Intravenous thrombolytic therapy for patients with ventricular assist device thrombosis: An attempt to avoid reoperation

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ABSTRACT

A growing number of patients are undergoing prolonged management of advanced heart failure with the use of continuous flow left ventricular assist devices (LVADs). Subsequently, an increasing number of patients are presenting with complications associated with these devices. Based on an analysis of three major LVAD institutions, the number of patients developing LVAD pump thrombosis may be much higher than originally projected. The management of this highly feared complication continues to be challenging, as the population of LVAD patients is very heterogeneous and heavily burdened with comorbidities. The standard protocol of increasing anticoagulation may fail to achieve successful resolution of thrombus. Difficulty and poor prognosis may make reoperation less than desirable. Here, we present a case of successful thrombolysis following intravenous administration of tissue plasminogen activator in the Intensive Care Unit setting.

Key words: Left ventricular assist devices thrombosis; Thrombolytic therapy; Ventricular assist device

INTRODUCTION

Ventricular assist device (VAD) pump thrombosis is one of the most morbid and feared complications associated with long-term dependence on continuous flow devices. There are many established risk factors for thrombosis both related to the patient and the device that may be difficult to control. The mainstay of conservative medical management of VAD thrombosis continues to begin with the augmentation of anticoagulation in combination with antiplatelet medication and treatment of heart failure symptoms with inotropes and diuretics. If this fails, depending on the individual institutional protocol, clinicians may select a direct thrombin inhibitor as a second line therapy.

After these conservative measures have failed, the remaining options for treatment are limited to surgical interventions. An algorithm published by Goldstein et al. [Figure 1] and several case reports have suggested that thrombolytic therapy may be able to spare more invasive management options such as left VAD (LVAD) exchange and explantation, or urgent heart transplantation, and their associated poor prognosis.[1] Here, we will review literature for current trends and recommendations regarding LVAD thrombosis, as well as present our experience with a case of LVAD thrombosis successfully treated with intravenous (IV) thrombolytics administered
at the bedside in a patient refusing any surgical intervention.

**CASE REPORT**

A 23-year-old man with a history of viral cardiomyopathy had undergone placement of a HeartWare LVAD as a bridge to transplantation (BTT) in August 2013. His postoperative course was complicated by subsequent right ventricular (RV) failure and was placed on continuous milrinone therapy. As an outpatient, he was on a regimen of warfarin and ASA/clopidogrel therapy. In August 2014, the flows on his LVAD device were increasing, and he presented to our institution. He was noted to have elevated lactate dehydrogenase (LDH) of 1442 units/dL as well as tea-colored urine [Figure 2]. The patient was compliant with his medications as an outpatient. His international normalized ratio (INR) on admission was 2.74. He had only mild heart failure symptoms of dyspnea on exertion. He was admitted to the Intensive Care Unit with the presumptive diagnosis of LVAD pump thrombosis and placed on argatroban infusion titrated to a goal partial thromboplastin time of 60–90 s.[2,3] His other medications included bumetanide, carvedilol, digoxin, spironolactone, and milrinone infusion, which were all continued. A transthoracic echocardiogram [Figure 3] and a computed tomography of the chest did not reveal an obvious thrombus. On the 3rd day of admission, there was a significant increase in...
LVAD flows and power as well as a steadily increasing LDH (peak >12,900) despite argatroban therapy within the therapeutic range. All options were discussed with the patient including LVAD exchange that he declined at that time. The decision was made to discontinue argatroban infusion, start a heparin drip, and administer tissue plasminogen activator (tPA) intravenously. Initial tPA dosing included a 10 mg IV bolus followed by 1 mg/min for 20 min and finally 1 mg/h for 24 h. There was an immediate improvement in the device parameters after administration of the initial tPA bolus (flow 10.1→8.2 and power 10 w→3.5 w). LDH levels continued to fall over the following days at which time the heparin drip was discontinued, and subcutaneous enoxaparin and warfarin were instituted. The patient was discharged after 13 days of stabilization to await, as an outpatient, a suitable transplant donor.

DISCUSSION

Several risk factors for continuous flow VAD pump thrombosis have been established. These include improper or inadequate anticoagulation (ASA <81 mg and/or INR <2), poorly controlled blood pressure (mean arterial pressure >90), and intermacs profile level >3.[4] In addition, patient-related factors including infection, hypovolemia, and prothrombotic state also predispose to the formation of a thrombus. There are sheer forces and blood surface contact areas that contribute to initial fibrin deposition and subsequent clot propagation. The complex interaction of the LVAD device and patient tissues also likely contributes to thrombosis by way of acquired Von Willebrand syndrome among other modifications of the coagulation cascade.[5,6]

Given that most patients are placed routinely on anticoagulants that may interfere with coagulation profile testing, evaluation for procoagulant states can become difficult to undertake once suspected. All these factors together make the selection of long-term anticoagulation an important and sometimes difficult decision that may contribute significantly to the predisposition of pump thrombosis.[7,8] In our patient with recurrent pump thrombosis, an extensive evaluation was undertaken by our hematology colleagues that revealed mildly reduced protein S levels difficult to interpret in the setting of warfarin therapy. He did, eventually, return a positive result for lupus anticoagulant as well. Several months following the initiating event, flow cytometry revealed increasing red blood cell particles and a positive Coombs test, which led to the theory that there may be ongoing subclinical thrombolysis allowing small particles of fibrin deposition providing a nidus for macro thrombus formation.

It is clear from this case that the interaction between the patient and VAD is extremely complex and that proper anticoagulation is exquisitely important, but may not preclude the need for management of pump thrombosis despite our best efforts.

The initial risk of pump thrombosis, specifically related to the Heartmate II device, was estimated to be 2–4%. However, a quality review and subsequent compilation and analysis of data from three major hospitals showed significantly higher values—12.3% confirmed during the first 24 months of support with Heartmate II.[1] The risk appears to be highest during the 1st month following implantation and then decreases, but continues at a steady monthly rate. Data related to the HeartWare device estimate the incidence as 8.1% in one reported cohort, though this study also included devices that were implanted prior to the design change to include sintering of the inflow cannula.[3] Though the specific device selected may contribute to thrombus formation, it is clear that all continuous flow devices have the potential for thrombosis.[6]

The diagnosis of LVAD thrombosis can be an equally complex issue as deciding how to treat this complication. Recommendations regarding the diagnosis of pump thrombosis will not be reviewed here. A one-size-fits-all approach to treatment is impractical, given the extreme variability in the patient population undergoing long-term LVAD therapy. However, as mentioned, an algorithm has been published and incorporated into the development of institutional protocols [Figure 1].[3] The initial approach includes assessment of the adequacy of outpatient anticoagulation. Both inadequate anticoagulation and antiplatelet management are well-established risk factors for thrombus formation. Anticoagulation management can then be augmented with IV heparin while continuing or implementing antiplatelet therapy. A review of optimal anticoagulation strategies has suggested at least 70% inhibition of platelet activity.[7] If the patient continues to deteriorate, additional anticoagulation with direct thrombin inhibitors or glycoprotein IIb/IIIa inhibitors have both been suggested. Finally, if more intensive management is needed, it is advisable to consider the patient as a candidate for thrombolytic therapy either in the cardiac catheterization lab or, as we describe below, via IV administration.[3] Signs of continued thrombus include
an elevated LDH, increased pump power, hematuria, progression of heart failure symptoms, or signs of thrombus on echocardiography.

Medical management of LVAD thrombosis includes the use of IV anticoagulants including heparin infusion, direct thrombin inhibitors, and glycoprotein IIb/IIIa inhibitors, individually or in combination, as well as thrombolytic therapy. A review of the currently available case reports and series on the medical management of LVAD thrombosis [Table 1] includes the successful treatment of LVAD thrombosis with the intracavitary administration of thrombolytics.[9,10] Vascular access for intracavitary drug administration, though typically performed by interventional cardiologists, is not without risk, and vascular injury has been reported in literature.[9] One case series also reports the administration of IV thrombolytics in five cases with subsequent resolution.[11] Even still there are cases when the thrombus is highly resistant to treatment and surgical intervention is unavoidable, as in our patient. However, we feel that if the patient has no absolute contraindication, thrombolytics would be an excellent option for medical treatment as a final attempt to avoid surgical intervention, though this decision would be made in a multidisciplinary meeting with the patient.

The role of the anesthesiologist in the setting of VAD thrombosis involves knowledge and expertise of the altered physiology that may present as the patient may require surgical intervention at any time. The cardiac anesthesiologist’s skill in echocardiography is invaluable to diagnose thrombosis as well as guide adjustment of the VAD parameters and manage fluid balance to optimize left ventricular offloading and improve RV function.

Our patient was unique in many ways including the development of high sensitivity and persistent elevated panel-reactive antibodies, despite plasmapheresis and IVIG administration. The patient, therefore, was expected to have a prolonged course of VAD support despite being classified as a bridge to transplant (BTT) status. The patient presented a month after hospital discharge with symptoms of recurrent thrombosis. Following a similar evaluation and course, he received a repeated administration of tPA intravenously. Unfortunately, the patient did not respond to the repeated dosing and subsequently agreed to undergo VAD exchange. The situation became increasingly difficult as even securing matched blood for transfusion was a challenge due to the patient’s high antibody burden. The patient developed thrombus of his new LVAD after replacement and was, at that time, deemed not to be a surgical candidate. He died 18 months later.

CONCLUSION

The use of LVADs is increasing due to the discrepancy between the number of patients listed for a heart transplant and the number of donor organs available. In addition, they have demonstrated improvement in functional status, quality of life, and survival in patients with advanced heart failure.[12] As a result of this, we will continue to face the challenging complication of pump thrombosis. Many patients, such as the case reported here, are predisposed to a pro-thrombotic state that is undiagnosed prior to VAD implantation. Here, we have

### Table 1: Reported Experience with Medical Management of LVAD Thrombosis

| Source         | Number treated | Thrombolytics? | Success rate | Type of device |
|----------------|----------------|----------------|--------------|----------------|
| Kieman et al. | 1              | Yes            | 100 (1/1)    | HVAD           |
| Aissaani et al. | 2             | Yes            | 100 (1/2)    | HVAD           |
| Al-Quatami et al. | 2        | N- GP 2B3A inhibitor | 100 (2/2)    | HM II          |
| Kamouth et al. | 1              | Yes            | 100 (1/1)    | HVAD           |
| Lenneman et al. | 2              | Yes            | 37.5 (9/24)  | Not specified  |
| Muthiah et al. | 5              | Yes- in 4 patients | 60 (3/5); tPA- 50 (2/4) | HVAD |
| Starling et al. | 38            | Yes- Not specified number | Not specified | HM II |
| Najjar et al. | 30             | Yes- in 19 patients | 50 (15/30); tPA- 63.2 (12/19) | HVAD |
| Schliendorf et al. | 8         | Yes- All       | 37.5 (3/8)   | HM II          |
| Tellor et al. | 17 (22 attempts) | N- GP 2B3A inhibitor | 22.7 (5/22); 17.6 (3/17) | Mixed- 16 HMII; 1 HVAD |
| Raffa et al. | 4 (9 attempts) | Yes- All endoventricular | 100 (5/5)   | HVAD           |

*Received “alteplase, eptifibatide, or both” but no further details provided, *Exact details not specified. However, mortality of patients who did not undergo transplant or pump exchange was reported as 48.2% at six months, *Also used heparin and GP 2b3a inhibitors alone or in combination, *5 of 22 attempts resulted in resolution of 1 indicator of thrombosis while 3 of 17 patients remained free of hemolysis, death, pump exchange or emergent transplant, *One patient required 5 separate attempts and one required 2 attempts before successful resolution of thrombosis.
presented one possible option for bedside management in a closely monitored setting. In patients who are at an appreciably low risk for subsequent bleeding and are hemodynamically stable, we believe it is reasonable to attempt thrombolytic therapy in an effort to avoid more invasive surgical interventions.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

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