], and John A. Kern, M.D.^{*}

^{*}Division of Thoracic and Cardiovascular Surgery, University of Virginia Health System, Charlottesville, Virginia

[†]University of Virginia School of Medicine, Charlottesville, Virginia

[‡]Division of Cardiovascular Medicine, University of Virginia Health System, Charlottesville, Virginia

[§]Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia

Abstract

Background and Aim of Study—The purpose of this study was to examine whether blood product utilization, one-year cell-mediated rejection rates, and mid-term survival significantly differ for ventricular assist device (VAD) patients compared to non-VAD (NVAD) patients following cardiac transplantation.

Methods—From July 2004 to August 2011, 79 patients underwent cardiac transplantation at a single institution. Following exclusion of patients bridged to transplantation with VADs other than the HeartMate II[®] LVAD (n = 10), patients were stratified by VAD presence at transplantation: VAD patients (n = 35, age: 54.0 [48.0–59.0] years) vs. NVAD patients (n = 34, age: 52.5 [42.8–59.3] years). The primary outcomes of interest were blood product transfusion requirements, one-year cell-mediated rejection rates, and mid-term survival post-transplantation.

Results—Preoperative patient characteristics were similar for VAD and NVAD patients. NVAD patients presented with higher median preoperative creatinine levels compared to VAD patients (1.3 [1.1–1.6] vs. 1.1 [0.9–1.4], p = 0.004). VAD patients accrued higher intraoperative transfusion of all blood products (all p = 0.001) compared to NVAD patients. The incidence of clinically significant cell-mediated rejection within the first posttransplant year was higher in VAD compared to NVAD patients (66.7% vs. 33.3%, p = 0.02). During a median follow-up period of 3.2 (2.0, 6.3) years, VAD patients demonstrated an increased postoperative mortality that did not reach statistical significance (20.0% vs. 8.8%, p = 0.20).

Address for correspondence: John A. Kern, M.D., University of Virginia Health System, Division of Thoracic and Cardiovascular Surgery, P.O. Box 800679, Charlottesville, VA 22908-0679. Fax: +434 243-5781; jkern@virginia.edu.

Conflict of interest: The authors acknowledge no conflict of interest in the submission.

Presentation disclosure: Pilot study findings presented at the American Heart Association, Orlando, Florida, November 12–13, 2012.

Conclusions—During the initial era as a bridge to transplantation, the HeartMate II® LVAD significantly increased blood product utilization and one-year cell-mediated rejection rates for cardiac transplantation. Further study is warranted to optimize anticoagulation strategies and to define causal relationships between these factors for the current era of cardiac transplantation.

The promise of left ventricular assist device (LVAD) technology has provided an answer for the increasing number of patients with end-stage heart failure facing a limited number of donor hearts.^{1,2} While this therapy is the current treatment standard for bridge to transplantation, debate persists regarding the effect of LVAD support on outcomes following heart transplantation.³

Blood product utilization is a specific concern for the HeartMate II® (Thoratec Corporation, Pleasanton, CA, USA) device with the inherent requirement for pharmacologic anticoagulation. Patients often present for transplantation at a therapeutic level of anticoagulation, with no established resuscitative protocols for reversal. In addition, the potential effects of LVAD support on inherent pathways of coagulation and posttransplant immune tolerance remain unknown.

Recent studies have established increasing blood product volume as an independent predictor of increased postoperative mortality following both coronary artery bypass grafting and LVAD implantation.^{4,5} Implications for blood product utilization in cardiac transplantation patients bridged with LVAD support remain undefined. The purpose of this study was to evaluate blood product resuscitation for patients bridged to transplant with LVAD support at a high-volume, single-center institution. In addition, incidences of one-year cell-mediated rejection and mid-term survival were reviewed to determine potential associations with pretransplant HeartMate II® LVAD support within the initial era of mechanical circulatory support as a bridge-to-transplantation.

PATIENTS AND METHODS

A retrospective medical and surgical record review was performed for all adult cardiac transplantation recipients at The University of Virginia Health System from July 2004 to August 2011. Appropriate Institutional Review Board approval was obtained. Patients were stratified according to the presence of LVAD support at the time of transplantation: VAD patients (n=35) and non-VAD (NVAD) patients (n=34). The primary outcome was the volume of intraoperative blood product resuscitation in patients with and without preoperative LVAD support. Preoperative demographic variables and comorbid conditions were classified utilizing the Society of Thoracic Surgeons (STS) definitions.⁶ Preoperative pharmacologic anticoagulation agents, coagulation panels, and percent reactive T and B lymphocytes pretransplantation were reviewed for each patient. Patients with percent reactive antibody levels greater than 10% were considered to be presensitized.⁷ Intraoperative variables for the transplantation operation were reviewed in coordination with pre- and postoperative markers of resuscitation. Intraoperative blood products were temporally defined by administration at the time of anesthesia induction until the time of patient arrival in the postoperative intensive care unit. Recombinant factor VIIa administrations both during the operation and immediate period of reexploration were

included within the reported intraoperative blood products. Blood product transfusions were administered at the discretion of care providers throughout the operative and postoperative resuscitation periods. Secondary outcomes included posttransplant atrial fibrillation, renal failure, stroke, requirement for reexploration, length of stay, in-hospital post-transplant infection, one-year cell-mediated rejection status, and mortality. Postoperative blood products were administered during the period following arrival in the intensive care unit and postoperative discharge or resultant mortality. Postoperative infections were defined by definitive radiographic criteria or culture-positive events during the hospital admission.

All patients received standardized immunosuppression during the study period. Methylprednisolone (1 g) and azathioprine (2.5 mg/kg) were administered during the operative phase of the transplantation operation. Basiliximab (20 mg) was used as the induction agent in all patients following July 2010. Immediately following transplant, antithymocyte globulin was administered for lympholytic induction in addition to solumedrol. On postoperative day 1, patients were started on sirolimus or azathioprine prior to 2006 and mycophenolate mofetil or azathioprine from 2006 onward. Patients were also given prednisone or solumedrol. Tacrolimus was initiated on postoperative days 2–4 dependent on patient recovery status with a dosing titration to maintain a target blood concentration of 8–10 ng/mL. Antithymocyte globulin was continued until tacrolimus concentration levels were greater than 5 ng/mL. Results from standardized monthly myocardial biopsy specimens within the first year posttransplant were reviewed from each cohort and were classified according to the standardized International Society for Heart and Lung Transplantation (ISHLT) nomenclature, revised in 2005.⁸ Patients with grade 2R and higher were classified as having acute cell-mediated rejection. Biopsy results prior to the revision of the classification system in 2005 were converted to the current nomenclature for standardization such that grade 3A and higher in the historic classification system were designated as acute cellular rejection.⁸ Follow-up mortality data were collected from the institutional central data repository and represented the patient's last visit to the study institution or a match to the State of Virginia Department of Health Death Registry. Categorical variables were evaluated utilizing the two-sided Fisher's exact test and continuous variables were analyzed by the Mann-Whitney *U* test. The log-rank Mantel-Cox test was used to evaluate mortality differences for NVAD and VAD patients and Kaplan-Meier curves were created for each group. Data analyses were performed using SPSS software, version 17 (SPSS, Inc.) and GraphPad Software, 2012.

RESULTS

Seventy-nine patients underwent cardiac transplantation during the study period. Ten patients were bridged to transplantation with devices other than the HeartMate II® LVAD and were therefore excluded from the analysis (HeartMate® XVE, n=9; HeartMate® IP LVAS, n=1). Ventricular assist device support was provided by the HeartMate II® LVAD in 35 (50.7%) patients, and 34 (49.3%) patients comprised the nonbridged cohort. Preoperative demographics, operative characteristics, and postoperative resuscitation variables are presented in Table 1. Automatic implantable cardioverter defibrillators (AICD) were more common in VAD patients (91.4% vs. 55.9%, *p* = 0.001). NVAD patients more commonly received Status 1 cardiac transplantation (61.8% vs. 2.9%, *p* < 0.001). At the time of

transplantation, VAD patients were more commonly receiving aspirin (94.3% vs. 44.1%, $p < 0.001$) and Coumadin® (97.1% vs. 50.0%, $p < 0.001$), while clopidogrel usage demonstrated no difference between groups ($p = 0.06$). VAD patients exhibited lower preoperative creatinine values (1.1 [0.9–1.3] vs. 1.3 [1.1–1.6], $p = 0.003$) and higher INR (2.0 [1.6–2.4] vs. 1.4 [1.1–2.2], $p = 0.003$) in comparison to NVAD patients. Prior to transplantation, one patient within in NVAD cohort ($n=1/34$, 3.8%) and two patients ($n=2/35$, 5.7%) within the VAD cohort demonstrated percent reactive antibody levels consistent with B cell sensitization, with one VAD patient having both B and T cell presensitization ($p > 0.99$). Operative characteristics were similar between groups, while VAD patients had higher initial postoperative creatinine levels compared to NVAD patients ($p = 0.03$).

VAD patients demonstrated significantly higher median intraoperative blood product resuscitation volumes in comparison to NVAD patients: packed red blood cells (3.0 vs. 0.0 units, $p < 0.001$), fresh frozen plasma (10.0 vs. 3.0 units, $p < 0.001$), platelets (2.0 vs. 1.0 units, $p = 0.001$), and cryoprecipitate (1.0 vs. 0.0, $p < 0.001$) (Table 2). In addition, more VAD patients received recombinant factor VIIa (34.3% vs. 2.9%, $p = 0.001$) and aminocaproic acid (100% vs. 52.9%, $p < 0.001$) in comparison to NVAD patients. Aprotinin was administered to more NVAD patients (41.2% vs. 0.0%, $p < 0.001$), representing a change in our routine resuscitation practice during the study period. No significant differences were demonstrated in postoperative blood product resuscitation volumes (all $p > 0.05$).

The incidences of atrial fibrillation ($p = 0.67$), renal failure ($p = 0.81$), hemodialysis requirement ($p = 0.54$), and stroke ($p > 0.99$) were comparable between VAD and NVAD patients posttransplantation (Table 3). VAD patients had a two-fold higher incidence of postoperative reexploration for bleeding compared to NVAD patients that did not achieve statistical significance ($p = 0.34$). Postoperative length of stay ($p = 0.30$) and total intensive care unit (ICU) hours ($p = 0.10$) were similar between groups. In addition, despite a higher incidence of composite (25.7 vs. 14.7%, $p = 0.37$) and multi-site infection (11.4 vs. 0.0%, $p = 0.11$) in VAD compared to NVAD patients, these incidences were not statistically different between groups.

Monthly myocardial tissue biopsy results were available for 68 of 69 (98.6%) patients within the first postoperative year. Following removal of presensitized patients (VAD, $n=2$; NVAD, $n=1$) and patients with rejection-free mortality within the first posttransplant year (VAD, $n=5$; NVAD, $n=3$), acute cell-mediated rejection rates were significantly higher in VAD compared to NVAD patients (66.7 vs. 33.3%, $p = 0.02$). Antibody-mediated rejection panels were not routinely applied during the study period and no patients undergoing such evaluation demonstrated isolated non-cellular antibody-mediated rejection. Posttransplant survival analysis over a 3.2 (2.0, 6.3) year median follow-up period demonstrated a marked divergence and increased early mortality for VAD compared to NVAD patients that did not reach statistical significance during the long-term follow-up period (20.0% vs. 8.8%, log-rank $p = 0.20$) (Fig. 1).

COMMENT

Left ventricular assist device support provides a life-sustaining bridge to transplantation for many with end-stage heart failure. Technologic advancement in mechanical circulatory support has supported a significant decline in mortality for patients awaiting heart transplantation from 20.7% to 13.7% over the past 12 years.⁹ Despite this promising trend and improved short-term graft survival, sustained long-term graft function remains poor with an estimated 53% of patients maintaining reliable cardiac function at 10 years.⁹ While this figure demonstrates significant potential for improvement, graft function outcomes are slowly improving. Proposed VAD-induced sensitization and the resuscitative demands of the transplantation operation in the setting of anticoagulation remain limitations to the progress of posttransplantation outcomes.

The current study demonstrates that VAD support necessitated a significantly increased resuscitative demand during the transplantation operation. Intraoperative blood product resuscitation volume has been demonstrated to be a significant risk factor for postoperative morbidity, mortality, and resource utilization in cardiac surgery and critical care medicine.^{5,10} A prior prospective study has demonstrated increased blood product resuscitation as an independent predictor of both short- and long-term mortality following cardiac surgery.¹¹ Despite comparable 30-day survival for the VAD and NVAD patients noted in the present study, a divergence to lower mid-term survival is presented for the VAD compared to NVAD cohort post-transplantation. While VAD support has significantly increased the number of potential transplantation recipients, no such survival benefit has been demonstrated in this and other series. This finding supports consideration of additional factors that may be limiting rejection-free survival posttransplantation. The finding that VAD support dramatically increases intraoperative blood product resuscitation identifies a potential area for further research to optimize patient coagulation status during the transplantation operation.

Sensitization is associated with an increased risk of longer waiting list time, increased acute rejection, and higher posttransplantation mortality.^{12,13} Debate persists regarding the effect of pretransplant left ventricular assist device support on the incidence of presensitization and postcardiac transplant acute cellular rejection.^{13–17} In comparison to nonbridged patients, prior studies have demonstrated that 20–66% of LVAD patients are sensitized prior to transplantation in contrast to only 5–6% of nonbridged recipients.^{13,14,16} Increasing rates of sensitization in patients bridged-to-transplantation with LVAD support have been demonstrated to be directly correlated to the duration of LVAD support.¹⁸ These findings have supported a significant research commitment to define optimal pretransplant immunomodulatory therapies, proposing potential immune-activating properties of the VAD.¹³ In addition to this proposed mechanism for the increased incidence of human leukocyte antigen (HLA) antibodies in VAD patients, a significant percentage of patients without presensitization develop rejection. Smaller series have demonstrated a 28% incidence of HLA antibody development in patients not presensitized prior to cardiac transplantation, and have suggested increased blood product resuscitation as a potential etiology for this finding.¹⁶ Additional study of pretransplantation panel reactive antibody (PRA) levels and type of blood product transfused have demonstrated an association

between increasing platelet transfusions and elevated PRA levels.¹⁹ This study demonstrates a much lower rate of pretransplant sensitization for VAD patients than prior reports.¹⁷ While prior studies have focused on blood product and platelet transfusions during the period six months prior to transplantation and the LVAD implantation operation until outcome, our series demonstrates a significant intraoperative resuscitation requirement for patients undergoing cardiac transplantation following a period of LVAD support. These findings suggest that resuscitative and anticoagulation reversal strategies are promising areas for further research to limit the volume of blood product resuscitation for patients bridged-to-transplantation.

It is suggested that blood transfusions result in the induction of alloantibodies and the activation of alloreactive T lymphocytes, while also downregulating the alloimmune response through unknown mechanisms.^{20,21} Allogeneic blood transfusion is an established mechanism for both presensitization and complement-mediated acute graft rejection.²² No protective effect against cellular or antibody-mediated rejection has been demonstrated in patients receiving blood products within the first two weeks posttransplantation.²³ Other experiences have demonstrated that cellular blood product transfusions are associated with less alloimmunization and acute rejection in VAD patients bridged-to-transplantation.^{18,23,24} In these series, the avoidance of perioperative leukocyte-filtered cellular blood products has been demonstrated to have no effect on HLA sensitization, with less packed red blood cells demonstrating the greatest protective advantage against sensitization.¹⁸ The lack of protection afforded by avoidance of transfusion supports additional factors that may promote sensitization including immunogenic components of the LVAD, soluble antigen in fresh frozen plasma, or latent and undetectable sensitization in critically ill or anergic patients.²⁵ While prior study has suggested no significant effect of the type of LVAD (continuous-flow LVAD vs. nonpulsatile flow LVAD) on posttransplantation allograft survival, paracorporeal biventricular support has been shown to independently increase mortality following transplantation.^{26,27} This study implicates LVAD support prior to transplantation and the associated increased blood product resuscitation volume as a potential etiology for increasing post-transplantation rejection.^{28,29}

Several limitations are recognized within the presented findings. First, the retrospective study design introduces the potential for selection bias. To control for this limitation, preoperative variables and postoperative outcomes were determined *a priori* and all heart transplantation patients at our institution during the study period were included in the analysis. The sample size is small and this limitation should be considered in the interpretation of presented findings. As a tertiary center, mortality rates for patients awaiting transplantation on medical therapy alone could not be determined and it can be inferred that the VAD cohort included patients that would have otherwise died prior to transplantation, thus limiting comparisons between groups. While this is a critical consideration, the present study does indicate that historical transplantation protocols for non-VAD patients should be revised for the current era as resuscitative demands and posttransplantation outcomes are different. Additionally, eight patients within the NVAD cohort and one patient within the VAD cohort had no record of pretransplant percent reactive antibody levels. These patients were included in the analysis, as no patient without recorded pretransplant PRA levels

developed posttransplantation cell-mediated rejection, thus not altering the aim or conclusions of the present analysis. The present study is also limited to one-year posttransplantation and no definitive conclusions can be inferred regarding long-term graft function. The incidence of acute cellular rejection following cardiac transplantation is estimated to peak within one month posttransplant, followed by a low constant risk of rejection after 12 months.³⁰ With this consideration and given the consistent maintenance of standardized follow-up, a one-year period of posttransplant rejection surveillance was selected. Additionally, the observed temporal differences in mortality demonstrate the most significant divergence within the first six months following transplantation. This finding may suggest a higher prevalence of primary graft dysfunction rather than antibody-mediated rejection in VAD compared to non-VAD patients. Further study is warranted to delineate these differences. In addition, the current study establishes an association between VAD support and posttransplant rejection and does not define a causal relationship between these variables. The use of aprotinin during the study period also offers a potential explanation for the observed differences in cell-mediated rejection, as this agent has been demonstrated in clinical study to decrease ischemia-reperfusion injury within the myocardium during cardiopulmonary bypass.³¹ Further, study within heart failure has demonstrated augmented regulation of proinflammatory pathways within cellular immunity, and it can be postulated that the rehabilitative effect of VAD support may facilitate a reversal of this deleterious proinflammatory environment associated with heart failure pretransplantation.³² We acknowledge that the stated differences in posttransplantation immunosuppression may have an effect on cell-mediated rejection, yet this potential effect was minimized by a universal adherence to the noted transplantation protocols. Additionally, we cannot conclusively comment on the effect of pretransplant VAD support duration and the temporal effect on PRA screening as such historical testing was not universally available in a tertiary care setting. Furthermore, a study in heart failure patients has recently adopted the practice of posttransplantation donor-specific antibody analysis yet these data were not available for the study period and may have additional implications for posttransplantation graft function. These practice patterns warrant further assessment to determine optimal and fiscally responsible regimens for the pretransplantation cross-match process and posttransplantation surveillance. Additionally, donor characteristics were not universally available and therefore not included in the analysis yet should be considered. We cannot exclude the presence of a confounding variable that may predispose patients to the development of posttransplant cell-mediated rejection. Rigorous data collection and analysis have minimized the likelihood of such an effect.¹⁵ Finally, there were no defined triggers for blood product transfusions, which were left to the discretion of the individual providers.

Acknowledgments

Grant sponsor: NIH T32 (ILK, MLS); **Grant number:** HL007849–10

REFERENCES

1. Frazier OH, Rose EA, McCarthy P, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. *Ann Surg*. 1995; 222:327–336. discussion 336–328. [PubMed: 7677462]

2. John R, Pagani FD, Naka Y, et al. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: Impact of duration of left ventricular assist device support and other variables. *J Thorac Cardiovasc Surg.* 2010; 140:174–181. [PubMed: 20447659]
3. Urban M, Pirk J, Dorazilova Z, et al. How does successful bridging with ventricular assist device affect cardiac transplantation outcome. *Interact Cardiovasc Thorac Surg.* 2011; 13:405–409. [PubMed: 21788304]
4. Paone G, Brewer R, Theurer PF, et al. Preoperative predicted risk does not fully explain the association between red blood cell transfusion and mortality in coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2012; 143:178–185. [PubMed: 22014719]
5. Schaffer JM, Arnaoutakis GJ, Allen JG, et al. Bleeding complications and blood product utilization with left ventricular assist device implantation. *Ann Thorac Surg.* 2011; 91:740–747. discussion 747-749. [PubMed: 21352991]
6. Surgeons SoT. STS Thoracic Surgery Database Version 22. 2012
7. Rasmusson K, Brunisholz K, Budge D, et al. Peripartum cardiomyopathy: Post-transplant outcomes from the United Network for Organ Sharing Database. *J Heart Lung Transplant.* 2012; 31:180–186. [PubMed: 22305380]
8. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant.* 2005; 24:1710–1720. [PubMed: 16297770]
9. Services USDoHaH. Annual data report: Scientific registry of transplant recipients. Minneapolis, MN: 2011.
10. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med.* 1999; 340:409–417. [PubMed: 9971864]
11. Bhaskar B, Dulhunty J, Mullany DV, et al. Impact of blood product transfusion on short and long-term survival after cardiac surgery: More evidence. *Ann Thorac Surg.* 2012; 94:460–467. [PubMed: 22626751]
12. Smith JD, Danskine AJ, Laylor RM, et al. The effect of panel reactive antibodies and the donor specific cross-match on graft survival after heart and heart-lung transplantation. *Transpl Immunol.* 1993; 1:60–65. [PubMed: 8081763]
13. John R, Lietz K, Schuster M, et al. Immunologic sensitization in recipients of left ventricular assist devices. *J Thorac Cardiovasc Surg.* 2003; 125:578–591. [PubMed: 12658200]
14. Pagani FD, Dyke DB, Wright S, et al. Development of anti-major histocompatibility complex class I or II antibodies following left ventricular assist device implantation: Effects on subsequent allograft rejection and survival. *J Heart Lung Transplant.* 2001; 20:646–653. [PubMed: 11404170]
15. Gonzalez-Stawinski GV, Cook DJ, Chang AS, et al. Ventricular assist devices and aggressive immunosuppression: Looking beyond overall survival. *J Heart Lung Transplant.* 2006; 25:613–618. [PubMed: 16730565]
16. McKenna DH Jr, Eastlund T, Segall M, et al. HLA alloimmunization in patients requiring ventricular assist device support. *J Heart Lung Transplant.* 2002; 21:1218–1224. [PubMed: 12431496]
17. Tsau PH, Arabia FA, Toporoff B, et al. Positive panel reactive antibody titers in patients bridged to transplantation with a mechanical assist device: Risk factors and treatment. *ASAIO J.* 1998; 44:M634–M637. [PubMed: 9804512]
18. Drakos SG, Stringham JC, Long JW, et al. Prevalence and risks of allosensitization in HeartMate left ventricular assist device recipients: The impact of leukofiltered cellular blood product transfusions. *J Thorac Cardiovasc Surg.* 2007; 133:1612–1619. [PubMed: 17532964]
19. Massad MG, Cook DJ, Schmitt SK, et al. Factors influencing HLA sensitization in implantable LVAD recipients. *Ann Thorac Surg.* 1997; 64:1120–1125. [PubMed: 9354538]
20. Vandekerckhove BA, Datema G, Zantvoort F, et al. An increase of donor-specific T helper precursors resulting from blood transfusions. *Transplantation.* 1990; 49:987–991. [PubMed: 2139988]
21. Claas FH, Roelen DL, van Rood JJ, et al. Modulation of the alloimmune response by blood transfusions. *Transfus Clin Biol.* 2001; 8:315–317. [PubMed: 11499985]

22. Qian Z, Lee CY, Murata K, et al. Antibody and complement mediated injury in transplants following sensitization by allogeneic blood transfusion. *Transplantation*. 2006; 82:857–864. [PubMed: 17038898]
23. Kotter JR, Drakos SG, Horne BD, et al. Effect of blood product transfusion-induced tolerance on incidence of cardiac allograft rejection. *Transplant Proc*. 2010; 42:2687–2692. [PubMed: 20832570]
24. Fernandez FG, Jaramillo A, Ewald G, et al. Blood transfusions decrease the incidence of acute rejection in cardiac allograft recipients. *J Heart Lung Transplant*. 2005; 24:S255–S261. [PubMed: 15993782]
25. Stringham JC, Bull DA, Fuller TC, et al. Avoidance of cellular blood product transfusions in LVAD recipients does not prevent HLA allosensitization. *J Heart Lung Transplant*. 1999; 18:160–165. [PubMed: 10194040]
26. Alba AC, McDonald M, Rao V, et al. The effect of ventricular assist devices on long-term post-transplant outcomes: A systematic review of observational studies. *Eur J Heart Fail*. 2011; 13:785–795. [PubMed: 21551162]
27. Lund LH, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: Thirtieth official adult heart transplant report–2013; focus theme: Age. *J Heart Lung Transplant*. 2013; 32:951–964. [PubMed: 24054804]
28. Healy AH, Mason NO, Hammond ME, et al. Allograft rejection in patients supported with continuous-flow left ventricular assist devices. *Ann Thorac Surg*. 2011; 92:1601–1607. discussion 1607. [PubMed: 21944258]
29. Baran DA, Gass AL, Galin ID, et al. Lack of sensitization and equivalent post-transplant outcomes with the Novacor left ventricular assist device. *J Heart Lung Transplant*. 2005; 24:1886–1890. [PubMed: 16297796]
30. Kubo SH, Naftel DC, Mills RM, et al. Risk factors for late recurrent rejection after heart transplantation: A multiinstitutional, multivariable analysis. *J Heart Lung Transplant*. 1995; 14:409–418. [PubMed: 7654724]
31. Karaca P, Konuralp C, Enc Y, et al. Cardioprotective effect of aprotinin on myocardial ischemia/reperfusion injury during cardiopulmonary bypass. *Circ J*. 2006; 70:1432–1436. [PubMed: 17062966]
32. Do, eZ; Fukumoto, Z.; Sugimura, Y., et al. Rho-kinase activation in patients with heart failure. *Circ J*. 2013; 77:2542–2550. [PubMed: 23883874]

Figure 1.
Postoperative follow-up Kaplan-Meier survival analysis for VAD and NVAD patients following transplantation.

TABLE 1

Preoperative Demographic Factors, Pretransplant Sensitization Incidences, Operative Variables, and Postoperative Markers of Resuscitation for Patients with (VAD) and Without (NVAD) HeartMate II® LVAD Support as a Bridge to Transplantation. Data Presented as n(%) or Median (25–75%)

Preoperative Variable	VAD n = 35	NVAD n = 34	P-value
Male gender	27, 77.1%	26, 76.5%	>0.99
Age (years)	54.0 [48.0–59.0]	52.5 [42.8–59.3]	0.48
Cerebrovascular disease	6, 17.1%	2, 5.9%	0.26
Chronic lung disease	5, 14.3%	6, 17.6%	0.75
Diabetes mellitus	10, 28.6%	10, 29.4%	>0.99
Hypertension	14, 40.0%	17, 50.0%	0.47
Infectious endocarditis	1, 2.9%	0, 0.0%	>0.99
Renal failure	9, 25.7%	7, 20.6%	0.78
Intra-aortic balloon pump	0, 0.0%	2, 5.9%	0.24
Prior CABG	6, 17.1%	5, 14.7%	>0.99
Prior valve replacement	6, 17.1%	1, 2.9%	0.11
Prior PCI	4, 11.4%	9, 26.5%	0.13
Prior pacemaker	26, 74.3%	22, 64.7%	0.44
Prior AICD	32, 91.4%	19, 55.9%	0.001
Status 1	1, 2.9%	21, 61.8%	<0.001
Status 2	34, 97.1%	13, 38.2%	
Aspirin	33, 94.3%	15, 44.1%	<0.001
Coumadin	34, 97.1%	17, 50.0%	<0.001
Clopidogrel	1, 2.9%	6, 17.6%	0.06
ACEI or ARB	5, 14.3%	18, 52.9%	0.001
Preoperative creatinine (mg/dL)	1.1 [0.9–1.3]	1.3 [1.1–1.6]	0.003
Preoperative INR	2.0 [1.6–2.4]	1.4 [1.1–2.2]	0.003
Preoperative hematocrit (%)	37.0 [34.0–40.2]	38.2 [32.0–41.7]	0.66
Ejection fraction, EF (%)	20.0 [17.0–23.0]	17.0 [15.0–30.0]	0.27
Pretransplant B cell sensitization *	2, 5.7%	1, 3.8%	>0.99
Pretransplant T cell sensitization *	1, 2.9%	0, 0.0%	>0.99
Operative variable			
Cross clamp time, min	68.0 [62.0–84.0]	80.0 [66.0–96.0]	0.17
Perfusion time, min	135.0 [115.0–173.0]	123.5 [105.5–150.0]	0.16
Postoperative variable			
Postoperative creatinine (mg/dL)	1.9 [1.5–2.7]	1.5 [1.1–2.2]	0.03
Postoperative hematocrit (%)	30.0 [25.0–32.0]	29.0 [25.8–34.0]	0.50

CABG, Coronary artery bypass grafting; PCI, percutaneous coronary intervention; AICD, automated implantable cardioverter-defibrillator; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; INR, international normalized ratio; EF, ejection fraction; VAD, ventricular assist device. One VAD patient had both T and B cell pretransplant sensitization.

* Presensitization data availability: NVAD (n=26), VAD (n=35).

TABLE 2

Intraoperative and Postoperative Blood Product Resuscitation Volumes for Patients With (VAD) and Without (NVAD) HeartMate IIW LVAD Support as a Bridge to Transplantation. Data Presented as n (%) or Median (25–75%)

Intra-operative Blood Product Component	VAD n = 35	NVAD n = 34	P-value
Packed red blood cells (units)	3.0 [2.0–7.0]	0.0 [0.0–2.0]	<0.001
Fresh frozen plasma (units)	10.0 [6.0–14.0]	3.0 [1.8–5.3]	<0.001
Platelets (units)	2.0 [1.0–2.0]	1.0 [1.0–1.3]	0.001
Cryoprecipitate (units)	1.0 [1.0–2.0]	0.0 [0.0–0.0]	<0.001
Cell saver (mL)	1192.0 [450–1608.3]	1096.5 [969.3–1600.0]	0.97
Recombinant factor VIIa	12, 34.3%	1, 2.9%	0.001
Vitamin K	15, 42.9%	5, 14.7%	0.02
Amikar	35, 100.0%	18, 52.9%	<0.001
Aprotinin	0, 0.0%	14, 41.2%	<0.001
Postoperative blood product component			
Packed red blood cells (units)	4.0 [2.0–7.0]	2.0 [1.0–4.0]	0.06
Fresh frozen plasma (units)	2.0 [0.0–6.0]	2.0 [1.5–5.0]	0.18
Platelets (units)	1.0 [0.0–2.0]	1.0 [0.0–1.0]	0.16
Cryoprecipitate (units)	0.0 [0.0–1.0]	0.0 [0.0–0.0]	0.28

TABLE 3

Postoperative Outcomes and Incidences of One-Year Cell-Mediated Rejection for VAD and NVAD Patients Following Cardiac Transplantation. Data Presented as n(%) or Median (25–75%)

Variable	VAD n = 35	NVAD n = 34	P-value
Atrial fibrillation	4, 11.4%	2, 6.1%	0.67
Renal failure	12, 34.3%	13, 38.2%	0.81
Hemodialysis requirement	5, 14.3%	7, 20.6%	0.54
Stroke	0, 0.0%	0, 0.0%	>0.99
Requirement for reexploration	8, 22.9%	4, 11.8%	0.34
Postoperative length of stay (days)	12.0 [11.0–15.0]	11.5 [9.0–15.0]	0.30
Total length of stay (days)	12.0 [11.0–15.0]	18.0 [11.0–28.0]	0.03
Total ICU hours	152.0 [116.0–218.0]	132.0 [99.8–170.0]	0.10
In-hospital posttransplant infection *	9, 25.7%	5, 14.7%	0.37
30-day mortality	3, 8.6%	3, 8.8%	>0.99
Follow-up mortality	7, 20.0%	2, 5.9%	0.2
One-year cell-mediated rejection **	18, 66.7%	10, 33.3%	0.02

ICU, intensive care unit; VAD, ventricular assist device.

* VAD, multisite (n=4); bacteremia, urinary tract, pneumonia, *C. difficile* (all n=1); NVAD, pneumonia (n=3), urinary tract (n=2).

** VAD, n=27; NVAD, n=30. Patients removed for presensitization (VAD, n=2; NVAD, n=1), one-year mortality (VAD, n=5; NVAD, n=3), and absence of biopsy follow-up (VAD, n=1).