

Thrombolytics in VAD management – A single-center experience



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ARTICLE INFO

Article history:

Received 4 January 2016

Accepted 4 March 2016

Available online 18 March 2016

Keywords:

LVAD thrombus

Thrombolytics

TPA

CF pumps

ABSTRACT

Background: With continued increase in the use of mechanical circulatory support, the incidence of device thrombus remains a challenge. This study is a retrospective analysis of data at a single center to assess the safety and efficacy of thrombolytic use in durable mechanical assist devices.

Methods: Data was analyzed retrospectively from 154 patients who underwent left ventricular assist device (LVAD) implantation from 1/1/2005 to 6/30/2014. The HMII device was implanted in 131 patients while 23 received the HVAD. LVAD thrombus was diagnosed when lactate dehydrogenase levels exceeded 1000 units/l accompanied by clinical signs of hemolysis and heart failure, echocardiographic data and surges in pump power. TPA (tissue plasminogen activator) protocol consisted of a 5 mg intravenous bolus followed by 3 mg/h infusion in normal saline for 10 h. If symptoms persisted another cycle of TPA at 1 mg/h was continued up to 48 h.

Results: The TPA group had a 70% success rate. Success was defined as complete resolution of hemolysis and clinical symptoms with no requirement for LVAD exchange at 30 days. 95% survival was noted at 30 days and 90% were free of a hemorrhagic stroke in the TPA group. The rates of hemorrhagic strokes in the TPA group and the control group were not different (OR = 0.92).

Conclusion: The TPA protocol described here was successful consistently. Though this study is limited by its size and retrospective nature it leads the way for larger studies to generate more robust comparisons between different types of mechanical assist devices as well as the tailored use of thrombolytics in this patient population.

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1. Background

Left ventricular assist devices (LVADs) have rapidly evolved as a standard therapy for end stage heart failure either as bridge to transplant (BTT) or as destination therapy (DT). The continuous-flow LVADs are smaller, less audible and more durable than the older pulsatile pumps. The smaller size allows placement in patients with a smaller body habitus [1]. With the extension of life and the more frequent use of these devices, complications have also evolved in this population of patients. Of these, bleeding and thrombosis have been the two major challenges.

The HeartWare HVAD (centrifugal pump) and the HeartMate II (axial-flow) provide unloading of the left ventricle throughout the cardiac cycle. This property leads to low pulse pressures and predisposition to arteriovenous malformations in the gastrointestinal tract contributing to bleeding. Bleeding is one of the most common adverse events in the first month after implantation [2]. Additionally the shear forces generated by these pumps accentuate the bleeding risk due to acquired

von Willebrand disease which is known to resolve after device explant [2]. Passive hepatic congestion secondary to biventricular failure can also predispose these individuals to increased bleeding complications.

Thrombus formation is the other complication that affects the mechanical circulatory support population. Mechanical causes of thrombosis include post-surgical ventricular debris, emboli secondary to clots in the left atrial appendage and endocardial surface of the LV as well as inflow cannula malposition [3]. Inadequate anti-coagulation or anti-platelet therapy can contribute to thrombus formation. Interaction of prosthetic material with blood, leads to significant prolongation of hematologic, inflammatory, or immunologic responses. Prolonged activation of endothelial and coagulation systems after continuous flow-VAD implantation also seem to contribute to observed thrombosis. Inter-cellular adhesion molecules, E-selectin, tissue factor and D-dimer have all been shown to be up regulated status post-implantation [4,5].

Both HeartWare (HVAD) and HeartMate II (HMII) patients are susceptible to thrombosis. Increasing incidence of pump thrombosis has been well documented in literature [6–8]. Pump thrombosis can cause life-threatening device malfunction and embolic strokes. Patients with end-stage heart failure also tend to be in a pro-inflammatory state which can promote thrombosis. Multiple mechanisms appear to contribute to pump thrombosis [3–8].

Pump thrombosis is typically diagnosed by combination of increasing lactate dehydrogenase (LDH)/plasma free hemoglobin, low

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haptoglobin, hematuria, low flow, cardiogenic shock, inability to unload the left ventricle, pump power surges and sustained power elevations [3]. Imaging modalities, such as CT and echocardiogram, are often used to help identify thrombosis [9,10]. The efficiency of these modalities to visualize the interior aspect of the pump is limited hence the entire clinical picture needs to be used to arrive at the diagnosis. There is limited data on the best therapy for pump thrombosis at present. Recommendations for management vary widely ranging from medical management to catheter-directed thrombolysis and/or pump exchange as the first option [7–20].

The incidence of device thrombosis has been estimated as 2–13% in adult continuous-flow devices [3,6,8,21,22]. Prevention of thrombosis would be the most ideal strategy, which seems far away in the present day. The optimal doses of antiplatelet and anticoagulation treatments are still undefined due to lack of well-designed/controlled clinical trials. Despite a fairly rigid regimen of anticoagulation and antiplatelet measures, pump thrombosis still occurs and has devastating consequences [23–27]. In addition to the existing routinely used regimens, other anticoagulants/antiplatelet agents reported in the literature include dipyridamole, pentoxifylline, dextran, and fluindione [28–31].

Several etiologies for pump thrombosis, and the dilemma faced with treatment options, make this an important area of ongoing research [6,8,22,32]. Though much knowledge has been gained in the field of anticoagulation, it is still difficult to pinpoint the few factors that predispose the patient to a device thrombus. Hence, the definition of a universal robust anticoagulation protocol still remains ambiguous.

As the standard of care in most centers is LVAD exchange which is a procedure associated with a high mortality and morbidity, a trial of TPA thrombolysis may be appropriate prior to such a major surgical undertaking in the absence of any contraindications. This retrospective study therefore seeks to examine results of thrombolytic treatment administered peripherally for LVAD thrombosis in both HVAD and HMII patients at a single center. The specific aims are 1) to determine if device thrombosis can be successfully treated with tissue plasminogen activator (TPA) protocol used in this center 2) to assess complications associated with TPA treatment.

2. Methods

This retrospective study was approved by Institutional Review Board Spokane (IRB#1942) in Spokane, Washington. A retrospective chart review was performed on patients who had either received a HeartMate II LVAD [Thoratec Corp., Pleasanton, CA] or a HeartWare HVAD LVAD [HeartWare Inc., Framingham, MA] for BTT or DT during the time period of January 1st, 2005 to June 30th, 2014. Patients who did not survive implant or received biventricular assist devices were excluded from the analyses. The sample included both men and women, who were 18 years or older. Patients included in this analysis were hemodynamically stable and underwent VAD exchange if they failed TPA treatment. The anticoagulation protocol consisted of aspirin and coumadin as per manufacturer's recommendations (target INR of 1.8 to 2.5 for HMII and 2.0 to 3.0 for HVAD). On admission PT/INR, PTT, CBC, complete metabolic panel, fibrinogen and a thromboelastogram with platelet mapping were obtained. A 2-D echocardiogram was also performed on admission.

2.1. Patient population and characteristics

Patient demographics collected included gender, age at LVAD implant, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, indication for LVAD (BTT or DT), type of LVAD and history of comorbidities such as ischemic cardiomyopathy, hypertension, diabetes mellitus, peripheral vascular disease, tobacco use, anemia or hypercoagulable syndrome.

Analyses of factors that predispose to LVAD thrombus included length of VAD support, type of LVAD, history of peripheral vascular

disease (PVD), tobacco use, hypercoagulable state, anemia, hypertension and diabetes. Additional outcome variables were evaluated for patients who met the criteria for suspected LVAD thrombus, including time to thrombus event, time to the second thrombus event (if applicable), use of TPA, and LVAD exchange. Any differences in time to occurrence of suspected thrombus between the two LVAD types were also evaluated. Adverse events such as renal failure, hemorrhagic CVA, and right ventricular failure were evaluated in conjunction with TPA administration. Success with TPA administration was defined as resolution of hemolysis and no indication for LVAD exchange for 30 days.

3. Study design

Retrospective analyses were performed on patient charts after IRB approval. The study population comprised of 154 patients who underwent left ventricular assist device (LVAD) implantation (131-HeartMate II and 23-HVAD) from 1/1/2005 to 6/30/2014. They were divided into four groups – HM II with device thrombosis, HVAD with device thrombosis, HM II with no device thrombosis, and HVAD with no device thrombosis (Fig. 1A). A total of 24 patients were diagnosed with LVAD thrombus. Of these, 20 patients received TPA infusions, 3 underwent LVAD exchange and 1 patient was placed on heparin and Plavix (Fig. 1B). Patients who were hemodynamically unstable underwent LVAD exchange.

3.1. Diagnosis of thrombosis

Occurrence of LVAD thrombus was suspected with elevated LDH, hematuria, elevated quantitative plasma free hemoglobin. Diagnosis of LVAD thrombus was made when lactate dehydrogenase levels exceeded 1000 units/l in addition to clinical signs of hemolysis and heart failure and echocardiographic findings listed above. The plasma free hemoglobin was monitored concomitantly but absolute cut off values were not used to make a diagnosis due to high variability in the assay values at this center. A cannula flow velocity of >2 m/s by echocardiography with more frequent opening of the aortic valve than at baseline in the context of increasing left ventricular internal dimension in diastole (LVIDD) without any manual speed changes was considered suggestive of a thrombus.

3.2. TPA protocol

TPA protocol typically consisted of a 5 mg intravenous bolus followed by 3 mg/h infusion in normal saline for 10 h. In cases where thrombus persisted as defined by laboratory data and clinical signs another cycle of TPA at 1 mg/h was continued up to 48 h. The total TPA dose never exceeded a maximum limit of 100 mg. All TPA infusions were performed via a peripherally inserted central intravenous line in the cardiac intensive care unit.

3.3. Statistical analysis

Descriptive statistics (mean, median, and standard deviation) were used to characterize the patient population, including baseline characteristics, thrombosis rates between devices, and results of TPA treatment and associated events. Success rates for TPA treatment were computed. Inferential statistics were used to test for independence between groups. A t-test was used to compare means for age and time to LVAD thrombosis, with confidence intervals denoted. The Chi-square test or Fischer's exact test (for small sample size) was used to test for independence between categorical variables. The Cramer's V test was utilized to calculate correlation. Odds ratios (OR) were calculated for categorical data. Statistical tests were performed using SPSS and Excel. Results were considered significant if $p < 0.05$.

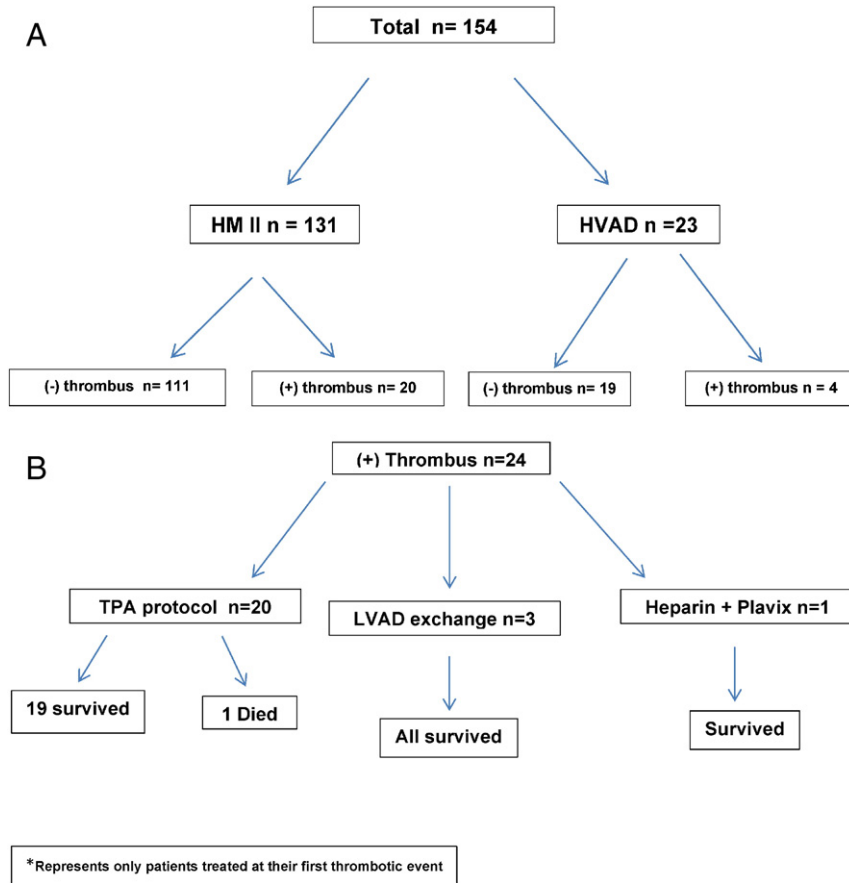


Fig. 1. A shows the distribution of the two types of continuous flow pumps in the study population. B shows survival at 30 days.

4. Results

4.1. Characteristics of study population

Table 1 outlines the baseline characteristics of the patients. The study population had 21% females and 78.6% males. Ischemic and non-ischemic cardiomyopathies were equally represented. Hypertension and diabetes were noted in 43% and 35% of the study subjects respectively. Only 8.4% of the subjects had peripheral vascular disease. History of tobacco use was noted in 55% of the study population. A higher number of HM II LVADs were placed as compared to HVADs (85.1% versus 14.9%) in the period studied from 2005 to 2014. Approximately one tenth of the patients were in INTERMACS class 1.

4.2. Factors influencing VAD thrombus formation

Table 2 outlines factors that could contribute to pump thrombus. However there was no significance between the non-thrombus group and thrombus group patient demographics with respect to age ($p = 0.637$), gender ($p = 0.64$), history of ischemic cardiomyopathy ($p = 0.73$), hypertension ($p = 0.7$), diabetes mellitus ($p = 0.46$), peripheral vascular disease ($p = 0.44$), tobacco use ($p = 0.22$), and anemia ($p = 0.11$). Patients in the thrombus group were found to have a history for hypercoagulable syndrome with intermediate association strength ($p < 0.000$, $V = 0.328$). There were no significant differences between the non-thrombus group and thrombus group in operative characteristics with respect to LVAD indication for BTT or DT ($p = 0.57$) or LVAD type ($p = 0.80$). The INTERMACS profile was not significant in either group ($p = 0.09$). Patients included had INR within the recommended therapeutic range on presentation.

Table 1
Baseline characteristics of study population.

	All study subjects (n = 154)	Patients without an LVAD Thrombus event (n = 130)	Patients with an LVAD Thrombus event (n = 24)
Mean age at implant	55.8	55.6	56.9
Gender	33 (21.4) F, 121 (78.6) M	27 (20.8) F, 103 (79.2) M	6 (25) F, 18 (75) M
Ischemic CM	85 (55.2)	71 (54.6)	14 (58.3)
Non-ischemic CM	69 (44.8)	59 (45.4)	10 (41.7)
HTN	65 (42.2)	54 (41.5)	11 (45.8)
OM	54 (35.1)	44 (33.8)	10 (41.7)
Peripheral vascular disease	13 (8.4)	10 (7.7)	3 (12.5)
History of tobacco use	85 (55.2)	69 (53.1)	16 (66.7)
HMII	131 (85.1)	111 (85.4)	20 (83.3)
HVAD	23 (14.9)	19 (14.6)	4 (16.7)
Length of pump support (days)	550 + 475	526 + 494	682 + 330
BTT	110 (71.4)	94 (72.3)	16 (66.7)
DT	44(28.6)	36 (27.7)	8 (33.3)
Pump exchange	14(9.1)	4(3.1)	10 (41.7)
GI bleed	40 (26)	33 (25.4)	7 (29.2)
Driveline infection	24 (15.6)	16 (12.3)	8 (33.3)
INTERMACS Profile 1	15(9.7)	15 (11.5)	0
INTERMACS Profile 2	54 (35.1)	50 (38.5)	4 (16.7)
INTERMACS Profile 3	40 (26.0)	31 (23.8)	9 (37.5)
INTERMACS Profile 4	30 (19.5)	22 (16.9)	8 (33.3)
INTERMACS Profile 5	8 (51.9)	6 (4.6)	2 (8.3)
INTERMACS Profile 6	6 (39)	5 (3.8)	1 (4.2)
INTERMACS Profile 7	1(0.6)	1 (0.6)	0

F—Female; M—Male.

Table 2
Analysis of factors contributing to VAD thrombus.

Characteristics	(–) Thrombus N = 130	(+) Thrombus N = 24	p value	Correlation coefficient
Age (years)	55.60%	56.40%	0.637	0.037
Gender (female)	27	6		0.266
HMII	84.70%	15.30%	0.796	0.021
HVAD	82.60%	17.40%		
History of PVD	7.70%	12.50%	0.436	0.063
History of Tobacco Use	53.10%	66.70%	0.219	0.99
History of Hypercoagulable Syndrome	0.00%	12.50%	0.000	0.328
History of Anemia	10.00%	0.00%	0.105	0.13
History of Hypertension	54 (41.5%)	11 (45.8%)	0.7	0.025
History of Diabetes	44 (33.8%)	10 (41.7%)	0.46	0.06

4.3. Average time to detection of pump thrombus

The average time to first thrombus event was 394 days (CI 256.6–531.3). The average time to first thrombus event for HMII LVAD patients was 357 days (CI 209.5–503.7). The average time to the first thrombus event for HVAD patients was 581 days (CI 81.6–1079.9). The average time from the first thrombus event to the second thrombus event was 314.7 days (CI 81.4, 548). No statistical significance was noted (Table 3).

4.4. Patient outcome variables in the thrombus versus No thrombus groups

Patient outcome variables showed no significant differences between the non-thrombus group and thrombus group in relation to length of LVAD support ($p = 0.06$), occurrence of GI bleed ($p = 0.70$), driveline infection (non-thrombus group vs. thrombus group, at any time, $p = 0.10$), hemorrhagic CVA ($p = 0.72$), renal failure ($p = 0.69$), or right ventricular failure ($p = 0.24$). Analysis of the study groups showed no statistically significant differences in driveline infections or GI bleeding pre- and post-thrombus formation. Approximately 17% ($n = 4$) of the patients who experienced an LVAD thrombus had a driveline infection prior to the thrombus event, which was not significant in comparison to the non-thrombus patient group ($p = 0.35$).

4.5. Outcomes and adverse events with TPA protocol versus LVAD exchange

Tables 4 and 5 show outcomes and adverse events with TPA treatment versus LVAD exchange. Approximately 83.3% ($n = 20$) of patients received TPA. 1 patient did not survive until 30 days post-TPA administration. Of the 20 patients who received TPA for a first thrombus event, 10% experienced a related hemorrhagic CVA, 20% experienced renal failure, and 5% experienced right ventricular failure following TPA administration or throughout the remainder of the hospital admission. For those patients who received TPA for a first thrombus event, the corresponding non-thrombus group was more likely to have right ventricular failure (OR: 3.1). Renal failure did not increase in patients who experienced an LVAD thrombus (OR: 0.91). Hemorrhagic CVA did not increase in patients who experienced an LVAD thrombus (OR: 0.92). All the 4 HVAD patients who experienced a first thrombus event received TPA and were treated successfully. Of the 16 HMII LVAD patients who experienced a first thrombus event and received TPA, 63% were treated

Table 3
Average time to diagnosis of thrombus.

	Time to 1st LVAD thrombus (HMII: $n = 20$, HVAD: $n = 4$)	Time from 1st to 2nd thrombus (HMII: $n = 5$, HVAD: $n = 2$)
HMII & HVAD ($n = 24$)	394 ± 326	315 ± 554
HMII ($n = 20$)	357 ± 315	382 ± 660
HVAD ($n = 4$)	581 ± 360	146 ± 124
$p = ns$		

Table 4
Outcomes with TPA protocol and LVAD exchange.

	1st thrombus ($n = 20$)	2nd thrombus ($n = 4$)
TPA protocol	83.3%	57.1%
Free of hemorrhagic stroke following TPA	90.0%	100.0%
Alive at 30 days post-TPA	95.0%	50.0%
Alive at 1 year post-TPA or ongoing	75%	25%
	1st thrombus ($n = 3$)	2nd thrombus ($n = 3$)
VAD exchange	12.5%	42.9%
Free of hemorrhagic stroke following VAD exchange	100.0%	100.0%
Alive at 30 days post-surgery	100.0%	100.0%

successfully. Sample size was too small for appropriate statistical analysis. Only 12.5% ($n = 3$) of patients received an LVAD exchange for the first suspected thrombus event, with all 3 patients surviving post-30 days of surgery. Of the 3 patients who received an LVAD exchange, 0% experienced hemorrhagic CVA, renal failure or right ventricular failure immediately following LVAD exchanges or throughout the remainder of the hospital stay. Sample size was too small for statistical analysis. 4.2% ($n = 1$) of patients did not receive either TPA or LVAD exchange, but instead received a combination of heparin and clopidogrel.

Of the 29.2% ($n = 7$) of patients who experienced a second suspected thrombus event, 4 received TPA and 3 received an LVAD exchange. From the group treated with TPA, 1 of the 4 experienced right ventricular failure. None experienced hemorrhagic CVA or renal failure following TPA administration or throughout the remainder of the hospital admission. 2 patients did not survive until 30 days post-TPA administration. From the group treated with LVAD exchange, 1 of 3 experienced right ventricular failure. None experienced hemorrhagic CVA or renal failure following LVAD exchange or throughout the remainder of the hospital admission.

5. Discussion

This study is different from earlier investigations in that a single defined protocol was used to treat LVAD thrombosis. Though the analyses were retrospective, the study showed a 95% survival rate with TPA at 30 days and 75% at 1 year for patients treated with TPA at the first incidence of pump thrombus. The number of patients treated at the second instance of pump thrombus was small, but a drop in survival was noted at 30 days at 50% and only 25% at 1 year. The sample sizes were too small to perform any meaningful statistical analyses. In our limited experience, TPA appeared to be the first choice instead of a pump exchange in hemodynamically stable individuals. A notable aspect of this protocol is that the adverse events were comparable in the thrombus and non-thrombus groups. The odds ratio points to a larger likelihood of developing right ventricular failure in the non-thrombus groups.

Some of the challenges in assessing VAD thrombus problems are the lack of adequate definition of the number of thrombi that are true versus suspected, and the lack of a unified anticoagulation/antiplatelet regimen. Additionally it is unclear if the length of pump support factors into the equation. The studies by Boyle et al. and Slaughter et al. [24,25] showed that patients can be maintained at lower INR and without the heparin bridging for optimal management.

In a recent report by Najjar et al. medical management in general showed a 50% success rate and a 63% success rate with TPA treatment in particular [3]. Schlendorf et al. found a 37.5% success with thrombolytic therapy [16]. Our study shows a success rate of 70% with TPA including both HMII and HVAD patients. It should be noted that our study included a majority of HMII pumps and lower number of HVADS as compared to the by Najjar et al. which focused on the

Table 5
Adverse event profile in study population.

	(-) Thrombus	TPA		LVAD exchange	
	No thrombus (n = 130)	1st thrombus event (n = 20)	2nd thrombus event (n = 4)	1st thrombus (n = 3)	2nd thrombus (n = 3)
Hemorrhagic stroke	9.2%	10.0%	0.0%	0.0%	0.0%
Renal failure	18.0%	20.0%	0.0%	0.0%	0.0%
RV failure	14.0%	5.0%	25.0%	0.0%	33.3%

HVADS only as a bridge to transplant. Our study included destination therapy patients also in the analysis.

The hemorrhagic CVA noted in 10% of patients which included those with both HM II and HVAD. Though reports of associations between earlier bleeding events followed by incidence of pump thrombus exist in the literature [33,34] a significant correlation between GI bleeds and pump thrombus events was not found in this retrospective analysis.

Patients with a history of hyper-coagulation syndromes were significantly predisposed to LVAD thrombosis. This is an area where rigorous investigation is required to define levels of anticoagulation. Anticoagulation requirements may be very different in these patients. Besides, hypercoagulability in the setting of heart failure may be more accentuated due to chronic inflammation and up regulation of coagulation factors in heart failure [35,36]. Systematic studies on the pathogenesis of heart failure will shed light on subsets of patients who may have a higher risk for hypercoagulation in the context of up regulation of markers of inflammation, fibrosis, and coagulation. Such tailored risk assessment may be helpful in high risk populations. Better risk stratification will help in better prognostication and management. Genotype driven anticoagulation regimens could be another useful approach in this population [37].

In this single center protocol thrombolytic treatment was used prior to initiating a VAD exchange if the patient had no contraindications. All patients were evaluated carefully for risk versus benefit before initiating a treatment protocol. A protocol for triaging patients with a suspected thrombus is shown in Fig. 2 which differs from the algorithm put forth by the ISHLT working group [26] in that the protocol presented here focuses on thrombolytics. The algorithm shown here is intended to help develop further investigations on these lines in larger studies using different types of mechanical pumps to gain further insight into optimal treatment options and outcome strategies.

6. Limitations

This is a small retrospective analysis which makes it difficult to perform meaningful statistics especially in terms of long term outcomes in comparison with LVAD exchange. The dilemma in definitively diagnosing a true thrombus versus signs and symptoms suggestive of a thrombus still remains. The data on the second thrombus event is too small for any comparison. The LVAD exchange group is also very small for any head to head comparison with the thrombolytic therapy group.

Being a retrospective study no log file analysis was done on the HVAD patients as this technique was not universally available at the time the patients were implanted. The hypercoagulable state noted in the study patients were only by history. No data was available regarding the types/etiology of the hypercoagulability in these patients. The percentage of patients in atrial fibrillation at the time of presentation could not be deciphered as this data was missing from the data set available for the analysis.

7. Conclusions

This was a retrospective study consisting of patient record analyses of 154 patients who underwent left ventricular assist device (LVAD) implantation (131-HM II and 23-HVAD) from 1/1/2005 to 6/30/2014. A single TPA protocol was used in this study population. The TPA protocol patients showed an overall 70% success including the HMII and HVAD pumps and the survival at 30 days post-thrombolytic therapy was 95%. At one year the survival was 75%. Success with VAD exchange was 100%. Survival at 30 days and 1 year was also a 100% in the VAD exchange population. The patients who underwent VAD exchange directly had contraindications to thrombolytic treatment. However the VAD exchange group was very small to perform any meaningful statistical

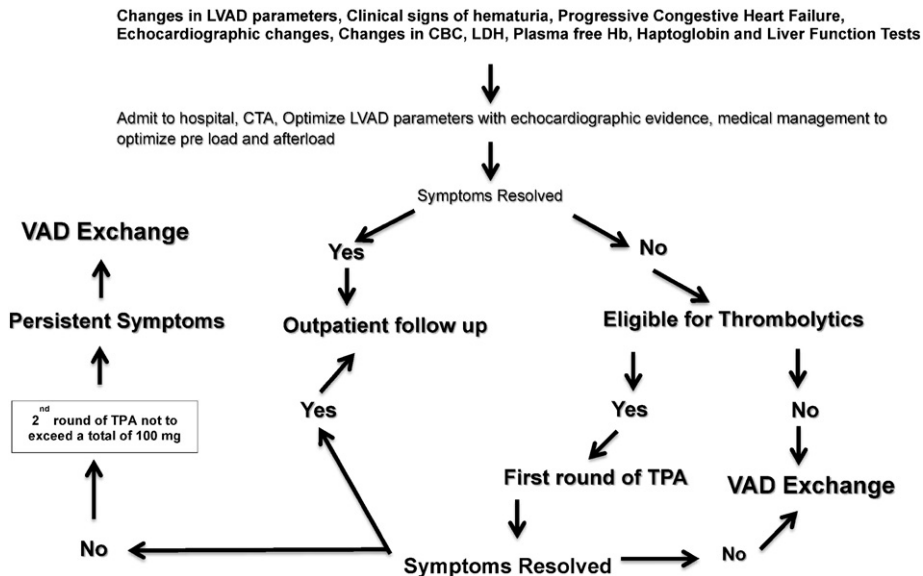


Fig. 2. A suggested algorithm for use of thrombolytic therapy in the mechanical assist device population.

analyses. A small group of patients underwent TPA treatment versus VAD exchange for a second thrombus event because these patients were poor surgical candidates. As the number of patients in the second thrombus group was small no statistical analyses was performed. Though this is a small retrospective study the TPA protocol presented here, when used appropriately appears to yield acceptable preliminary results in terms of safety and survival. The protocol needs validation in large multicenter trials for further definition and optimization in different patient subsets and varied anticoagulation patterns.

Disclosures

None of the authors have any disclosures that are relevant to this work.

Funding sources

None.

Acknowledgment

This paper is dedicated to the memory of our beloved colleague Dr. David Sandler, an astute cardiothoracic surgeon who dedicated his life to the field of surgical therapies for advanced heart failure.

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