Clinical Investigations

Thrombolytic Therapy for Thrombosis of Continuous Flow Ventricular Assist Devices

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ABSTRACT

Background: Despite chronic systemic anticoagulation, advanced heart failure patients treated with a continuous-flow left ventricular assist device (LVAD) remain at risk for pump thrombosis. Pump thrombosis may initially be suspected in the setting of clinical and biochemical evidence for intravascular hemolysis, putatively related to shear stress on red blood cells propelled through a partially occluded pump. Limited data exist to guide management in these patients.

Methods and Results: We present a series of 8 LVAD patients who presented with intravascular hemolysis secondary to pump thrombosis who were treated with intraventricular thrombolytic therapy. In 3 patients, thrombolytic therapy led to complete and lasting resolution of hemolysis, suggesting successful dissolution of pump thrombus. In the remaining 5 patients, thrombolytic therapy ultimately failed to halt or reverse pump thrombosis and hemolysis: 1 patient required emergent pump exchange, 2 patients progressed to cardiogenic shock and died, 1 patient suffered a debilitating stroke after which care was withdrawn, and 1 patient underwent cardiac transplantation.

Conclusions: In the setting of LVAD thrombosis, thrombolytic therapy is an alternate treatment strategy in a subset of patients. Candidacy for this alternate procedure must carefully weigh the risks of complications, including hemorrhage and thromboembolism. (*J Cardiac Fail 2014;20:91–97*)

Key Words: Circulatory support, thrombosis, heart failure.

Pump thrombosis in advanced heart failure (HF) patients supported with a continuous-flow (CF) left ventricular assist device (LVAD) can result in pump malfunction or catastrophic thromboembolism. Thrombosis can occur despite adequate use of systemic anticoagulation and can be complicated by stroke, device failure, and the need for urgent or emergent pump exchange. Despite technologic advances, this thrombosis risk has persisted with 2nd- and 3rd-generation CF devices owing to the innate thrombogenicity associated with artificial surfaces in contact with the circulatory system.

A now well established clinical sign of pump thrombosis is intravascular hemolysis (IH) often detected only by routine laboratory evaluation. Red blood cells propelled through a partially occluded, thrombus-burdened pump are subjected to increased shear stress and destroyed, releasing their contents into the bloodstream.[1,2] Indeed, LVADs explanted from patients with marked elevations in lactate dehydrogenase (LDH) and plasma free hemoglobin (PFH) have confirmed the presence of thrombus within the device.[3] Pump-related hemolysis may be accompanied by hemoglobinuria, jaundice, alterations in LVAD power consumption, clinical HF, thromboembolic events, or it may be asymptomatic. The range of values above which asymptomatic IH should be considered clinically significant and suggestive of thrombus has not been clearly defined. Some single-center studies have suggested that event-free

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survival is decreased in patients with LDH >600 U/L and PFH >40 mg/dL[4] and that thresholds for considering thrombosis should be lower than previously described.[5] These thresholds have yet to be validated in a larger, multicenter experience and we previously considered IH associated with an absolute serum LDH >1000 U/L or >2.5-fold its previous level as a marker for pump thrombosis.

We have adopted a stepped approach to the management of LVAD thrombosis at our institution. Stable outpatients without a history of bleeding or thrombosis are maintained on warfarin (international normalized ratio [INR] goal 1.5−2.5) and daily aspirin (81 mg) with LDH determined monthly. Patients demonstrating signs, symptoms, or biochemical evidence of IH (LDH >1,000 U/L or >2.5-fold its previous level) are treated with unfractionated heparin (UFH; goal: activated partial thromboplastin time [PTT] 60−90 seconds), regardless of prothrombin time or INR, for ≥48 hours. Concomitant treatment with a glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor may then be used for a total of 72 hours, in combination with high-dose aspirin (325 mg daily). In many cases, this gradual escalation in therapies adequately leads to resolution of IH (reversal of signs/symptoms of hemolysis accompanied by sustained decline in LDH to baseline levels), and the patient's outpatient regimen is modified to include dual-antiplatelet therapy with addition of clopidogrel (75 mg daily) or dipyridamole (75 mg 3 times daily) and an INR goal of >2.0. In a subset of patients, however, hemolysis becomes refractory or clinical instability warrants more aggressive therapy such as thrombolysis.

The efficacy of this strategy and associated risks of bleeding and thromboembolism remain undefined beyond case reports of successful therapy. These risks are important to consider when attempting to deliver a therapy that may lead to severe neurologic injury. Data suggest that administration of thrombolytic therapy via a catheter-directed intra-arterial route, as opposed to an intravenous route, allows for clot lysis with the use of smaller doses of tissue plasminogen activator (tPA) and reduces the likelihood of induction of a systemic lytic state.[6] These factors were taken into account when we adopted a strategy to treat patients with refractory hemolysis with thrombolysis during a period when there were limited data regarding risks associated with surgical pump exchange. We present our experience of 8 LVAD patients with refractory IH treated with intraventricular thrombolytic therapy.

Methods

Data Abstraction

We treated 8 patients with intraventricular thrombolytic therapy from September 2011 to May 2012 for refractory hemolysis as an alternative to systemic lytic therapy or device exchange. Retrospective chart review was used to abstract the data from the clinical course of these patients to understand the clinical response to this therapy. In accordance with Duke University policies, Institutional Review Board approval was obtained to perform data abstraction from the patient medical record and present the results. A waiver of consent was requested and approved before data abstraction. Because this was the primary strategy for therapy during this time period, no comparator group (ie, immediate device exchange) is reported.

Thrombolytic Therapy Administration

Patients were deemed to be candidates for tPA according to criteria similar to those used in other clinical settings in which tPA might be considered (eg, myocardial infarction, acute stroke). Patients with active internal bleeding, history of intracranial hemorrhage, or recent stroke or head trauma were not candidates for tPA. After arterial access was obtained, a pigtail catheter was advanced across the aortic valve under fluoroscopic guidance and positioned near the LVAD inflow cannula in the left ventricular apex. The tPA alteplase (1 mg/mL) was infused via the catheter at 1 mg/min over 30−50 minutes with concomitant UFH to achieve an activated clotting time >200 seconds. Following the infusion, arterial sheaths were removed 2 hours after the lytic infusion, and UFH was restarted with a target PTT of 50−80 seconds. UFH was selected as the post-lytic anticoagulant to monitor for overanticoagulation. Pharmacologic therapies were used as necessary to maintain Doppler mean arterial pressure <80 mm Hg. Serial LDH values were recorded daily following the procedure (Fig. 1).

Results

From September 2011 to May 2012, 8 LVAD-treated patients with recurrent and/or refractory hemolysis were treated with thrombolytic therapy in our catheterization laboratory (Table 1). Each of these patients was being supported by the Heartmate II LVAD (Thoratec Corp., Pleasanton, California) Over the same time period, a total of 58 durable LVADs were implanted at our center, including 34 Heartmate II devices. Rates of confirmed or suspected thrombosis (based on elevated LDH levels) with this device over the same time period increased from ∼4% to ∼8% at 3 months of support. This relationship over time has recently been published in a multicenter study and emphasizes the increased rates of thrombosis that our center was observing during the period described in this report.[7]

Patient 1 was a 44-year-old woman with nonischemic cardiomyopathy (NICM) and a history of heparin-induced thrombocytopenia who presented with recurring transient ischemic attacks accompanied by refractory IH. She underwent LVAD exchange 33 months after initial device implantation. Inspection of her explanted device confirmed the presence of thrombus within the pump housing. Five months later, routine laboratory values demonstrated recurrent IH associated with hemoglobinuria and elevations in pump power. She was treated unsuccessfully with bivalirudin and a GPIIb/IIIa inhibitor and underwent intraventricular tPA. Hemolysis resolved and power consumption returned to baseline. One year later she remained free of recurrent hemolysis and other signs of pump thrombosis.