Characterization of ventricular assist device–mediated sensitization in the bridge-to-heart-transplantation patient

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Objective: Ventricular assist devices (VADs) are associated with increased anti–human leukocyte antigen antibody production. The purpose of this study is to characterize differences in sensitization patterns in patients receiving axial flow, implantable VADs versus pulsatile, paracorporeal biventricular assist devices (BIVADs) as bridges to transplantation.

Methods: The study is a retrospective review of 68 patients who were bridged to transplantation with either a VAD or a BIVAD, as described, from January 2007 to June 2010, at a university medical center.

Results: Five of 15 (33.3%) VAD patients became sensitized during treatment, compared with 30 of 53 (56.6%) BIVAD patients, $P = .15$. Multivariable analysis comparing BIVAD with VAD, while controlling for previous cardiac surgery, pregnancy, and packed red blood cell transfusion produced an odds ratio of 2.99, $P = .14$. Of sensitized patients, all 5 (100%) of the VAD patients had pre-existing antibodies before VAD placement, compared with 9 of 30 (30.0%) BIVAD patients, $P = .006$. Maximum cumulative mean fluorescence intensities for BIVAD were 46,259 ± 66,349 versus 42,540 ± 12,840 for VAD, $P = .90$. Time to maximum antibody expression was shorter for the VAD group (34 ± 28 days vs 5.8 ± 9 days, $P = .04$).

Conclusions: Device type was not a factor in patient sensitization after implantation. However, VAD patients required pre-existing sensitization before implantation to produce antibodies during their treatment interval, whereas more than two thirds of BIVAD patients developed de novo antibodies. These data suggest that the mechanism of sensitization between VAD and BIVAD patients may differ, and further mechanistic studies into the impact of device types on patient sensitization are warranted. (J Thorac Cardiovasc Surg 2015;149:1161-6)

See related commentary on pages 1166-7.

The presence of circulating anti–human leukocyte antigen (HLA) antibodies, or their sensitization, in heart transplant recipients is associated with decreased survival, increased episodes of acute cellular and antibody-mediated rejection, and increased development of allograft vasculopathy.[1-3] Multiparity, previous cardiac surgery, and history of blood transfusions are the most commonly implicated etiologies. Recently, however, ventricular assist devices (VADs), commonly used as bridges to transplantation (BTTs) in the sickest orthotopic heart transplant candidates, are increasingly associated with the increased expression of circulating HLA antibodies.[4,5]

One important proposed etiology is host immune-cell interactions with the surfaces of the respective devices. This possibility is consistent with data showing that the latest generation of axial flow pumps, such as the HeartMate II left VAD (HMII) (Thoratec Corporation, Pleasanton, Calif), lead to lower rates of sensitization (8% vs 28%, $P = .02$) than their older, pulsatile counterparts, such as the paracorporeal biventricular assist device (BIVAD) or the HeartMate XVE (both from Thoratec Corporation, Pleasanton, Calif).[6] The older pumps have bigger chamber surface areas and valves, whereas the HMII relies on a spinning rotor to propel blood in continuous fashion through a relatively small channel. The aim of the present study is to characterize the sensitization patterns for BTT patients undergoing HMII versus BIVAD implantations in our institution.

METHODS

Records for 68 patients, between the ages of 18 and 70 years, undergoing VAD insertion as a BTT, between January 2007 and June 2010, were retrospectively reviewed with approval of the UCLA (University of California, Los Angeles) Institutional Review Board. Patients were evaluated for previous cardiac surgery, pregnancy, and blood-product utilization during the VAD support interval. Patient sera samples were collected according to the existing clinical protocols at our institution and analyzed for antibodies directed against HLA class I (A, B, and C) and class II (DR,

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Abbreviations and Acronyms

BIVAD = biventricular assist device
BTT = bridge to transplantation
HLA = human leukocyte antigen
HMII = HeartMate II left ventricular assist device
VAD = ventricular assist device

DQ, and DP) antigens utilizing Luminex reagents (Gen-Probe, San Diego, Calif) according to manufacturer specifications and antibody specificity reagents according to manufacturer specifications. Particle fluorescence was measured using the Luminex 100 IS system (Luminex Corporation, Austin, Tex). Additional Luminex-based single-antigen bead assays (One Lambda Inc, Canoga Park, Calif) were run on positive sera to confirm the antibody specificity and strength as indicated by the mean fluorescence intensity. Antibodies were considered positive when these intensity values were $\geq$1000 for HLA-A, -B, -DR, -DQ, and -DP and $\geq$2000 for HLA-C.[7] The maximum value was determined by the selection of the sample date with the highest total summed mean fluorescence intensity values.

Device selection was made by a multidisciplinary team that included a cardiac surgeon and cardiologist. Patients were categorized as having INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) level 1 or 2 heart failure with impending multiorgan failure and/or death from malperfusion. In the setting of isolated left-ventricular failure, the axial flow HMII was utilized. Temporary CentriMag centrifugal right VAD support was used when appropriate (Thoratec Corporation, Pleasanton, Calif). Profound biventricular failure prompted paracorporeal VAD placement in the right and left ventricles, respectively. All right VADs placed in the BIVAD group were thus permanent and remained in place until the time of orthotopic heart transplantation. Both the HMII and paracorporeal BIVADs are produced by Thoratec Corporation (Pleasanton, Calif) and are approved by the U.S. Food and Drug Administration for BTT indications.

Statistical Analysis

Calculated panel reactive antibody percentages were calculated, entering all unacceptable antigens for HLA-A, -B, -C, -DR, and -DQ, defined as those with signal strength mean fluorescence intensity $\geq$1000 in the UNet computer system at the U.S. Department of Health & Human Services Organ Procurement and Transplantation Network website (http://optn.transplant.hrsa.gov). Noncontinuous variables were analyzed using $\chi 2$ analysis and the Student *t* test. Continuous variables were compared using analysis of variance with Bonferroni correction. Multivariable regression analysis was performed to quantify the association between sensitization etiologies and outcomes.

RESULTS

Of 68 patients, BIVADs were placed in 53, and HMIIs were placed in the remaining 15. A total of 56 (82%) patients were men. Etiologies of heart failure were idiopathic dilated cardiomyopathy in 30 (44%), ischemic cardiomyopathy in 26 (38%), postpartum cardiomyopathy in 3 (4%), and "other" in 9 (13%). The average age of VAD recipients was 52 $\pm$ 11.7 years. Differences in history of cardiac surgery, pregnancy, and blood-product utilization between the BIVAD and HMII groups are shown in Table 1. Only fresh frozen plasma administration differed significantly between the 2 groups.

Multivariable analysis comparing development of HLA antibodies in BIVAD versus HMII patients, while controlling for each of these variables, demonstrated an odds ratio of 2.99 (95% confidence interval 0.71-12.6), $P = .14$. Five of 15 (33.3%) HMII patients produced anti-HLA antibodies during their VAD treatment intervals, compared with 30 of 53 (56.6%) BIVAD patients ($P = .15$). Table 2 shows common etiologies for patient sensitization, of which only packed red blood cell transfusion differed significantly between the sensitized and nonsensitized groups.

Of sensitized patients, all 5 (100%) of the HMII patients had pre-existing antibodies before VAD placement, compared with 9 of 30 (30.0%) of the BIVAD patients, $P = .006$ (Figure 1). Thus, all HMII patients who expressed anti-HLA antibodies had evidence of presensitization, whereas more than two thirds of BIVAD patients developed de novo antibodies during their VAD treatment course. Representative patterns of sensitization are shown in Figure 2, for both presensitized individuals (*top*) and patients who became sensitized after device placement (*bottom*). Two of the HMII patients had temporary right VADs, from which they were weaned before orthotopic heart transplantation. Neither patient became sensitized during their VAD treatment course.

Single-antigen bead assays were compared to determine HLA class I and II expression in patients with BIVADs versus HMIIs. Figure 3 shows that no HMII patients expressed class II antibodies alone, in contrast to 13.8% of the BIVAD patients in this group. A total of 51.7% of the BIVAD patients had just class I, compared with 80% of the HMII patients. The BIVAD and HMII patients expressing both class I and class II antibodies were 34.5% and 20%, respectively ($P = .81$).

The mean of the maximum mean fluorescence intensity values for class I antibodies for BIVADs was 46,422 $\pm$ 66,264 versus 42,540 $\pm$ 12,840 for HMII, $P = .90$. Time to maximum antibody expression was shorter for the HMII group (5.8 $\pm$ 8.6 days vs 33.8 $\pm$ 27.8 days, $P = .04$). With regard to class II antibodies, BIVADs reached a maximum of 29,937 $\pm$ 31,468 at a mean of 30.7 days, whereas the single HMII patient who had expression of class II antibodies had a maximum mean intensity value of 1499 at 19 days (Table 3).

To gauge the breadth of antibody specificities, we calculated the mean panel reactive antibody percentages for sensitized patients in both the HMII and BIVAD groups (Table 4). The mean initial percentage was significantly higher in the HMII group, compared with the BIVAD patients; however, the mean maximum percentage level was essentially equivalent between the 2 categories. Thus, the percentage change in the calculated panel reactive antibody percentages was significantly higher in the BIVAD group during the VAD treatment interval (34.1% $\pm$ 31.4% vs 4.0% $\pm$ 7.9%, respectively, $P = .045$).

To validate the findings of this study, we examined an additional 24 patients who had HMIIs put in place at our institution between July 2010 and December 2013. Nine of these patients produced HLA antibodies during their

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