Relationship Between Bridging With Ventricular Assist Device on Rejection After Heart Transplantation

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Background: Ventricular assist devices (VADs) are commonly used to bridge patients to heart transplantation. Recipients of VADs may develop anti-human histocompatibility leukocyte antigen antibodies, as reflected by elevated panel-reactive antibodies (PRA). The purpose of this study was to evaluate the relationship between bridging with VAD before heart transplantation and development of cellular rejection, humoral rejection, and allograft vasculopathy after transplantation.

Methods: Data on all patients who underwent cardiac transplantation between July 1994 and February 2001 at Rush Presbyterian St Luke's Medical Center were retrospectively reviewed. Data collected included sex, age, etiology of cardiomyopathy, percentage panel reactive antibodies (by cytotoxic method), type and duration of mechanical circulatory support, transfusion history, rejection history (both cellular and humoral) after cardiac transplantation, and development of allograft vasculopathy. Cellular rejection was treated when International Society of Heart and Lung and Transplantation Grade 2 or greater in the first 12 months after transplant and Grade 3 or greater after 12 months and treated with intensification of immunosuppression. Humoral rejection was defined clinically as allograft dysfunction by echocardiography without evidence of cellular rejection on endomyocardial biopsy or allograft vasculopathy. Allograft vasculopathy was defined by presence of any degree of luminal narrowing or pruning of distal vessels by coronary arteriography. Statistical analyses were performed by chi-square test, Fisher's exact test, and Wilcoxon rank sum test, as appropriate.

Results: Ninety-eight patients underwent cardiac transplantation during the study period (87 men, mean age 49 years, 46 ischemic etiology). Of these, 48 were bridged with HeartMate VAD (20 patients received vented electric device, 28 received pneumatic device). Nineteen percent of VAD patients had a peak pretransplant PRA $\geq$10% vs 2% of patients without VAD ($p = 0.014$). PRA $\geq$10%, use of VAD, or duration of VAD support did not predict development of humoral rejection. Use of VAD did not predict development of cellular rejection or allograft vasculopathy. VAD use was not associated with sudden death after heart transplantation. In the entire group of 98 patients, neither humoral nor cellular rejection predicted development of allograft vasculopathy. Longer ischemic time correlated with increased cellular rejection and humoral rejection after transplantation ($p = 0.01$).

Conclusions: Some patients bridged to cardiac transplantation with VADs have increased PRA before heart transplantation, but this does not appear to translate into increased risk of either humoral or cellular rejection after transplantation or development of allograft vasculopathy as detected by coronary angiography. J Heart Lung Transplant 2005;24:310–5. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

In the current era of a shrinking donor pool coupled with an expanding population of patients with end-stage cardiomyopathy, ventricular assists devices (VADs) are commonly being used to bridge patients to cardiac transplantation. Patients who were either too ill to be transplantation candidates or who would have died before receiving an organ are now being successfully supported until a donor organ becomes available. Over time, a higher proportion of patients waiting for a heart transplant are being bridged with VADs.[1] Data from the Cardiac Transplant Research Database (CTRD) showed the percentage of patients with VADs at the time of transplantation increased steadily from 2% in 1990 to 16% in 1997.[2] Most recent data from the CTRD showed this percentage to be 27% in 2002 (David Naftel, PhD, personal correspondence). As a result, the

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influence of bridging with VAD on outcomes after heart transplantation has become an important issue in peritransplant management.

It is generally accepted that VAD use results in humoral sensitization as measured by panel-reactive antibody (PRA) testing for circulating anti–human leukocyte antigen (HLA) Class I and Class II antibodies. The percentage of patients, previously unsensitized, who develop anti-HLA antibodies during VAD support ranges from 14% to 66% in different series.[1,3–7] The significance of this after transplantation is less clear. It has been demonstrated that an elevated PRA results in reduced long-term survival and increased incidence of acute and chronic rejection after transplantation, with the threshold for sensitization being a PRA of more than 10% in one landmark study[8] and more than 25% in another.[9] In contrast, more recent studies specifically comparing populations bridged with VADs vs those unbridged have not been able to demonstrate differences in posttransplant survival, despite high rates of HLA alloimmunization.[1,5]

In this context, we sought to evaluate the relationship between bridging to cardiac transplantation with VAD, development of anti-HLA antibodies as measured by PRA, and subsequent graft outcomes including cellular rejection, humoral rejection, and allograft vasculopathy.

METHODS

Patient Population

All patients referred to the Rush Heart Failure and Cardiac Transplant Program who underwent cardiac transplantation during the study period were eligible.

Data Collection

Data from the Rush Heart Failure and Cardiac Transplant Database were reviewed from July 1994 to February 2001. The database was approved for research purposes by the institutional review board at Rush Presbyterian St Luke's Medical Center. All data were given to the investigators for analysis as a deidentified data set. Data collected included the following:

1. Age, sex, race, etiology of cardiomyopathy, and cytomegalovirus (CMV) status of the recipient.
2. Age, sex, race, CMV status of the donor.
3. Type and duration of VAD support in those bridged before cardiac transplantation.
4. PRA as measured by cytotoxic method. In those patients who had multiple determinations (the majority), the greatest measured value was recorded as the peak PRA value. If a patient had only one PRA determination, this was recorded as the peak value. Generally, PRA was measured at time of evaluation/listing, 2 weeks after VAD implantation, 2 weeks after a blood product transfusion, every 3 to 6 months for those listed without a VAD, and every month for those listed with a VAD. A peak PRA of $\geq$10% was considered to indicate significant sensitization to HLA antigens. These patients may have been treated before cardiac transplantation with one or more of cyclophosphamide, plasmapheresis, and/or intravenous gamma globulin (IVIG) at the discretion of the transplant cardiologist. Generally, after transplantation, cyclophosphamide replaced azathioprine or myophenolate mofetil in the triple-drug immunosuppressive regimen, which included cyclosporine and prednisone. All patients with a peak PRA $\geq$10% had prospective cross-match before transplantation.
5. Transfusion history including all packed red cells (leukocyte reduced and nonreduced) and platelets (leukocyte reduced and nonreduced). Only transfusions received at our institution were recorded in the database. No transfusion data were available in patients with previous cardiac surgery or who received blood products at outside institutions.
6. Rejection history. Cellular rejection, as demonstrated by endomyocardial biopsy, was treated with intensification of immunosuppression when International Society of Heart and Lung Transplantation (ISHLT) Grade 2 or greater in the first 12 months after cardiac transplantation and Grade 3 or greater thereafter. Humoral rejection was a clinical diagnosis based on graft dysfunction on echocardiography and/or hemodynamic compromise as measured by pulmonary artery catheterization with no evidence of cellular rejection by endomyocardial biopsy and treated by one or more of pulse steroids (oral or intravenous), cyclophosphamide, plasmapheresis, IVIG, or total lymphoid irradiation.
7. Allograft vasculopathy was detected by coronary angiography and defined as the presence of any luminal narrowing or distal vessel pruning. Studies were performed on a yearly basis, unless a clear contraindication or access issue existed.

Statistical Methods

Chi-square and two-tailed Fisher's exact tests were performed to test for associations between dichotomous variables such as humoral rejection and having a left VAD (LVAD). Wilcoxon rank sum tests were used to test for differences in continuous variables between groups. Nonparametric Wilcoxon rank sum tests were used because of concerns about the normalcy of the underlying distributions. Continuous values were summarized by using the mean, standard deviation, median, minimum, and maximum. All analyses were performed by SAS software, version 9.0 (SAS Institute, Cary, NC).

RESULTS

During the study period, 98 patients underwent orthotopic cardiac transplantation. All patients survived the initial hospitalization after cardiac transplantation. Forty-eight of these patients were bridged to cardiac transplantation with a HeartMate (Thoratec Corporation, Woburn, MA) LVAD. Earlier in the study period, the pneumatic device was used, which required the patients to remain hospitalized until the time of cardiac transplantation. When the vented electric device became available, patients were able to be discharged home to await cardiac transplantation. Twenty-eight patients received the HeartMate pneumatic device, and 20 received the vented electric device. The number of days patients were bridged with an LVAD ranged from 3 to 493, with a mean of 87. Demographic data for the group bridged with LVAD vs the group not bridged are presented in Table 1. There were no differences in distribution of age, sex, race, and etiology of heart failure. The group without LVAD bridging had longer allograft ischemic time. After transplantation, the mean follow-up time for the LVAD bridged group was 1287 days vs 1494 for the group not bridged (p = not significant) [NS].

Over the course of the study period, 2170 endomyocardial biopsies were performed in the group of 98 patients. There were 221 episodes of treated rejection. Of these, 112 were categorized as cellular rejection occurring in 50 patients, and 110 were categorized as humoral rejection in 50 patients.

Of 88 patients who had PRA measured before orthotopic heart transplantation (OHT), 1 of 45 patients without an LVAD had a peak PRA of ≥10% vs 8 of 43 patients who were bridged with an LVAD (p = 0.01) (Table 2). Of these 9 sensitized patients, 2 were women, both in the LVAD group. Treatment of elevated PRA is outlined in Table 3 . In the 9 patients with pretransplant peak PRA ≥10%, there was no association with increased humoral rejection after OHT (p = NS). Bridging with LVAD itself was not associated with increased humoral rejection after OHT (p = NS). Time to humoral rejection between the 2 groups did not differ, as illustrated in Figure 1. Duration of LVAD support before OHT did not predict humoral rejection (p = 0.08). Mean duration of LVAD support in the 27 patients without humoral rejection was 99 ± 96 days vs 72 ± 75 days in the 21 patients with humoral rejection after OHT. None of donor sex, age, race, or CMV status, recipient CMV status, or donor/recipient CMV mismatch was associated with humoral rejection. There was no association between bridging with LVAD and cellular rejection (p = 0.3). Time to cellular rejection between the 2 groups did not differ, as illustrated in Figure 2. Longer ischemic time was found to be associated with both cellular rejection (mean of 170 ± 61 minutes vs 197 ± 55 minutes) and humoral rejection (mean of 173 ± 58 minutes vs 198 ± 58 minutes) (p = 0.01 for both).

Table 1. Characteristics of Left Ventricular Assist Device Bridged Versus Nonbridged Groups

Characteristic	LVAD group (n = 48)	Nonbridged group (n = 50)
Sex		
Male	45	42
Female	3	8
Mean age ± SD, year	49 ± 13	48 ± 13
Race		
White	25	35
African American	17	14
Other	6	1
Etiology		
Ischemic	20	26
Nonischemic	27	18
Other	6	1
Ischemic time ± SD	171 ± 49	200 ± 65*

*p = 0.01 vs LVAD group. LVAD, left ventricular assist device; SD, standard deviation.

Table 2. Peak Panel-Reactive Antibodies Before Orthotopic Heart Transplantation in Patients With and Without Left Ventricular Assist Device as Bridge*

	LVAD		
Peak PRA	No	Yes	Total
<10%	44	35	79
≥10%	1	8	9
Total	45	43	88

*p = 0.014. PRA, panel-reactive antibodies; LVAD, left ventricular assist device.

Number of red cell transfusions (overall, leukocyte reduced or nonleukocyte reduced) was not associated with increased humoral or cellular rejection. Number of leukocyte or nonleukocyte platelet transfusions was not associated with increased humoral or cellular rejection. LVAD patients received more overall red cell transfusions (leukocyte plus nonleukocyte reduced units combined) compared with patients without an LVAD, 10 ± 8 units versus 6 ± 6 units (p < 0.01) and more overall platelet transfusions, 5 ± 5 units vs 2 ± 2 units (p < 0.01).

Development of allograft vasculopathy was not associated with cellular rejection (p = 0.3), humoral rejection (p = 0.3), or bridging with LVAD (p = 0.9). Bridging with LVAD was not associated with sudden death after OHT (p = 0.6). There was no difference in overall survival after OHT between the patients bridged with LVAD vs those not bridged, as presented in Figure 3.

DISCUSSION

The principal finding of this study was that patients bridged with an LVAD did not have increased rejec-

Table 3. Treatment of Sensitized Patients*

Patient	Treatment
A	Received no preop therapy. Postop on methylprednisolone IV initially, then oral prednisone, cyclosporine, mycophenolate mofetil.
B	Received plasmapheresis 13 treatments with IVIG; cyclophosphamide oral 50 mg ×12 days preop. Postop plamapheresis 6 treatments; methylprednisolone IV initially, then oral prednisone, cyclosporine, cyclophosphamide.
C	Received plasmapheresis 2 treatments; methylprednisolone IV 500 mg pulse ×3, cyclophosphamide oral 110 mg, 50 mg, 75 mg preop. Postop plamapheresis 6 treatments; methylprednisolone IV initially, then oral prednisone, cyclosporine, cyclophosphamide.
D	Received no preop therapy. Postop received methylprednisolone IV, cyclosporine, azathioprine; cyclosporine held and OKT3 started ×11 days, then oral cyclosporine, azathioprine, prednisone.
E	Received plasmapheresis 17 treatments; cyclophosphamide oral 150 mg, then 75 mg for several months preop. Postop plasmapheresis 7 treatments; methylprednisolone IV initially, then prednisone, cyclosporine, cyclophosphamide.
F	Received no preop therapy. Postop, methylprednisolone IV initially, then prednisone, cyclosporine, mycophenolate mofetil.
G	Received no preop therapy. Postop, methylprednisolone IV initially, then prednisone, cyclosporine, cyclophosphamide.
H	Received no preop therapy. Postop ATG initially, then cyclosporine, azathioprine, methylprednisolone IV. Home with cyclosporine, mycophenolate mofetil, prednisone.
I	Received plasmapheresis 7 treatments preop; cyclophosphamide oral 75 mg, then 50 mg daily until transplantation. Postop plasmapheresis 7 treatments; methylprednisolone IV initially, then prednisone, cyclosporine, cyclophosphamide.

*Peak panel-reactive antibodies (PRA) ≥10%. Preop, preoperative; postop, postoperative, IV, intravenous; IVIG, intravenous gamma globulin; ATG, antihuman thymocyte globulin.

tion episodes (cellular or humoral), allograft vasculopathy, or decreased survival after OHT as compared with those nonbridged individuals, despite higher rates of sensitization as reflected in higher peak PRA in the LVAD-bridged patients. Higher PRA observed in the LVAD-bridged patients may have been due to significantly higher rates of both red blood cell (RBC), and platelet transfusion in this group. This is in keeping with the findings of McKenna et al.[5] In their study, VAD patients who developed HLA antibodies had significantly more peri- and postoperative blood transfusions (RBC, platelet, and plasma) than did those who remained negative. As in our study, sex, age, etiology of heart failure, previous cardiac surgery, and duration of VAD support showed no statistically significant correlation with formation of HLA antibodies.[5] Other investigators showed that only platelet transfusions were associated with either an increased peak PRA or with the development of HLA Class I immunoglobulin G antibodies.[4,10] In contrast, other reports indicate that VAD support is associated with increased production of anti-HLA antibodies independent of blood transfusions, suggesting immunogenicity of the VAD itself.[11] This hypothesis is supported by the finding of increased T and B cell activation in response to placement of a VAD.[12]

Regardless of the cause of allosensitization in LVAD-bridged patients, the clinically relevant question is whether VAD-related immune activation is associated with increased rejection rates and mortality after cardiac transplantation. We did not find this to be the case in our study. There were no differences in survival between LVAD-bridged and non bridged patients. LVAD-bridged patients did not have differing rates of cellular rejection, humoral rejection, or allograft vasculopathy. It is possible that observed rates of rejection in patients with, vs those without, preoperative VAD support were similar because of the modified immunosuppression and a prospective crossmatch for all patients with a PRA ≥10%, regardless of the need for VAD. This is in keeping with findings of Rajit et al, who examined a series of 521 adult cardiac allograft recipients, 105 of whom were bridged with an LVAD. Despite higher rates of sensitization in the LVAD patients compared with the non-LVAD patients, 5-year survival and development of allograft vasculopathy after transplantation was similar in the 2 groups. However in this study, sensitized LVAD patients received cyclophosphamide and IVIG. When examined as a separate group, the sensitized, untreated LVAD recipients had

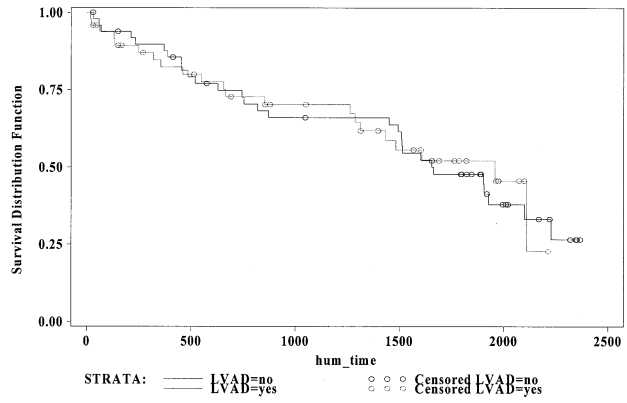

Figure 1. Time to humoral rejection between the 2 groups. LVAD, left ventricular assist device. p = not significant.

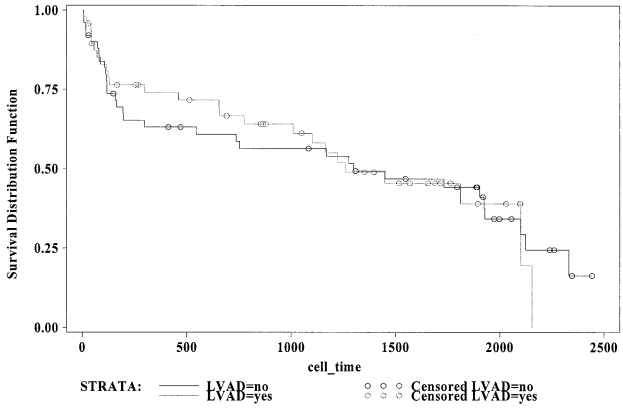

Figure 2. Time to cellular rejection between the 2 groups. LVAD, left ventricular assist device. p = not significant.

a 2.7-fold increase in at least one high-grade rejection within the first posttransplant year ($p < 0.05$), which, however, was not associated with increased mortality.[6] In another study, sensitized, untreated LVAD patients did not have higher rates of cellular rejection, humoral rejection, allograft vasculopathy, or mortality in the first posttransplant year.[1] Pagani et al found no difference in allograft rejection rates and survival between heart transplant recipients with and without previous LVAD support, without performing prospective cross-matching.[7] And in yet another study, rejection rates were significantly lower in LVAD-bridged recipients than in patients who did not require mechanical support before heart transplantation.[3]

Although PRA ≥10% has been previously identified as a risk factor for rejection after transplantation, it is possible that improved immunosuppression strategies have reduced the risk of rejection associated with preoperative sensitization.[8] In the most recent report of the ISHLT, PRA >10% was found to be a significant risk factor for 1-year mortality after adult heart transplant in the years 1995 to 1998 (odds ratio 1.25, $p = 0.03$), but not from 1999 to June 2001 (odds ratio 1.26, $p = 0.1$).[13] However, PRA >20% was identified as a risk factor for development of allograft vasculopathy within 5 years after heart transplant (odds ratio 1.74, $p = 0.0009$).[13]

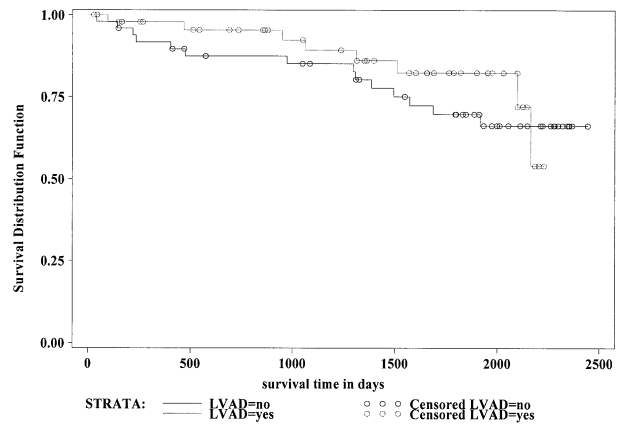

Figure 3. Does survival time differ between those with and without left ventricular assist device (LVAD)? p = not significant.

PRA determination in our study was by cytotoxic methodology, which is less sensitive than flow cytometry. De Nofrio et al measured Class I anti-HLA antibodies by flow cytometry in PRA-negative LVAD patients and found more moderate to severe rejection in the first 2 months in those with detectable antibodies. There were no differences in 1-year survival between patients with and without anti-HLA antibodies.[14] The role of flow cytometry as a useful clinical tool in evaluating LVAD patients at increased risk for rejection is an area that will require further study.

In our study, of all the factors analyzed, only prolonged ischemic time was associated with increased frequency of both cellular and humoral rejection. This finding is consistent with a previous report.[15] The sequence of immunologic events leading to rejection after prolonged ischemic time is largely speculative. Possible explanations may include increased expression of antigens from the damaged tissue, cytokine release, and activation of complement.[16]

Limitations

Sensitized patients with PRA ≥10% had modification of immunosuppressive strategy, regardless of whether or not they were bridged with a VAD. This may have influenced posttransplant rejection rates, development of allograft vasculopathy, and mortality. No data were available on incidence of pregnancy, which may have affected PRA in women. Coronary angiography was used to diagnose allograft vasculopathy, which is less sensitive than intravascular ultrasound. This was a retrospective review, with its inherent limitations.

Conclusions

With a growing population of patients with end-stage cardiomyopathy presenting with more advanced disease, use of LVADs has increased. Although LVADs may be associated with higher rates of allosensitization, in the current era of transplantation, this does not appear to translate into higher rates of rejection, allograft vasculopathy, or mortality after OHT.

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