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Factors associated with anti-human leukocyte antigen antibodies in patients supported with continuous-flow devices and effect on probability of transplant and post-transplant outcomes

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BACKGROUND: One major disadvantage of ventricular assist device (VAD) therapy is the development of human-leukocyte antigen (HLA) antibodies. We aimed to identify factors associated with HLA antibodies during continuous flow (CF)-VAD support and assess the effect on transplant probability and outcomes.
METHODS: We included 143 consecutive heart failure patients who received a CF-VAD as a bridge-to-transplant at 3 institutions. Factors associated with post-VAD peak panel reactive antibodies (PRA) among several measurements were identified using multivariable linear regression. A parametric survival model was used to assess transplant waiting time and probability, risk of rejection, and a composite outcome of rejection, graft failure, and death.
RESULTS: Thirty-six patients (25%) were female; mean age was 47 ± 13 years. Eighty-one patients (57%) had a pre-VAD PRA of 0%, and 16 were highly sensitized (PRA > 80%). Age, female sex, and pre-VAD PRA were independently associated with post-VAD PRA. A 10-year increase in age was associated with a 5% decrease in post-VAD PRA ($p = 0.03$). Post-VAD PRA was 19% higher in women vs men ($p < 0.01$). A 10%-increase in pre-VAD PRA was associated with a 4.7% higher post-VAD PRA ($p < 0.01$). During a mean follow-up of 12 ± 11 months, 90 patients underwent cardiac transplantation. A 20% increase in post-VAD PRA was associated with 13% lower probability of transplant (hazard ratio, 0.87; 95% confidence interval, 0.76–0.99). A high PRA was not associated with adverse post-transplant outcomes.
CONCLUSIONS: Younger age, female sex, and pre-VAD PRA were independent predictors of elevated PRA post-VAD. Higher PRA was significantly associated with lower transplant probability but not increased rejection, graft failure, or death after transplant.
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Advanced heart failure (HF) affects 10% of the HF population and is associated with poor quality of life, recurrent hospitalizations, and high mortality at 1 year.[1–3] Heart transplantation remains the best therapeutic option;

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however, 10% to 30% of patients die waiting for a donor heart due to organ shortages and long waiting times.[4,5] Ventricular assist devices (VADs) are increasingly being adopted as a bridge to transplant, with excellent survival approaching 85% at 1 year.[6]

VADs improve functional status, quality of life, and survival of patients with advanced HF.[6–10] Complications post-VAD are not uncommon, however, and include post-operative bleeding, stroke, infection, and renal failure. In addition, patients may develop anti-human leukocyte antigen (HLA) antibodies, a process known as sensitization. HLA antibodies are commonly reported as a percentage panel reactive antibody (PRA), reflecting the frequency of donors considered incompatible for the patient based on identified antibodies.[11] The risk of sensitization, defined as a PRA $>$ 10%, may be 3-fold higher in HF patients bridged to transplant with a VAD vs non-bridged transplant recipients.[12] Sensitization is associated with a higher risk of rejection, a higher risk of cardiac allograft vasculopathy, and inferior post-transplant survival.[13–16] Moreover, sensitized transplant candidates face longer waiting times and increased overall waiting time mortality.[17]

Several factors have been proposed to increase sensitization after VAD implant. One predisposing factor is the immunologic response to the biomaterial on the VAD surface.[18–21] Sensitization may also be related to requirements for peri-operative blood products and an increased exposure to infection. Other risk factors for sensitization have been identified, including female sex, black race, and prior pregnancies.[22] The purpose of this study was to identify factors associated with anti-HLA antibodies after continuous-flow (CF) VAD implant and to assess the effect of PRA levels on transplant waiting time and probability of heart transplantation.

Methods

Study population and variables

This was a retrospective cohort study of 143 consecutive patients with end-stage HF undergoing CF-VAD implant as a bridge to transplant at 3 institutions (Rigshospitalet, Denmark; Royal Perth Hospital, Australia; and Toronto General Hospital, Canada) between 2006 and 2013. Appropriate Institutional Review Board approval was obtained.

Variables obtained included clinical characteristics (age, sex, body mass index [BMI], etiology of cardiomyopathy [CMP], previous sternotomy), laboratory values (creatinine, hemoglobin, class I and II HLA antibodies, and total PRA before and after VAD implant), hemodynamic parameters using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification,[23] peri-operative support (days on mechanical ventilation, type and amount of blood product required, and days in the intensive care unit), and outcomes during VAD support, including sensitization (defined in this study as PRA $>$ 10%), death, and cardiac transplantation.

Measurement of anti-HLA antibodies

Anti-HLA antibodies were measured immediately before VAD implantation, 30 days after VAD support, and every 3 to 6 months thereafter using 2 different assays: complement-dependent cytotoxicity (CDC) in 65 patients and solid-phase assay in 78 patients (55%). In the CDC-based assay, HLA antibodies were measured using T-cell panels at room temperature, with immunoglobulin (Ig) M antibody excluded by heat treatment. PRA was then calculated based on the percentage of different cells in the panel where cytotoxicity was present with the patient sample. Solid-phase assays were performed using phenotype ID beads (Gen-Probe, San Diego, CA) as a screening test on the Luminex platform (Luminex Corp, Austin, TX), with single-antigen beads (One Lambda Inc, Canoga Park, CA) for confirmation and specificity identification where the screening test was positive. Class I, class II, and total PRA were determined by the percentage of beads that reacted positively with the serum (ID beads), and PRA was calculated using the Canadian Blood Services Web-based cPRA calculator, which includes the HLA type A, B, Bw, Cw, DR, DP, and DQ phenotypes.

Statistical analysis

We described PRA levels as binary variables and proportions using different thresholds.

Multivariable linear regression was used to identify factors independently associated with the peak PRA measured during VAD support. We used peak PRA during VAD support instead of closest available PRA before transplant because the presence of memory response may be reactivated after transplant, enhancing the risk of rejection.[24] Variables associated with sensitization identified in prior studies were used to consider the variables of female sex, black race, age, previous sternotomy, and type of VAD implanted, pre-VAD PRA, units of platelets and red blood cells, and the total number of transfusions received during the peri-operative period. VAD types were categorized into 3 groups: HeartMate (HM) II (Thoratec, Pleasanton, CA), HeartWare (HeartWare International, Framington, MA), and other (VentrAssist [Ventracor, Sydney, NSW Australia], Jarvik 2000 [Jarvik Heart Inc, New York, NY], and DuraHeart [Terumo Heart Inc, Ann Arbor, MI]) devices. The latter group was a single category due to the small number of patients supported with each device.

Female sex, age, pre-VAD PRA, and platelet units met the pre-specified p-value of <0.20 in univariable analysis and were simultaneously entered into a final multivariable model, which was adjusted for antibody detection method (CDC assay vs solid-phase assay) and center. The interaction effect between sex and age, and sex and pre-VAD PRA levels was not statistically significant ($p = 0.85$ and $p = 0.61$, respectively); therefore, no interactions were included in the final model. To obtain a meaningful value for the intercept (when all the predictors equal 0), age was centered at 50 years and units of platelets was centered at 1 unit.

We conducted a sensitivity analysis to evaluate factors associated with class I and class II PRA levels including the 78 patients in whom PRA was measured using solid-phase assay.

We assessed model assumptions through the analysis of residuals, which were fulfilled. The results were expressed using β coefficients and their respective 95% confidence interval (CI). Estimated β coefficients express the differences between groups of post-VAD PRA in the case of binary variables and the change of post-VAD PRA associated with a unit change in the case of continuous variables. A p-value of <0.05 was considered to indicate a statistically significant association.

The effect of post-VAD PRA on transplant probability and waiting time was assessed using the Weibull survival parametric model. The outcome of interest was time to transplant. Patients