The impact of bridge-to-transplant ventricular assist device support on survival after cardiac transplantation

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Objective: To determine the impact of bridge-to-transplant ventricular assist device support on survival after cardiac transplantation.

Methods: From January 1, 1993, to April 30, 2009, a total of 525 cardiac transplants were performed. Ventricular assist devices were placed as a bridge to transplant in 110 patients. We focused our analysis on the 2 most common causes of end-stage heart failure requiring transplantation: idiopathic dilated cardiomyopathy ($n = 201$) and coronary artery disease ($n = 213$). Data including gender, age, date of transplant, cause of heart failure, prior heart transplant, placement of a ventricular assist device, type of ventricular assist device, and panel-reactive antibody sensitization were analyzed to derive Kaplan–Meier survival probabilities and multivariable Cox regression models.

Results: In patients with idiopathic dilated cardiomyopathy who received a ventricular assist device as a bridge to transplant, survival was decreased at 1 year ($P = .008$) and 5 years ($P = .019$), but not at 10 years, posttransplant. In patients with coronary artery disease, the use of a ventricular assist device as a bridge to transplant did not influence survival at 1, 5, and 10 years posttransplant. In patients with idiopathic dilated cardiomyopathy who received a Heartmate I (Thoratec Corp, Pleasanton, Calif) ventricular assist device as a bridge to a cardiac transplant, elevation in the pretransplant panel-reactive antibody correlated with a decrease in long-term survival.

Conclusion: In patients with idiopathic dilated cardiomyopathy, placement of a Heartmate I ventricular assist device as a bridge to a cardiac transplant is associated with an elevation in the pretransplant panel-reactive antibody and a decrease in 1- and 5-year survivals after cardiac transplantation. (*J Thorac Cardiovasc Surg* 2010;140:169-73)

Cardiac transplantation remains the gold standard for the treatment of end-stage heart failure. The major factor limiting the number of heart transplants performed in the United States today is the availability of donor hearts. Ventricular assist devices (VADs) allow for the successful bridging of patients who otherwise would not be expected to survive long enough to receive a heart transplant.¹⁻³ Previous studies have reported equivalent survival at 1, 2, and 5 years in patients who were bridged with a VAD compared with the

broader population of heart transplant recipients.^{4,5} More recent studies, however, have found that bridge-to-transplant VADs are associated with an increase in mortality within 6 months and more than 5 years after cardiac transplantation.⁶ We examined our experience with the use of bridge-to-transplant VADs, with particular attention to heart failure cause, to determine their impact on survival after cardiac transplantation.

MATERIALS AND METHODS

This study was reviewed and approved by the institutional review board at the University of Utah Health Sciences Center. All patients undergoing cardiac transplantation from January 1, 1993, to April 30, 2009, in the Utah Transplant Affiliated Hospitals (UTAH) heart transplant program were included in the analysis. The UTAH heart transplant program had its inception in 1985. The start date for this analysis is 1993 because this was the inception of the VAD program within the UTAH heart transplant program. Patients undergoing heart–lung transplantation were excluded from the analysis. Specific data regarding date of transplant, mortality, cause of death, gender, age, cause of heart failure, prior heart transplant, United Network for Organ Sharing status, previous cardiac surgery, placement of a VAD, type of VAD, transfusion of cellular blood products, duration of VAD support, panel-reactive antibody (PRA) sensitization, use of pretransplant and perioperative plasmapheresis for desensitization in patients with a PRA more than 90%, immunosuppressive agents, immunosuppression

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Abbreviations and Acronyms

CAD	= coronary heart disease
CI	= confidence interval
HR	= hazard ratio
IDC	= idiopathic dilated cardiomyopathy
LVAD	= left ventricular assist device
PRA	= panel-reactive antibody
UTAH	= Utah Transplant Affiliated Hospitals
VAD	= ventricular assist device

protocols, incidence and severity of acute cellular and humoral rejection posttransplant, and incidence of cardiac allograft vasculopathy were collected for each patient. Patients who did and did not receive a VAD as a bridge to a cardiac transplant were compared with regard to each of the above listed variables with a 2-sample *t* test for continuous variables and a chi-square or Fisher's exact test, as appropriate, for categorical variables. These 2 groups were then analyzed using multivariable Cox regression. Only 3 patients had 2 transplants in the dataset, which was not enough to introduce lack of independence among the observations. Therefore, there was no need to account for lack of independence with a shared frailty Cox regression, which is the Cox regression analog of a mixed-effects linear regression. On the basis of the limited sample size of this study, multivariable Cox regression rather than propensity score matching was used to control for the potentially confounding variables in the analysis. For this particular analysis, the use of propensity score matching in the limited sample size of the study would have required loose matching to maintain an adequate sample size, leaving several residual confounding variables in the analysis.

Given that the posttransplant follow-up was measured as a continuous variable, accurate to a day, rather than a predetermined time interval such as a year, the Kaplan–Meier approach was used to obtain survival estimates for specific time points, rather than the actuarial method, which is designed for data aggregated by time interval.

The data were analyzed to derive Kaplan–Meier survival probabilities and to fit the multivariable shared frailty Cox regression models. Hazard ratios (HRs), confidence intervals (CIs), and *P* values were calculated for each variable. The primary end point of the analysis was the impact of pretransplant VAD support on patient survival after cardiac transplantation. The secondary end point of the analysis was the impact of pretransplant PRA on patient survival after cardiac transplantation. Data are reported as the mean $\pm$ standard deviation.

RESULTS

From January 1, 1993, to April 30, 2009, a total of 525 cardiac transplants were performed in the UTAH heart transplant program. The most common indications for transplantation were ischemic cardiomyopathy as a result of coronary artery disease (CAD, *n* = 213) and idiopathic dilated cardiomyopathy (IDC, *n* = 201) (Table 1). Among the cardiac transplants, VADs were placed as a bridge to transplant in 110 patients. Among the 110 patients receiving VADs, the cause of heart failure was CAD (*n* = 59) or IDC (*n* = 45) in 104 patients (Table 1). We therefore focused our analysis on the patients with a history of CAD and IDC because these 2 subgroups had sufficient numbers of patients with and without VADs for statistical analysis.

For the entire cardiac transplant program, Kaplan–Meier survival probability at 1, 5, 10, and 15 years posttransplant was 90%, 77%, 59%, and 44% respectively. In patients with CAD, the use of a VAD as a bridge to transplant did not influence survival at 1, 5, and 10 years posttransplant. In patients with IDC, the use of a VAD as a bridge to transplant was associated with a decrease in Kaplan–Meier survival probability at 1 year (84% vs 96%, *P* = .008) and 5 years (66% vs 82%, *P* = .019) posttransplant (Table 2, Figure 1). Specifically, the use of a Heartmate I (Thoratec Corp, Pleasanton, Calif) VAD was associated with a decrease in survival in patients with IDC at 1 year (HR = 4.33; CI, 1.46–12.90) and 5 years (HR = 2.25; CI, 1.14–4.42) posttransplant. There was no significant difference in survival, however, for patients with IDC at 10 years posttransplant when comparing patients with and without VADs (62% vs 67%, *P* = .11, Figure 1).

Patients with IDC receiving VADs as a bridge to transplant were more likely to have a PRA greater than 10% than the precardiac transplant population without VADs. In patients with IDC who received a VAD as a bridge to transplant, the pretransplant PRA was elevated to 35% $\pm$ 40% versus only 5% $\pm$ 14% in the patients without VADs (*P* < .001). In addition, among the patients with IDC, 40% of the patients who received a VAD had a PRA greater than 10%, compared with only 10% of the patients without VADs (*P* < .001). Some 32% of patients with IDC with a VAD had a PRA greater than 40% (*P* < .001), and 20% of patients with IDC with a VAD had a PRA greater than 75% (*P* < .001).

In both the IDC and CAD groups, the transfusion of cellular blood products, the duration of VAD support, and the use of pretransplant and perioperative plasmapheresis for desensitization in patients with a PRA greater than 90% did not affect long-term survival after transplantation. Similarly, United Network for Organ Sharing status and the incidence of reoperative cardiac surgery did not affect long-term survival. The incidence and severity of acute cellular and humoral rejection, immunosuppressive agents, immunosuppression protocols, and cardiac allograft vasculopathy did not differ between those with and without VADs in the IDC and CAD groups. Finally, although 1- and 5-year survivals were decreased for patients with VADs in the IDC group, the incidences of mortality cause (ie, acute rejection, infection, cardiac allograft vasculopathy, and malignancy) did not differ between patients with and without VADs.

During the time period analyzed, the predominant bridge-to-transplant VADs used in the UTAH heart transplant program were the Heartmate I and Heartmate II systems. The Heartmate I system was used exclusively until 2004, when the Heartmate II system also began to be placed as a bridge-to-transplant device. An interesting finding with regard to these 2 VAD systems is that PRA elevation greater than 10% was seen only in those patients who received

TABLE 1. Patient characteristics

	CAD (n = 213)		<i>P</i> value	IDC (n = 201)		<i>P</i> value
	VAD support			VAD support		
	Yes (n = 59)	No (n = 154)		Yes (n = 45)	No (n = 156)	
Age at transplant, y mean ± SD	54 ± 8	54 ± 9	.88	42 ± 17	43 ± 16	.91
Female, n (%)	5 (8)	10 (6)	.61	9 (20)	46 (29)	.21
PRA > 10% (%)	16 (27)	12 (8)	.006	18 (40)	15 (10)	<.001
HeartMate I (Thoratec Corp, Pleasanton, Calif) (%)	57 (97)	0 (0)	–	41 (91)	0 (0)	–
HeartMate II (%)	2 (3)	0 (0)		4 (9)	0 (0)	

CAD, Coronary artery disease; IDC, idiopathic dilated cardiomyopathy; VAD, ventricular assist device; SD, standard deviation; PRA, panel-reactive antibody. Characteristics of patients with CAD or IDC with and without bridge to transplants in the UTAH heart transplant program from 1993 to 2009.

a Heartmate I device. Patients who received a Heartmate II device did not have an elevation in their measured PRA. Elevation in the pretransplant PRA was correlated with a decrease in survival in patients with IDC at 1 year (HR = 4.42; CI, 1.11–17.67, *P* = .035) and 5 years (HR = 1.91; CI, 0.82–4.46, *P* = .04) after cardiac transplantation.

DISCUSSION

To our knowledge, this is the first report in the literature examining the impact of VADs as a bridge to transplant on long-term (ie, ≥10 years) survival after cardiac transplantation. Conducting such a study has only recently become possible, because VADs were not widely adopted for bridging to cardiac transplantation until the 1990s.^{1–5} Previous reports have not found a difference in survival in patients with and without VADs at 1, 2, and 5 years posttransplant.^{4,5} These previous reports, however, grouped their patients with bridge-to-transplant VADs, regardless of heart failure cause, and compared them with the general population of heart transplant recipients.^{4,5} More recent studies have found that bridge-to-transplant VADs are associated with an increase in mortality within

6 months and beyond 5 years after cardiac transplantation.⁶ An important distinction between these prior reports and our study is that we have sufficient numbers of patients with and without VADs in the 2 most common groups presenting for transplantation, IDC and ischemic cardiomyopathy, to allow for a more detailed analysis of the direct impact of VAD support in each group. In patients with IDC, the decrease in survival among the patients receiving VADs became manifest at 1 year posttransplant and continued through 5 years posttransplant. In patients with ischemic cardiomyopathy, the use of VADs as a bridge to transplant did not affect survival after cardiac transplantation. These differences in outcomes based on heart failure cause may explain why prior reports, which have not taken heart failure cause into account, have not found a difference in survival between patients with and without VADs at 1, 2, or 5 years posttransplant.

Among all the potential variables that were examined in this study, the only important contributors to the decrease in posttransplant survival in the patients with IDC who received a VAD as a bridge to cardiac transplantation were the presence of a PRA greater than 10% and the use of a Heartmate I device. Previous reports have suggested that the need for transfusion of cellular blood products at the time of VAD placement increases the incidence of humoral sensitization in left ventricular assist device (LVAD) recipients.^{7–9} Our group has previously reported, however, that avoidance of perioperative leukocyte-filtered cellular transfusions does not decrease the incidence or degree of human leukocyte antigen sensitization in LVAD recipients.^{10,11} In this study, we found no correlation between the incidence or extent of blood transfusion and the long-term survival in patients with and without VADs posttransplant. We also found that the duration of VAD support before transplant did not affect long-term survival after transplantation. Further, the use of a VAD as a bridge to transplant did not change the incidence or severity of acute cellular or humoral rejection or the development of cardiac allograft vasculopathy after cardiac transplantation. Although 1- and 5-year survivals were decreased for patients with VADs in the IDC group, the incidences of mortality cause (ie, acute rejection, infection,

TABLE 2. Kaplan–Meier survival probabilities in patients with idiopathic dilated cardiomyopathy by ventricular assist device support

Follow-up	IDC (n = 201)		Entire transplant program (N = 525)
	VAD support		
	Yes (n = 45)	No (n = 156)	
1 y	0.84 (0.70–0.92) n = 38	0.96 (0.92–0.98) n = 148	0.90 (0.88–0.93) n = 472
5 y	0.66 (0.48–0.79) n = 18	0.82 (0.74–0.87) n = 90	0.77 (0.73–0.81) n = 284
10 y	0.62 (0.43–0.76) n = 8	0.67 (0.57–0.75) n = 43	0.59 (0.53–0.64) n = 121
15 y	0.53 (0.30–0.72) n = 1	0.50 (0.36–0.63) n = 9	0.44 (0.37–0.52) n = 21

IDC, Idiopathic dilated cardiomyopathy; VAD, ventricular assist device. Survival probabilities and 95% CIs for the entire transplant program and in patients with IDC by VAD support at 1, 5, 10, and 15 years posttransplant.

FIGURE 1. Comparison of long-term survival after cardiac transplantation in IDC patients with a VAD as bridge to transplant and IDC patients who did not receive a VAD as bridge to transplant. *IDC*, Idiopathic dilated cardiomyopathy; *VAD*, ventricular assist device.

cardiac allograft vasculopathy, and malignancy) did not differ between patients with and without VADs.

The development of immunoglobulin-G antibodies to human leukocyte antigen class I and II antigens by PRA screening occurs in up to 60% of patients after placement of an LVAD.⁴ Humoral sensitization after placement of an LVAD is defined as the development of an elevation in PRA greater than 10%.¹² The degree of sensitization has been reported to differ by LVAD device type,¹² occurring most frequently in patients receiving Thoratec, Heartmate I, and Novacor (World Heart Inc, Salt Lake City, Utah) devices.¹² Despite the increased incidence of humoral sensitization in patients with LVADs, the incidence of acute and chronic rejection in LVAD recipients is not increased post-transplant.^{4,12}

The type of VAD placed as a bridge to transplant does not seem to influence the incidence of posttransplant rejection or survival at 1 year posttransplant, but it does influence survival at 5 years posttransplant.¹³ In addition, the rate and severity of posttransplant rejection has been noted to be higher in LVAD recipients with continuous-flow devices than in patients with pulsatile devices.¹⁴ This is particularly interesting given the finding in our series that the implantation of the Heartmate II device was not associated with an increase in the PRA. The interaction between blood elements and the biomaterials of the VAD, specifically the textured chamber surface found in the Heartmate I, may be the mechanism responsible for the increased immunologic and inflammatory response seen in this group of patients.¹⁵ The textured surface of the Heartmate I device results in the formation of a pseudointima that contains an abundance of T cells, macrophages, and monocytes as a result of the continuous

dynamic interaction of the blood with the device.¹⁵ Aberrant T-cell activation, defective T-cell proliferation, and polyclonal B-cell hyperreactivity with CD40 ligand interaction have all been reported in association with use of the Heartmate I device.¹⁵⁻¹⁷

Next-generation axial-flow devices, such as the Heartmate II, have been hypothesized to lower the immunologic and inflammatory response seen after LVAD implantation. In this study, our finding that the Heartmate II is not associated with an increase in the PRA after implantation supports this hypothesis. Possible reasons for the decreased immune response seen with the Heartmate II device are the decrease in the textured surface area and the absence of biologic chamber valves compared with the Heartmate I device. In the Heartmate II device, the textured surfaces are found only along the course of the inflow cannula of the device. Other investigators have also noted that patients receiving an axial-flow VAD do not become sensitized after device implantation.¹⁸ A recent study comparing sensitization rates between axial flow devices and Heartmate I devices found that the Heartmate I was associated with a significantly increased incidence of allosensitization compared with axial flow devices.¹⁹

Taken in aggregate, these findings suggest that an as yet unidentified alteration of the immune response is activated in some patients by the placement of a Heartmate I VAD. This alteration of the immune response seems to manifest itself initially as an elevation in the pretransplant PRA. As stated above, the placement of a Heartmate I device has been associated with aberrant T-cell activation, defective T-cell proliferation, and polyclonal B-cell hyperreactivity with CD40 ligand interaction.¹⁵⁻¹⁷ Whether there is a direct

causal relationship between an increase in the pretransplant PRA and these immune system alterations is unknown at the present time. Our study suggests, however, that this alteration of the immune response may persist and have implications for survival in patients with IDC after cardiac transplantation. The major limitation in the analysis of this study is the relative paucity of information regarding the specific immune system alterations that are present in these patients before and after cardiac transplantation. As a result, the significance of an increase in the pretransplant PRA of more than 10% in an individual patient remains unclear, particularly with regard to what intervention should be made, if any, when this finding is encountered clinically. At the present time, we are actively trying to identify the specific immune mediators that may be responsible for the increase in PRA and decrease in survival after cardiac transplantation in patients with IDC who received a Heartmate I as a bridge to a cardiac transplant. The ongoing transition to the use of continuous axial-flow assist devices for bridge to transplant may have previously unrecognized beneficial effects with regard to long-term survival after cardiac transplantation.

CONCLUSIONS

There are several important limitations to this study that should be noted. This is a retrospective analysis from a single regional heart transplant center of patients who were not randomized as to whether they received a VAD or proceeded directly to a cardiac transplant. As a result, important variables, including patient functional status and technical aspects of the operative procedures, that might influence whether a patient received a VAD and, in turn, might impact long-term survival, may not be included in this analysis. Given the retrospective nature of the analysis, the reasons for the observed differences in survival between the VAD and non-VAD subgroups among the patients with IDC cannot be directly identified. We plan additional prospective studies in the future to better elucidate the factors determining long-term survival in these patients after cardiac transplantation.

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