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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

A multicenter analysis of clinical hemolysis in patients supported with durable, long-term left ventricular assist device therapy

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KEYWORDS:
ventricular assist device;
hemolysis;
thrombosis;
outcomes;
survival

BACKGROUND: Despite the beneficial effects of mechanical circulatory support (MCS), the majority of patients ultimately will have an adverse event. Although hemolysis is common among temporary devices, the incidence and clinical significance of hemolysis in patients managed with long-term, durable left ventricular assist device (LVAD) therapy is largely unknown.

METHODS: Data were obtained from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). All adults who received a continuous-flow LVAD (CF-LVAD) between June 2006 and March 2012 were included. A hemolytic event was defined as a plasma-free hemoglobin >40 mg/dl in association with clinical signs of hemolysis occurring at least 72 hours after LVAD implant. Descriptive statistics, time-dependent analyses and multivariable modeling were employed for statistical purposes.

RESULTS: A total of 4,850 patients followed for a mean of 11.1 months comprised the final study population. There were 340 hemolytic events in 260 patients. Freedom from hemolysis was 97% at 3 months, 94% at 1 year and 91% at 2 years. Mean time from implant to first hemolysis event was 7.4 months. Younger age (<60 years) was independently associated with greater hemolysis ($p < 0.001$). Thrombotic device malfunction, device exchange and mortality were all significantly higher after hemolysis, with the greatest risk for each occurring within 6 months.

CONCLUSIONS: Hemolysis is not a rare event after CF-LVAD implantation and is associated with an early increase in morbidity and death. Future study should focus on other device and implant characteristics that may lead to hemolytic events, as well as appropriate strategies for managing affected patients.

J Heart Lung Transplant 2015;34:701–709

Despite the beneficial effects of left ventricular assist device (LVAD) therapy for those with advanced heart failure, most patients ultimately will have an adverse event after device implantation.[1] Hemolysis is a known complication of mechanical circulatory support (MCS). Among individuals managed with short-term LVADs, hemolysis represents one of the most common complications, affecting almost 1 of every 10 patients.[2] Although limited data would suggest that hemolysis after placement of a durable, intracorporeal LVAD is rare in the first 60 days after surgery,[1] the incidence of hemolytic events is largely unknown with longer durations of support.

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2014.10.002

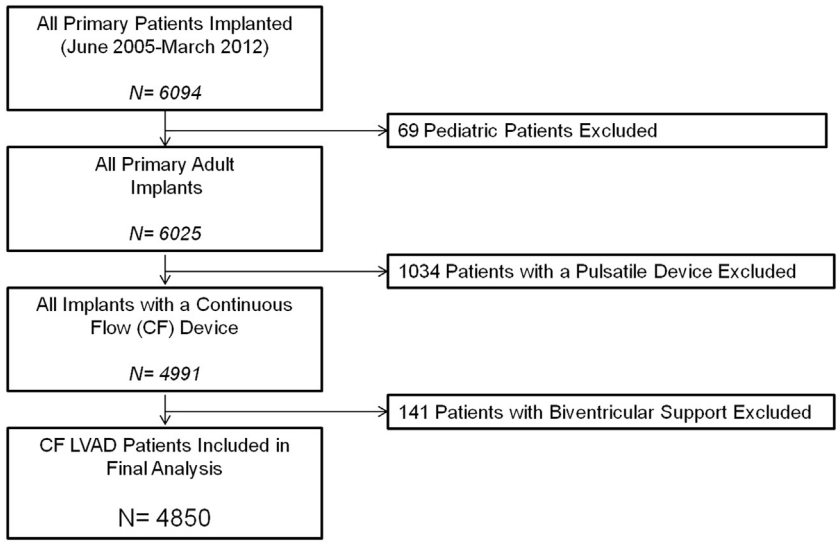

Figure 1 Derivation of study population.

Physiologic studies have shown that contemporary, axial-flow LVADs are susceptible to hemolysis.[3] Device hemocompatibility after implantation may be affected by abnormal blood-surface interactions and altered flow dynamics, leading to red blood cell fragmentation through increased sheer stress. Changes in both coagulation and host immunity may also increase hemolysis risk.[4] The exact etiology of clinical hemolysis during MCS, however, remains poorly elucidated.

Not only is the epidemiology of hemolysis in VAD-supported patients incompletely understood, but so too are the consequences of a hemolytic event. Given the rapid growth and implementation of LVAD technology among a burgeoning population of eligible heart failure patients, there is a need to more fully understand this complication and its sequelae. This is particularly pertinent given the recent increase in reporting of device thromboses,[5–7] and the implication that markers of hemolysis may herald such events.[7,8] We conducted the present study to provide a more robust evaluation of the clinical characteristics, risk factors and outcomes of hemolysis among patients supported with a durable, continuous-flow LVAD (CF-LVAD).

Methods

Data were obtained from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), representing 117 centers that perform LVAD implants. The study cohort included all adult patients (>18 years of age) who received a primary, intracorporeal CF-LVAD between June 2006 and March 2012. For descriptive purposes, categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as means if normally distributed, or as medians if the distribution was skewed. Discrete variables were compared using the chi-square test of significance, unless the frequencies were small, in which case Fisher's exact test was used. Continuous variables were compared using either the *t*-test or non-parametric Wilcoxon's rank sum test as indicated.

In INTERMACS, during this study period, a hemolytic event was defined a priori as a plasma-free hemoglobin >40 mg/dl in association with clinical signs of hemolysis, when occurring at least 72 hours after VAD implantation. Any hemolytic episode related to a non-device-related cause, if documented as such by the participating site, was excluded.

Survival analyses were performed using the Kaplan-Meier method, with censoring for heart transplantation or cardiac recovery. Stratified time-to-event curves were compared using the log-rank test. Parametric survival analysis in the hazard domain was used to identify risk factors for hemolysis. $P \leq 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.1 software (SAS Institute, Cary, NC).

Results

Demographics and comorbidities

A total of 4,850 patients were included in the final analysis (Figure 1). Among these, there were 340 hemolytic events occurring in 260 patients, with 207 patients (79.6%) having 1 hemolytic episode, 36 (13.9%) with 2 episodes, 10 (3.9%) with 3 episodes and 7 (2.7%) with >3 episodes. Pre-implantation baseline characteristics, stratified by the presence or absence of hemolysis, are presented in Table 1. Individuals who had a hemolytic event were more likely to be younger, female, and have a greater body mass index compared with those without hemolysis. Medical comorbidities were common throughout the study population, although patients with hemolysis were more likely to carry a diagnosis of chronic obstructive pulmonary disease (COPD) and less likely to have had previous coronary artery bypass graft (CABG) surgery.

Pre-implantation laboratory and hemodynamic findings

Table 1 also shows pre-implantation laboratory values. There were no significant differences in any of the biochemical, hematologic or coagulation studies between patients with and without subsequent hemolysis. Similarly,