Persistent Blood Stream Infection in Patients Supported With a Continuous-Flow Left Ventricular Assist Device Is Associated With an Increased Risk of Cerebrovascular Accidents

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ABSTRACT

Background: Common adverse events in patients supported with Continuous-flow left ventricular assist devices (CF-LVAD) include infections and cerebrovascular accidents (CVA). Some studies have suggested a possible association between blood stream infection (BSI) and CVA.

Methods and Results: Medical records of patients who received Heartmate II (HMII) CF-LVADs in 2008−2012 at a single center were reviewed. CVA was categorized as either hemorrhagic (HCVA) or ischemic (ICVA). BSI was divided into persistent (pBSI) and nonpersistent (non-pBSI). pBSI was defined as BSI with the same organism on repeated blood culture >72 hours from initial blood culture despite antibiotics. Univariate and multivariate analyses were performed to determine predictors. A total of 149 patients had HMII implanted; 76% were male, and the overall mean age was 55.4 ± 13 years. There were a total of 19 (13%) patients who had CVA (7 HCVA and 12 ICVA) at a median of 295 days (range 5−1,096 days) after implantation. There were a total of 28 (19%) patients with pBSI and 17 (11%) patients with non-pBSI. Patients with pBSI had a trend toward greater BMI (31 kg/m^2 vs 27 kg/m^2; $P = .09$), and longer duration of support (1,019 d vs 371 d; $P < .001$) compared with those with non-pBSI. Persistent BSI was associated with an increased risk of mortality and with all-cause CVA on multivariate analysis (odds ratio [OR] 5.97; $P = .003$) as well as persistent *Pseudomonas aeruginosa* infection (OR 4.54; $P = .048$).

Conclusions: Persistent BSI is not uncommon in patients supported by CF-LVAD and is highly associated with all-cause CVA and increased all-cause mortality. (*J Cardiac Fail 2015;21:119−125*)

Key Words: Left ventricular assist device, cerebrovascular accident, *Pseudomonas aeruginosa*, infection.

Left ventricular assist devices (LVADs) are an established and growing therapeutic option for patients with advanced heart failure either as bridge to transplant or destination therapy, with actuarial survival of ∼80% at 1 year and ∼70% at 2 years.[1] Despite the major improvements in survival and quality of life in patients supported with LVADs,[2] several hurdles remain. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) reports that only 30% of LVAD patients are free from any major adverse events at 1 year.[1] Infection,[3,4] device malfunction,[5] bleeding,[6−8] and cerebrovascular accidents (CVA; 11% incidence at 1 year) compose the majority of complications. Cerebrovascular accidents have detrimental consequences in any patient population but are particularly devastating in heart failure patients supported with LVADs because they may preclude these

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patients from candidacy for heart transplantation. In the general population, antecedent infection and inflammation are associated with an increased risk of CVA[9,10]; similarly, patients with infective endocarditis[11,12] are more prone to develop CVA than the general population.

A few studies have found an increased incidence of CVA in patients who develop blood stream infection (BSI) while supported with LVADs.[13,14] Most of these studies included patients with both continuous-flow LVADs (CF-LVADs) and pulsatile-flow devices, thus limiting the extrapolation of these studies to contemporary LVAD usage, because CF-LVADs comprise >95% of current implantations. Patients with CF-LVADs have lower rates of both infection and CVA compared with patients who receive pulsatile-flow LVADs.[4] Therefore, it is crucial to explore this association specifically in the CF-LVAD population. A recent pilot study found an association between CVA and any BSI in patients supported with Heartmate II (HMII; Thoratec Corp, Pleasanton, California) LVADs.[13] We conducted a retrospective study to explore these observations further with the specific aim to determine if persistent BSI (as opposed to transient BSI) is associated with an increased risk of all-cause CVA (hemorrhagic and/or ischemic) and all-cause mortality in patients who underwent HMII implantation at our institution.

Methods

Patient Population

We retrospectively reviewed the charts of consecutive patients who underwent HMII LVAD implantation from 2008 to 2012 either as bridge to transplant (BTT) or as destination therapy at our institution. Baseline clinical demographics and laboratory data as well as medical histories were obtained from medical records under an approved Institutional Review Board protocol. Brain computerized tomographic (CT) scans and cerebral angiograms, when available, were also reviewed to evaluate for CVA and mycotic aneurysms, respectively.

Definitions

International normalized ratio (INR) data were collected for the previous 4 weeks at 6 different time points before the CVA. To compare INR between groups, mean time from implantation to CVA was calculated, and this mean was used in the non-CVA cohort to match both groups for time on VAD support. For patients without CVA, INR data were collected at 6 time points in the 4 weeks before this matched time point. Lowest and highest INRs were recorded at the same time points for all patients.

To address the accuracy of blood pressure (BP) measurements in patients supported on continuous-flow pumps, we used the following protocol. If radial pulse was palpable, we collected data from manual cuff systolic and diastolic BP measurements and calculated mean BP. If radial pulse was not palpable, then we obtained Doppler opening pressure. Mean BP with the use of Doppler pressure was calculated as Doppler opening pressure minus 5 mm Hg. In cases where the presence or absence of radial pulse was not documented or was indeterminate, echocardiography (if available within 7 days of blood pressure recording) was used to determine presence or absence of aortic valve (AV) opening. If the AV opened, the systolic and diastolic BPs were used to calculate a mean BP; otherwise the Doppler pressure was used. Blood pressure measurements were averaged for a 4-week period preceding CVA in the CVA cohort. In patients without CVA, we used the median time from HMII implantation to event from the CVA cohort and applied the same time period from which to measure 4 weeks of antecedent BPs to calculate a mean BP.

BSI was determined by means of laboratory testing per standard of care at our center, and was divided into persistent (pBSI) and nonpersistent (non-pBSI). Unfortunately there is no universally accepted temporal definition of persistent bacteremia. Several studies have arbitrarily defined it with the use of a 72-hour period.[15,16] We classified BSI a priori as persistent if the same organism grew in the blood on cultures >72 hours apart despite antibiotics. All other BSI was classified as nonpersistent. All patients with BSI were treated by an infectious disease specialist with appropriate antibiotics at the time of infection; patients with recurrent LVAD-related infections were treated aggressively with chronic lifelong oral antibiotics on discharge from the hospital. CVAs were defined as a clinical neurologic deficit with brain CT findings that correlated with the deficit.

The anticoagulation protocol for patients with HMII LVADs consisted of warfarin and aspirin except for those with contraindication to the medication and/or active bleeding. At our institution, patients are started on warfarin early after surgery with dose adjustments for therapeutic INR 1.8−2.5 without the use of heparin as a bridge to therapeutic warfarin levels. All patients received perioperative antibiotic prophylaxis consisting of vancomycin, fluconazole, rifampin, and levofloxacin. The duration of device support was calculated from the implantation date to the date of data collection, death, or transplantation.

Statistical Analysis

We performed descriptive and inferential statistical analysis. All continuous variables are presented as mean ± SD and compared with the use of Mann-Whitney test or, when more than 2 groups, Kruskall-Wallis with Dunn post test. All categoric variables are presented as number and percentage and compared with the use of Fisher exact test. Univariate logistic regression analysis was performed, and multivariate analysis included variables with P values of <.2 to determine predictors of outcomes. Kaplan-Meier curves were constructed for overall mortality and freedom from stroke. P values of <.05 were considered to be significant.

Results

There were a total of 153 LVADs implanted from 2008 to 2012. Four patients were excluded because they expired the day of LVAD implantation; therefore, 149 patients were included in the final analysis. The mean age of the cohort was 55.4 ± 13 years, 76% were male, and 59% had ischemic cardiomyopathy (Table 1). The average duration of support was 642 ± 532 days (median 637, range 2−2,015). A total of 45 patients (30%) developed bacteremia. Of these, 28 (19%) had pBSI and 17 (11%) had non-pBSI (Table 1). The mean time to 1st BSI was significantly different between pBSI and non-pBSI: 343 ± 323 (median 240) days and 146 ± 154 (median 58) days, respectively (P = .02). All patients in the pBSI group cleared their