Association of device surface and biomaterials with immunologic sensitization after mechanical support

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Supplemental material is available online.

Objective: Biomaterials and textured surfaces in early pulsatile left ventricular assist devices (HeartMate I; Thoratec Corporation, Pleasanton, Calif) may increase immunologic risk through allosensitization. We hypothesized that axial-flow devices without biologic membranes or textured surfaces (HeartMate II; Thoratec; and DeBakey; MicroMed Cardiovascular, Inc, Houston, Tex) would cause less allosensitization than devices with such membranes and surfaces.

Methods: HeartMate II and DeBakey (n = 24) and HeartMate I (n = 36) devices were implanted from 1999 to 2006 in patients with severe heart failure cohort-matched for age, etiology, and support duration. Serum samples reacting with more than 10% of the HLA reference panel were considered positive for anti-HLA antibodies. Endomyocardial biopsy samples were collected after transplant.

Results: There were no significant cohort differences in age, etiology, sex, blood transfusion, or support duration. Anti-HLA antibodies were not detected at implantation of either HeartMate II and DeBakey or HeartMate I devices; however, significant increases in anti-HLA antibodies were present within 1 and 3 months of support with HeartMate I but not HeartMate II and DeBakey devices. Overall, fewer patients with HeartMate II and DeBakey devices demonstrated positive anti-HLA antibodies during support (8% vs 28%, $P = .02$), and fewer episodes of acute rejection per patient were seen within the first 9 posttransplant months (0.31 vs 0.69, $P = .052$). Long-term posttransplant survival was not different between groups.

Conclusion: Hemodynamic support with HeartMate II and DeBakey devices produced less allosensitization than did HeartMate I devices. Device selection may improve clinical outcomes for high-risk patients.

Left ventricular assist devices (LVADs) have become an established surgical therapy for patients with end-stage heart failure who require hemodynamic support as a bridge to transplant or as destination therapy. Allosensitization, the development of circulating class I and II HLA antibodies, has become increasingly common in the LVAD population and is estimated in some studies to be as high as 66%.¹ Mechanical circulatory support with a first-generation pulsatile LVAD has been shown to initiate a vigorous localized host immunologic response that may, in conjunction with traditionally associated risk factors such as blood transfusions, previous operations, and pregnancy, be responsible for allosensitization in these patients. The clinical consequences of allosensitization are not insignificant and negatively affect rates of allograft rejection, transplant vasculopathy, and overall survival.²⁻⁶

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Abbreviations and Acronyms

HMI	= HeartMate I
HMII-DB	= HeartMate II or DeBakey
IL-2	= interleukin 2
IL-6	= interleukin 6
IVIG	= intravenous immunoglobulin
LVAD	= left ventricular assist device
OHT	= orthotopic heart transplant
PRA	= panel-reactive antibody

Newer generation axial-flow devices achieve blood flow with a rotary impeller, lack biologic chamber valves, and possess a substantially smaller inner surface than do pulsatile LVADs. It has been hypothesized that the lower surface area and absence of biologic membranes in axial-flow devices influences immunologic response relative to pulsatile LVADs, and preliminary studies have reported low rates of sensitization associated with axial-flow devices.⁷ To date, no study has systematically compared the rate of allosensitization between the two device types. Accordingly, the objectives of this study were as follows: (1) to determine the extent to which device type influences allosensitization and (2) to describe the impact of this immunologic response on allograft rejection in orthotopic heart transplant (OHT) recipients. The effects of the device type on the host immune system could have potentially important clinical consequences when considering LVAD implantation as a bridge to transplant in patients at high risk for development of sensitization.

Methods**Study Design**

Between June 1999 and April 2006 at Columbia University Medical Center, 36 pulsatile HeartMate I (HMI group) LVADs (HeartMate I VE, n = 11, HeartMate I XVE, n = 25; Thoratec Corporation, Pleasanton, Calif) and 24 axial-flow HeartMate II or DeBakey (HMII-DB group) LVADs (HeartMate II, n = 16; Thoratec; DeBakey, n = 8; MicroMed Cardiovascular Inc, Houston, Tex) were implanted in patients with severe heart failure. All patients met accepted criteria for implantation. Pretransplant and posttransplant clinical data were prospectively collected and retrospectively analyzed for the purposes of this study. Patients who died while on the waiting list were included in this analysis. This study was approved by the institutional review board, and all procedures were in accordance with institutional guidelines and policies.

HLA Typing and Crossmatch

Standard microcytotoxicity techniques were used to determine HLA-A and HLA-B serotypes, whereas serologic analysis was performed to determine HLA-DR types. A donor-specific lymphocytic direct crossmatch was performed before OHT for all patients with a panel-reactive antibody (PRA) value greater than 20% and retrospectively (after OHT) for all patients.

Detection of Anti-HLA Antibodies and Determination of Anti-HLA Antibody Specificity

Lymphocytotoxic antibodies were detected by screening serum samples against T and B lymphocytes collected from 70 persons representing all HLA class I and II antigens in the North American population to determine a PRA value. IgG antibodies against HLA class I or class II molecules reacting with more than 10% of the HLA reference panel, for a PRA value greater than 10%, were considered positive, as previously described.⁸ Testing was performed on all patients, beginning at the time of LVAD implantation, every 2 weeks until OHT and at the time of each posttransplant endomyocardial biopsy.

Immunosuppressive Regimen

The posttransplant immunosuppressive regimen consisted of combination therapy with cyclosporine, methylprednisolone, and mycophenolate mofetil, as previously described.¹

Patients in whom an elevated PRA (greater than 10%) was detected after listing for transplant were subsequently treated with immunotherapy in 1- to 3-month course treatments with intravenous cyclophosphamide (1.0 g/m²) and pooled human intravenous immunoglobulin (IVIG, 2 g/kg in four divided doses). This protocol from our institution has been described previously.¹ Briefly, weekly testing for anti-HLA antibodies was performed, and two treatments of plasmapheresis were given if a significant drop in antibody levels was not seen after several treatments. This was followed by intravenous cyclophosphamide given in monthly doses. This treatment was repeated as necessary, and patients with a negative direct crossmatch could proceed to OHT during this time period. Transplant recipients who were sensitized at any point during device support received monthly cyclophosphamide for 4 to 6 months after OHT.

Acute Rejection

Endomyocardial biopsies were performed after OHT as standard protocol weekly for the first 4 weeks, every second week for 2 months, every month for the next three biopsies, and then every 2 months for the first year. An International Society for Heart and Lung Transplantation histologic grade of 2 or higher was considered to represent allograft rejection for the purposes of this study. Treatment for acute rejection consisted of a 3-day steroid pulse. Antithymocyte globulin or murine antibody was used in patients with hemodynamically significant rejection.

Interleukin 6

Interleukin 6 (IL-6), an important regulatory immunocytokine involved in B-cell differentiation and interleukin 2 (IL-2) expansion, was measured at the end of LVAD support at the time of OHT in serum samples from 6 HMII-DB and 11 HMI patients to determine whether levels varied according to device type or correlated with the incidence of rejection after OHT. A commercially available enzyme-linked immunosorbent assay (Human IL-6; Bender MedSystems, Vienna, Austria) was used to determine absorption curves for standards and samples at 450 nm. A linear regression was performed to determine values according to manufacturer specifications.

Statistics

Continuous variables are expressed as mean $\pm$ SD and were compared with independent 2-tailed t tests. Categorical variables were compared with χ^2 and Mann-Whitney tests, and when necessary

TABLE 1. Clinical characteristics

	HMI	HMII-DB	P value
No.	36	24	
Age (y, mean $\pm$ SD)	52.0 $\pm$ 12.5	53.1 $\pm$ 12.0	.723
Male (No.)	30 (83%)	20 (83%)	>.999
LVAD implanted			
HeartMate I (No.)	36 (100%)	0 (0%)	<.001
HeartMate II (No.)	0 (0%)	16 (67%)	<.001
DeBakey (No.)	0 (0%)	8 (33%)	<.001
Etiology of CHF (No.)			
Ischemic	18 (50%)	10 (42%)	1.000
Nonischemic	18 (50%)	14 (58%)	1.000
Pre-LVAD ejection fraction (%; mean $\pm$ SD)	17.6% $\pm$ 4.5%	17.5% $\pm$ 4.2%	.820
Duration of CHF (mo, mean $\pm$ SD)	51.2 $\pm$ 59.7	71.0 $\pm$ 64.6	.209
Duration of LVAD support (d, mean $\pm$ SD)	107.3 $\pm$ 112.2	91.9 $\pm$ 117.8	.610
Previous pregnancy (No.)	1 (2.8%)	2 (8.3%)	.337
Bridge to transplant (No.)	36 (100%)	22 (92%)	.081
Successful bridge to transplant (No.)	32 (89%)	13 (54%)	<.001
Awaiting transplant (No.)	0 (0%)	6 (25%)	.014
Died during LVAD support (No.)	4 (11%)	5 (38.4%)	.306
Died after transplant (No.)	7 (22%)	2 (15%)	.242
Medications (No.)			
β -Blocker	4 (11%)	8 (33%)	<.001
Diuretic	9 (25%)	12 (50%)	.049
Angiotensin-converting enzyme inhibitor	3 (8%)	6 (25%)	.079
Aspirin	8 (22%)	13 (54%)	.001
Antibiotic	7 (19%)	6 (25%)	.612
Steroid	3 (8%)	1 (4%)	.530
Statin	1 (3%)	2 (8%)	.337
Infections (No.)			
Device	8 (22%)	1 (4%)	.001
Wound	7 (19%)	0 (0%)	<.001
Cerebrovascular accident (No.)	3 (8%)	3 (13%)	.601
Previous surgery (No.)			
Cardiac	5 (14%)	0 (0%)	.059
Other	5 (14%)	3 (13%)	.878
Previous transplant (No.)	1 (3%)	1 (4%)	.771

HMI, HeartMate I group; HMII-DB, HeartMate II and DeBakey group; LVAD, left ventricular assist device; CHF, congestive heart failure.

with Fisher exact tests. Kaplan–Meier analysis was used to calculate survival, and groups were compared with a 2-sided log-rank test at the $P = .05$ significance level. Actuarial survivals at 6 months and at 1 and 2 years after OHT were calculated by constructing life tables. All data were analyzed with the software package SPSS 11.5 (SPSS Inc, Chicago, Ill).

Results

Demographics

Table 1 summarizes demographic and clinical characteristics of HMI and HMII-DB groups. Age, sex, etiology of congestive heart failure, pre-LVAD ejection fraction, and duration of heart failure were similar between HMI and HMII-DB groups. Patients in the HMI cohort were supported for 107.3 ± 112.2 days, versus 91.9 ± 117.8 days in the HMII-DB cohort ($P = .610$). All HMI devices were

implanted as a bridge to transplant; all but two HMII-DB devices were implanted as bridge to transplant. Previous pregnancy was uncommon in both groups. A slightly higher percentage of HMII-DB patients than HMI patients died while awaiting OHT ($P = .306$); a significantly higher percentage of HMII-DB patients were awaiting OHT at the time of analysis ($P = .014$), contributing to the lower rate of successful bridging to transplant in the HMII-DB group ($P < .001$). The medical regimens of patients during LVAD support were similar except for a higher proportion of HMII-DB patients treated with β -blocker therapy ($P < .001$), aspirin ($P = .001$), and diuretics ($P = .049$). A higher rate of wound and device infections was observed in the HMI group than in the HMII-DB group ($P = .001$). Rates of previous surgery and previous transplant were comparable among both groups.

Blood Transfusions During LVAD Support

The transfusion histories for all patients during LVAD support at our institution are listed in Table E1. Most transfusions in both HMI and HMII-DB groups were leukofiltered red blood cells, and total rates of transfusions per patient were similar between groups ($P = .953$).

Anti-HLA Antibodies and Immunotherapy

A total of 10 HMI (27.7%) and 2 HMII-DB (8.3%) patients developed detectable anti-HLA antibodies reacting with greater than 10% of the HLA reference panel during the course of LVAD support, ($P = .025$; Figure 1, A). A higher percentage of patients in the HMI group than in the HMII-DB group were found to be sensitized on examination within 1 and 3 months after device implantation ($P < .001$, $P = .021$, respectively; Figure 2, A), and a trend toward increased mean peak PRA levels was observed in the HMI group at 3 months ($P = .09$; Figure 2, B). In the HMI group, 3 of 10 sensitized patients (30%) had IgG antibodies to class I molecules, 5 (50%) had IgG antibodies to class II molecules, and 2 (20%) had antibodies to both class I and class II molecules. In contrast, both the sensitized patients in the HMII-DB group had IgG antibodies against both class I and class II molecules. Immunotherapy with IVIG and cyclophosphamide was instituted in both HMI (IVIG $n = 10$, cyclophosphamide $n = 5$) and HMII-DB (IVIG $n = 2$, cyclophosphamide $n = 2$) patients with sensitization ($P = .001$), resulting in only 20% of HMI and 7.7% of HMII-DB patients with elevated antibodies at OHT (Figure 1, B).

Sensitized patients from the HMI and HMII-DB groups had average durations of LVAD support of 128.0 ± 91.2 and 79.0 ± 59.4 days, respectively ($P = .437$). Seven of 10 sensitized HMI patients and 1 of 2 sensitized HMII-DB patients were male, and 1 HMII-DB patient had a previous pregnancy. Rates of infection and previous surgery were

comparable between sensitized groups, and the HMI group averaged 34.7 ± 3.74 total transfusions vs 40.5 ± 0.7 the for HMII-DB group ($P = .753$). There was no significant difference in waiting times between sensitized and nonsensitized patients in this study (229.5 ± 144.9 days vs 168.0 ± 173.2 days, respectively, $P = .418$).

Donor and Recipient Characteristics

The clinical characteristics of 32 HMI and 13 HMII-DB patients successfully bridged to transplant are listed in Table 2. The age, duration of heart failure, duration of support, transfusion rate, cytomegalovirus status, waiting time, and donor characteristics were comparable between HMI and HMII-DB groups. Almost three quarters of all transplant recipients were listed as United Network for Organ Sharing status 1A.

Acute Rejection

Patient follow-up after OHT was 9 months for both HMI and HMII-DB groups. Acute rejection within the first 9 months after OHT was documented in 16 patients in the HMI group (50%, 0.69 episodes/patient) and only 3 in the HMII-DB group (23%, 0.31 episodes/patient, $P = .052$; Figure 2, C). Sensitization, or the development of anti-HLA antibodies during LVAD support, may translate to a higher rate of acute rejection within the first 9 months, as evidenced by the fact that 5 HMI patients (50%) and 0 HMII-DB patients (0%) who were sensitized had rejection occur ($P = .455$).

Actuarial Survival

Kaplan–Meier survival curves after OHT with life tables for sensitized and nonsensitized HMI and HMII-DB patients were constructed for 6-month and 1-year time points. Sensitization did not statistically affect short-term survival after OHT in either LVAD group at 6 months (HMI 88.9% vs

Figure 1. A, Overall percentage of patients sensitized at any time during left ventricular assist device support by device type. Asterisk indicates $P = .025$ versus HeartMate I. HMI, HeartMate I; HMII-DB, HeartMate II or DeBakey. B, Percentage of sensitized patients before transplant ($P = .590$). HMI, HeartMate I; HMII-DB, HeartMate II or DeBakey.

Figure 2. A, Percentage of patients sensitized during first 3 months of left ventricular assist device (LVAD) support by device type. Asterisk indicates $P < .001$ versus HeartMate I at 1 month; dagger indicates $P = .021$ versus HeartMate I at 3 months. HMI, HeartMate I; HMII-DB, HeartMate II or DeBakey. B, Mean peak panel reactive antibody (PRA) levels during first 3 months of left ventricular assist device (LVAD) support and before transplant by device type (HeartMate II or DeBakey vs HeartMate I, $P = .09$ at 3 months). HMI, HeartMate I; HMII-DB, HeartMate II or DeBakey. C, Acute rejection within first 9 months after transplant was increased after HeartMate I (HMI) support versus HeartMate II or DeBakey (HMII-DB) support when examining all patients undergoing transplant. Asterisk indicates $P = .052$ versus HeartMate I.

HMII-DB 100%) or at 1 year (HMI 77.8% vs HMII-DB 100%, log-rank $P = .78$).

Interleukin 6

IL-6, measured after device support at the time of OHT, was significantly lower in the HMII-DB group than in the HMI group, despite equivalence in duration of support, age, etiology of heart failure, previous operation rate, previous pregnancy rate, and transfusion rate (6.44 ± 2.45 vs 22.02 ± 5.39 ng/mL, respectively, $P < .001$). In the group of patients with IL-6 levels measured, none of the HMII-DB patients and only 1 HMI patient had a clinically relevant infection.

Discussion

The population of patients with congestive heart failure who receive LVAD support as a bridge to transplant has increased, as have hazards associated with device exposure, namely allosensitization. The ability to characterize and modulate factors affecting long-term outcomes after mechanical support and OHT is of paramount importance because of the scarcity of donor organs for transplant. In this study, the rate of allosensitization in patients after mechanical support with either HMII-DB or HMI devices was studied, and the primary clinical outcomes of acute rejection and survival were compared. The primary findings were as follows: (1) patients with HMII-DB devices demonstrated lower rates

TABLE 2. Donor and recipient characteristics of patients undergoing orthotopic heart transplant

	HMI	HMII-DB	P value
Recipient			
No.	32	13	
Age (y, mean $\pm$ SD)	51.9 $\pm$ 13.0	51.2 $\pm$ 12.7	.865
Male (No.)	28 (88%)	11 (85%)	.799
LVAD implanted (No.)			
HeartMate I	32 (100%)	0 (0%)	>.999
HeartMate II	0 (0%)	7 (54%)	>.999
DeBakey	0 (0%)	6 (46%)	>.999
Etiology (No.)			
Ischemic	16 (50%)	7 (54%)	.817
Nonischemic	16 (50%)	6 (46%)	.817
Duration of congestive heart failure (mo, mean $\pm$ SD)	48.1 $\pm$ 56.3	60.7 $\pm$ 47.8	.245
Duration of LVAD support (d, mean $\pm$ SD)	117.3 $\pm$ 114.9	132.2 $\pm$ 145.4	.745
Anti-HLA antibodies >10% (sensitized, No.)	9 (28.1%)	1 (7.7%)	.002
Transfusions during LVAD support			.0123
Total	1034	562	
Per patient (mean)	32.3	43.2	
United Network for Organ Sharing status (No.)			
1A	20 (63%)	9 (69%)	.672
1B	12 (37%)	4 (31%)	.732
Positive cytomegalovirus status after transplant (No.)	21 (66%)	11 (85%)	.281
Waiting time (d, mean $\pm$ SD)	187.5 $\pm$ 300.2	185.0 $\pm$ 145.9	.971
Donor			
Age (y, mean $\pm$ SD)	31.4 $\pm$ 11.2	31.6 $\pm$ 10.4	.949
Ischemic time (min, mean $\pm$ SD)	181.6 $\pm$ 49.0	208.9 $\pm$ 45.5	.179
HLA locus complete mismatch (No.)			
HLA-A	22 (69%)	8 (62%)	.797
HLA-B	26 (81%)	10 (77%)	.931
HLA-DR	18 (56%)	8 (62%)	.611
Positive direct crossmatch (No.)	1 (3%)	0 (0%)	.524

HMI, HeartMate I group; HMII-DB, HeartMate II or DeBakey group; LVAD, left ventricular assist device.

of allosensitization through the duration of support, and (2) sensitization did not affect short-term survival in either the HMII-DB or the HMI group. Clinical follow-up suggested a trend toward lower rejection rates in the HMII-DB group, particularly in sensitized patients. These findings in the two device groups were independent of duration of support, number of previous operations and blood transfusions, and age.

Patients traditionally at risk for allosensitization include those with increased antigenic exposure, such as patients receiving multiple blood products, those undergoing multiple transplants, those with other previous operations, and those with a history of pregnancy.⁹⁻¹² LVAD support with the HMI device has increased the percentage of transplant recipients with anti-HLA antibodies to class I and class II immunoglobulins anywhere from 17% to 66% in some studies.^{1,13} Host interactions with device biomaterials, specifically the textured chamber surface, polyurethane diaphragm, and polytetrafluoroethylene components found in the HMI LVAD, have been proposed as one mechanism responsible for an increased immunologic and inflammatory response seen after

LVAD support. A number of important immunologic observations have been made in support of this hypothesis: aberrant T-cell activation on the LVAD surface,⁸ defective T-cell proliferation,¹⁴ and polyclonal B-cell hyperactivity with CD40 ligand interactions.¹⁴⁻¹⁶ The pseudointima formed on the textured surface of the Thoratec HMI device contains an abundance of T cells, macrophages, and monocytes and reflects the constant interaction of blood with the device. The presence of both LVAD material and IL-2 is required for cultured T cells from this membrane to survive, indicative of a heightened cellular response to the LVAD surface.¹⁷ High levels of CD95, a T-cell activation marker associated with apoptosis, are found in circulating CD4 and CD8 cells after LVAD implantation, reflecting systemic activation. The cytokine profile associated with pulsatile LVADs has also been examined, showing selective loss of T cells with expression of T_H1-type cytokines. IL-6, a critical cytokine involved in B-cell differentiation, IL-2 expansion, C5a-mediated complement activation, and intrinsic coagulation activation, may contribute to both proimmunologic and

fibrinolytic pathways after LVAD support.^{18,19} Finally, patients with LVAD support have been shown to possess higher levels of circulating anti-HLA antibodies and antiphospholipid antibodies, consistent with systemic polyclonal B-cell activation.

Axial-flow devices have been hypothesized to lower the immunologic and inflammatory response seen after prolonged support as a result of lower overall textured surface area (textured surfaces are found only along the inflow cannula of the HeartMate II device) and absence of biologic chamber valves. As reported in a previous case series of 14 patients,⁷ support with the DeBakey device resulted in no patients with detectable anti-HLA antibodies as measured by complement dependent cytotoxicity. This study's data support those findings in a larger number of patients; axial-flow devices were associated with a significantly lower rate of allosensitization than were pulsatile devices when compared in a standardized clinical regimen. Our rate of sensitization with pulsatile devices of 27.7% was similar to most previously reported rates and lower than the previously reported rate at our institution (66%).¹ Conflicting rates of sensitization exist, however, for axial-flow devices; one series of 19 consecutive patients receiving the DeBakey device reported a sensitization rate of 10.5%,¹² whereas Grinda and colleagues⁷ found that no patients of 14 with the same device became sensitized. The inability to account for differences in transfusion rates and the small sample size, respectively, limit conclusions from these studies.

The comorbidities of both cohorts highlight the recent trend toward LVAD support for sicker patients who have had more previous operations, more blood transfusions, and longer duration of heart failure. The two LVAD cohorts had equal rates of previous operations, amounts of blood transfusions, previous transplants, duration of heart failure, etiology of heart failure, and duration of LVAD support. Specific risk factors for allosensitization, such as previous pregnancy and platelet transfusions, were comparable between HMI and HMII-DB groups. The high rate of anti-HLA antibodies in the HMI group suggests that an intrinsic component of pulsatile devices accounted for immunologic sensitization. Patients in the HMI group produced anti-HLA antibodies earlier in the course of LVAD support than did those in the HMII-DB group, and they required more immunotherapy. The success of immunotherapy, as documented in other series,¹ resulted in fewer patients in our study undergoing OHT with elevated anti-HLA antibodies. As a result of our common use of immunotherapy,¹ sensitization did not increase the waiting time for transplant in our study. Finally, the higher rate of sensitization in the HMI group did not affect the rate of successful bridge to transplant.

Allosensitization may have important clinical consequences for the short and long-term outcomes of cardiac transplant recipients. In a large cohort study, 3-year survival after OHT was significantly lower for patients with a PRA

level greater than 11%.⁶ The degree of sensitization has also been shown to be an independent risk factor for decreased survival,²⁰ and higher rates of acute rejection and transplant vasculopathy have been associated with sensitization.²⁻⁶ These findings have been confirmed for sensitization occurring in the setting of LVAD support as well.¹⁵ Other complications, such as infections, thromboembolism, and increased waiting times, are due in part to logistic constraints imposed by the necessity of crossmatching before transplant and a smaller donor pool. More recent data suggest that outcomes of sensitized patients after immunotherapy do not differ from those of non-sensitized patients.^{1,21} Despite the small sample sizes, a lower overall rate and fewer total episodes of rejection were seen in HMII-DB patients in this study; of the HMII-DB patients with sensitization, none had rejection, whereas a higher proportion of sensitized HMI patients eventually had acute rejection. This finding is consistent with the hypothesis that systemic immune response is heightened and more vigorous in patients supported with pulsatile devices, possibly as a result of sustained and persistent stimulus of B- and T-cell activation by device biomaterials. In support of this theory, elevated levels of IL-6, a regulatory cytokine critical in IL-2 induction, B-cell expansion, and the acute-phase reaction, were found in the HMI group and could not be accounted for by other causes of IL-6 elevation, such as bacteremia, autoimmune diseases, proliferative diseases, or neoplastic conditions. IL-6 may also be involved in acute rejection, with elevated levels found before acute rejection in kidney transplant recipients.^{19,22} It is also notable that infection may be temporally related to immunologic sensitization, because 7 of 8 HMI patients with an infection showed sensitization during the same observation period; the possibility of synergistic mechanisms has yet to be studied. Finally, survival was not affected by sensitization in either the HMI or the HMII-DB group, because immunotherapy was effective in lowering the percentage of patients with elevated antibodies before OHT. Improved immunosuppression and surveillance may also contribute to better overall post-LVAD and posttransplant care.

A number of limitations in this study must be noted. The HMI group had a slightly higher rate of wound and device infection, and although this did not result in sustained bacteremia, it may have influenced overall outcomes after OHT. The small sample sizes and disparity in number of HMI and HMII-DB patients undergoing OHT require our findings to be confirmed in the future, as axial-flow device use becomes more prevalent. A distinct learning curve exists with LVAD technology, and this data set included patients with LVADs implanted more than 5 years ago. Newer and improved surgical techniques may have affected the overall care and medical regimen of the patients, thus affecting outcomes and sensitization. Finally, although patients were matched for risk factors, the study population was not randomized, and the possibility of selection bias exists.

Despite these shortcomings, this study presents convincing evidence that axial-flow devices are associated with lower rates of allosensitization than are pulsatile devices in a case-control setting. Patients in the HMII-DB group had fewer anti-HLA antibodies later in the course of support, and this resulted in fewer severe episodes of acute rejection. The high number of multiple rejections and elevated cytokine profile in the HMI group suggests sustained immunologic activation by device biomaterial components, which may contribute significantly to the development of sensitization. Finally, immunotherapy is an effective treatment for allosensitization during LVAD support when given before OHT. An increased understanding of host interactions with LVAD biomaterials may improve outcomes in the future, warranting further study into specific immunologic mechanisms.

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TABLE E1. Transfusions during left ventricular assist device support

	HMI	HMII-DB	<i>P</i> value
Total red blood cells	544 (15.11)	394 (16.42)	.703
Washed	0 (0)	1 (0.04)	.328
Irradiated	6 (0.17)	0 (0.0)	.419
Leukofiltered	1 (0.03)	15 (0.63)	.170
Leukofiltered and irradiated	492 (13.67)	278 (11.58)	.958
Leukofiltered and tested for sickle cell	1 (0.03)	1 (0.04)	.783
Leukofiltered, irradiated, and tested for sickle cell	44 (1.22)	46 (1.92)	.329
Total fresh-frozen plasma, thawed	247 (6.86)	83 (3.46)	.078
Total liquid plasma	172 (4.78)	99 (4.13)	.794
Total platelets (pheresis)	123 (3.42)	63 (2.63)	.550
Total factor VII	0 (0)	4 (0.17)	.103
Total cryoprecipitate, thawed	111 (3.08)	115 (4.79)	.200
Total cryoprecipitate, depleted	64 (1.78)	33 (1.38)	.561
Total transfusions	1261 (35.0)	846 (35.3)	.953

All values represent total units administered to group, with mean units per patient in parentheses. *HMI*, HeartMate I group; *HMII-DB*, HeartMate II or DeBakey group.