Clinical Investigation

Acquired and Hereditary Hypercoagulable States in Patients with Continuous Flow Left Ventricular Assist Devices: Prevalence and Thrombotic Complications

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ABSTRACT

Background: Thrombotic events in patients with continuous flow left ventricular assist devices (CF-LVADs) are associated with significant morbidity and mortality. The objective of this study was to delineate the frequency, clinical characteristics, and outcomes of patients with hypercoagulable states who undergo CF-LVAD implantation.

Methods: We performed a retrospective review of 168 consecutive patients who underwent CF-LVAD implantation between 2010 and 2013. Chart and laboratory data were reviewed for the presence of a hereditary and/or acquired hypercoagulable state. Adverse outcomes were defined as death, confirmed pump thrombosis, aortic root clot, stroke, deep vein thrombosis, and pulmonary embolism. Fisher's exact test and Kaplan-Meier estimate were used to analyze frequency of adverse outcomes and event free survival, respectively.

Results: A hypercoagulable state was identified in 20 patients (11.9%). There were 18 patients with acquired, 1 with a congenital, and 1 with both congenital and acquired hypercoagulable states. The median follow-up was 429 days and 475 days in patients with and without hypercoagulable states, respectively. During the study period, 15% (3/20) of the patients with a hypercoagulable state had a diagnosis of deep vein thrombosis vs 3% (4/148) of the patients without a hypercoagulable state ($P = .030$). Only patients with a hypercoagulable state had a subarachnoid hemorrhage (3/20 vs 0/148; $P < .01$). The event-free survival was lower in the patients with hypercoagulable states ($P = .005$).

Conclusion: Hypercoagulable states are not uncommon in patients with CF-LVADs and may be associated with increased morbidity. Prospective studies are needed to more accurately identify the incidence, prevalence, and significance of hypercoagulable states in patients being considered for CF-LVAD. (*J Cardiac Fail 2016;22:501–511*)

Key Words: Hypercoagulable states, thrombosis, left ventricular assist device, HIT.

Mechanical circulatory support (MCS) is an evidence-based strategy shown to increase survival in carefully selected patients with end-stage heart failure.[1] Complications, however, are frequent, and more than 50% of patients on second-generation continuous-flow left ventricular assist devices (CF-LVADs) will have an unplanned admission during the first year after implant, and more than 50% of those admissions are associated with the device.[2] Thrombotic complications including stroke, pump thrombosis, and aortic root thrombosis are less frequent than infection or bleeding, but are associated with substantial morbidity and mortality.[3] Clinical experience with the HeartMate II, in comparison to first-generation LVADs, is associated with a decrease in thrombotic

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events.[4,5] However, recently, an increase in pump thrombosis has been reported in patients with CF-LVADs.[6] The cause of this phenomenon remains unclear but is considered multifactorial.

A hypercoagulable state can be defined as a hereditary or an acquired tendency for venous and/or arterial thromboembolism.[7] Heart failure has been recognized as a prothrombotic state; however, systematic anticoagulation has been shown to be harmful.[8,9] Heparin-induced thrombocytopenia (HIT) has been reported as a complication in a large series of patients supported by first-generation LVADs.[10–12] Three patients with antiphospholipid syndrome and MCS have been reported, and only 1 was diagnosed pre-HeartMate II implantation.[13–15] Another report describes a patient supported by an axial-flow LVAD who developed a giant left atrium thrombus and was subsequently diagnosed with concomitant protein S deficiency, heterozygous factor V Leiden mutation, and heterozygous MTHFR C667T mutation.[16] Additionally, carboxyhemefibrinogen has been described as a potential culprit of hypercoagulable states during hemolysis.[17] A recent report of patients with prior hematologic conditions that included 7 patients with hypercoagulable states (factor V Leiden, 1; elevated factor VIII, 1; HIT, 2; undefined hypercoagulable state, 3) showed an increase in morbidity and mortality in this patient population.[18] Pivotal trials with HeartMate II have not looked at HIT or underlying hypercoagulable states in a systematic manner.[4,19]

Current guidelines recommend that "patients with a history of thrombophilia (hypercoagulable state) have a hypercoagulable assessment before implant" (class I, level of evidence C).[20] However, there are no clear recommendations on how to use this information to guide prognosis and clinical decision-making.[21] Therefore, the aim of this study was to delineate the frequency, clinical characteristics, and adverse outcome event rate of patients with hypercoagulable states who underwent CF-LVAD implantation.

Methods

Study Population

Under an institutional review board–approved protocol, we retrospectively reviewed the charts of 168 consecutive patients who underwent HeartMate II CF-LVAD implantation either as a bridge to transplant or destination therapy from January 2010 to December 2013. Examined data included: demographic information, comorbidities (eg, diabetes), laboratory test results, and transthoracic echocardiogram data. Perioperative medical management was also recorded for each patient, including antiplatelet and anticoagulation treatments. Laboratory data pre- and postimplantation were examined for the presence of lupus anticoagulant (LAC) and anti-heparin platelet factor 4 (HPF4) antibodies. All available LAC and HPF4 antibody measurements were performed at the Houston Methodist Hospital clinical laboratory and ordered as part of routine medical care because of clinical suspicion and not as part of a surveillance protocol. HPF4 antibodies were measured by immunoglobulin G–specific enzyme-linked immunoabsorbent assay (GTI Diagnostics, Waukesha, WI). HPF4 qualitative assessment and optical density (OD) value were recorded.[21] LAC-sensitive partial thromboplastin time (PTT) was measured initially and, if prolonged, a hexagonal phase phospholipid assay was done to confirm the presence of LAC. Exposure to heparin and warfarin was documented for each patient. When available, results of beta-2 glycoprotein 1 (B2GP1) and anticardiolipin antibodies tests were also reported.

Definitions

Hypercoagulable State. History of an acquired and/or hereditary hypercoagulable state was identified. The following were classified as hereditary hypercoagulable states: factor V Leiden, prothrombin G20210A gene mutation, high factor VIII activity, hyperhomocysteinemia, antithrombin deficiency, and protein C or S deficiency. Myeloproliferative disorders (thrombocythemia or polycythemia vera), antiphospholipid syndrome, and HIT were classified as acquired hypercoagulable states[20] (Table 1).

Lupus Anticoagulant. If LAC was positive, patients were classified as follows: (1) isolated LAC, if there was no history of previous thrombotic events; (2) probable antiphospholipid syndrome, if LAC was positive and the patient had a history of previous thrombotic events; and (3) definitive antiphospholipid syndrome, if the patient met the International Consensus criteria.[22] If the patient had definitive antiphospholipid syndrome, it was categorized as secondary if it was associated with systemic lupus erythematosus or primary if this association was not present.

HIT. If HPF4 antibodies' OD was greater than 1, the patients were classified as follows: (1) HIT unlikely, if there was no thrombotic events and platelets were within normal limits or not significantly decreased (<30% decrease from normal); (2) isolated HIT, if thrombocytopenia or a significant decrease in platelets was recorded; (3) HIT thrombosis, if documented thrombosis was associated with thrombocytopenia and positive HPF4 results; or (4) delayed-onset HIT, if objectively proven venous or arterial thromboembolism and/or thrombocytopenia occurred after heparin cessation and a reasonably benign hospital course was noted without recognized HIT.[23] The OD value 1.0 was chosen because this cutoff has been associated with a high incidence of thrombotic complications and low incidence of false-positive results.[24] Serotonin release assay is not readily available at our institution because it is not used as part of routine clinical care; therefore, it was not included in this assessment.

Timing of Diagnosis of Hypercoagulable State. The diagnoses of hypercoagulable state were categorized as follows: as an established diagnosis if the hypercoagulable state was documented and proven before the index hospitalization for CF-LVAD implantation, as preimplantation if the diagnosis was done during the index hospitalization for CF-LVAD implantation, and as postimplantation, which was subsequently categorized as early (during the index hospitalization for CF-LVAD implantation) or late (after the patient was discharged).