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MINI-FOCUS ISSUE: MECHANICAL CIRCULATORY SUPPORT: OPPORTUNITIES AND CHALLENGES

Identification and Management of Pump Thrombus in the HeartWare Left Ventricular Assist Device System

A Novel Approach Using Log File Analysis

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ABSTRACT

OBJECTIVES The study sought to characterize patterns in the HeartWare (HeartWare Inc., Framingham, Massachusetts) ventricular assist device (HVAD) log files associated with successful medical treatment of device thrombosis.

BACKGROUND Device thrombosis is a serious adverse event for mechanical circulatory support devices and is often preceded by increased power consumption. Log files of the pump power are easily accessible on the bedside monitor of HVAD patients and may allow early diagnosis of device thrombosis. Furthermore, analysis of the log files may be able to predict the success rate of thrombolysis or the need for pump exchange.

METHODS The log files of 15 ADVANCE trial patients (algorithm derivation cohort) with 16 pump thrombus events treated with tissue plasminogen activator (tPA) were assessed for changes in the absolute and rate of increase in power consumption. Successful thrombolysis was defined as a clinical resolution of pump thrombus including normalization of power consumption and improvement in biochemical markers of hemolysis. Significant differences in log file patterns between successful and unsuccessful thrombolysis treatments were verified in 43 patients with 53 pump thrombus events implanted outside of clinical trials (validation cohort).

RESULTS The overall success rate of tPA therapy was 57%. Successful treatments had significantly lower measures of percent of expected power (130.9% vs. 196.1%, $p = 0.016$) and rate of increase in power (0.61 vs. 2.87, $p < 0.0001$). Medical therapy was successful in 77.7% of the algorithm development cohort and 81.3% of the validation cohort when the rate of power increase and percent of expected power values were <1.25% and 200%, respectively.

CONCLUSIONS Log file parameters can potentially predict the likelihood of successful tPA treatments and if validated prospectively, could substantially alter the approach to thrombus management. (J Am Coll Cardiol HF 2015;3:849–56)

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ABBREVIATIONS AND ACRONYMS

BTT = bridge to transplant

CAP = continued access protocol

EPPY = events per patient year

HM II = HeartMate II

HVAD = HeartWare ventricular assist device

tPA = tissue plasminogen activator

VAD = ventricular assist device

Due to the lack of available donors, many patients with advanced heart failure receive mechanical circulatory support devices as a bridge-to-transplant (BTT) therapy (1). Left ventricular assist devices (VADs) have proven to be very effective at improving functional capacity, quality of life, and the survival rates of these patients (2,3). The HeartWare ventricular assist device (HVAD) (HeartWare Inc., Framingham, Massachusetts) is a miniaturized, continuous flow, and centrifugal blood pump that had a survival rate >86% after 1 year in the U.S. BTT trial (4). While continuous flow VADs are becoming more common in the treatment of those with advanced heart failure, there still exist potential risks and complications associated with mechanical circulatory support such as device thrombosis (5–7).

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Pump thrombus is defined as an obstruction that limits blood entering/exiting the pump or otherwise impinges the impeller from properly rotating. However, the location and histology of the clot formation can differ depending on the type of VAD. Globular clot formations have been reported on the inflow bearings and in regions of sharp angulation of the HeartMate II (HM II) inflow/outflow grafts (8,9). In contrast, laminar fibrin formations may develop on the impeller of HVAD pumps if a thrombus event occurs (10). Pump thrombus requiring exchange occurred at a rate of 0.04 events per patient year (EPPY) with a total suspected thrombus rate of 0.08 EPPY in patients implanted with an HVAD from the HeartWare BTT and CAP (Continued Access Protocol) trials (7). Most baseline demographics including mean pump power were not significantly different between patients with and without thrombus events. A multivariate analysis did identify certain risk factors for pump thrombus such as mean arterial pressure >90 mm Hg, aspirin dose ≤81 mg, or international normalized ratio ≤2 (7).

It is well known to clinicians that the presence or ingestion of a thrombus will often lead to a rise in the log file power signal (11,12). As seen in **Figure 1**, occlusion, ingestion, and build-up thrombi have very different effects on the pump power consumption. Further analysis of the log files, beyond measuring an average power, is warranted to determine if there are characteristics in the power signal that could indicate the presence of thrombus. Studies have suggested that recognition of changes in pump power can allow early treatment with thrombolytics to resolve the event (13–15). Improved thrombus detection, prediction of successful management with medical therapy, and thereby avoidance of unnecessary pump exchange surgery would have tremendous clinical value. In the current study, patient log files were analyzed with the goal of developing a tool to aid the diagnosis and management of pump thrombosis.

METHODS

LOG FILE POWER ANALYSIS. The HVAD system has a unique controller log file that records the pump power (mW), rotational impeller speed (rpm), and VAD flow (ml/min) every 15 min (11). The patient's baseline power was calculated by averaging a period of stable behavior prior to the thrombus event. The beginning of the thrombus event was defined as the time when the power had a 3 SD difference from the baseline power for at least 1.5 h. The difference between the time of treatment and beginning of the thrombus event was defined as the "time until treatment."

There were several measures of the power used to assess the thrombus events. The first was the maximum power reached during the thrombus event. The second was the change in power, calculated as the difference between the maximum and baseline power for each patient. The third measure of power accounts for the interpatient variability in pump speed and power and is termed "percent of expected power." An analysis of normal HVAD pump operation parameters showed that there is an "expected value" of power consumption based on the motor speed setting (11). Dividing the maximum power by the expected power for the given motor speed (Equation 1) gives a measure of the difference of the power from normal operating values. This normalization process allows

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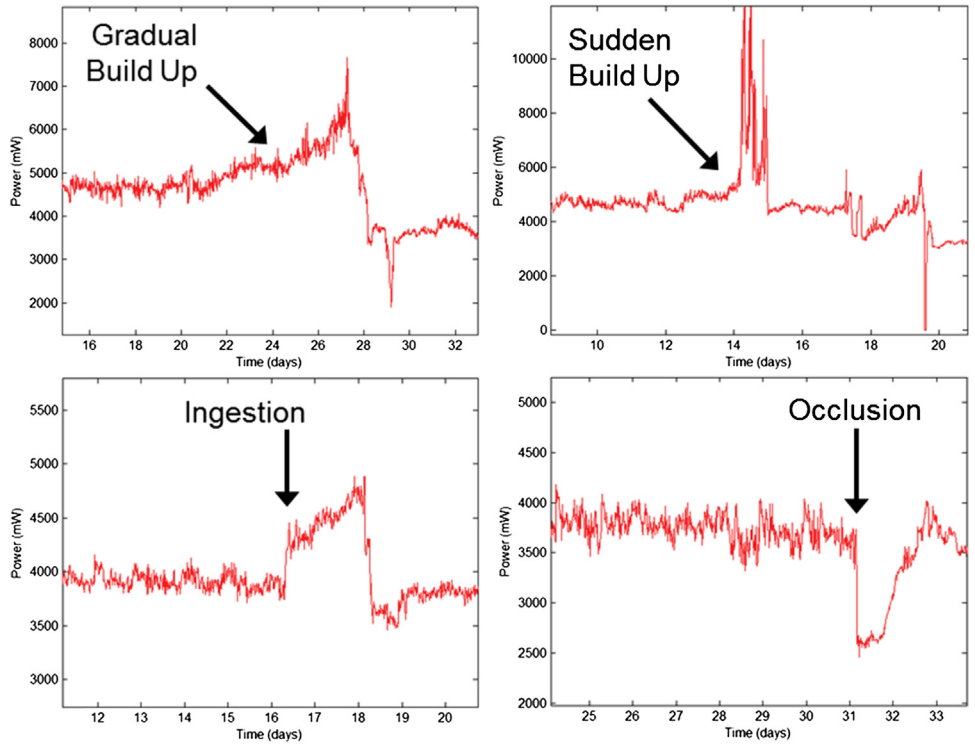
FIGURE 1 Different Appearances of Pump Thrombus



Differences in pump power consumption due to gradual build-up, sudden build-up, occlusion, and ingestion thrombus events.

for more accurate comparisons between patients with different pump speeds and baseline powers.

$$\%\ \text{of Expected Power} = \frac{\text{Maximum Power}}{\text{Expected Power}} \times 100 \qquad \text{[Equation 1]}$$

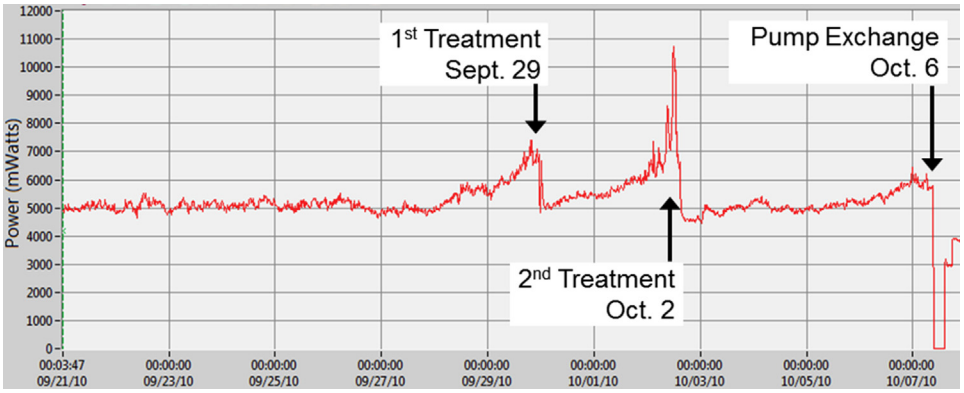
EXPONENTIAL GROWTH MODEL. As seen in Figure 1, in situ clot formation can result in gradual or a sudden increase in power. Further complexities occur with occlusion and ingestion types of thrombi. In order to quantify the time dependency of the power change, the log file data was fitted with an exponential model (Equation 2) in which the coefficient B is a time constant and corresponds to the rate of increase in the pump power consumption, termed the "growth rate." Coefficients A and C correspond with power stretch factor and power shift but are primarily fitting parameters and do not carry the biological significance of the time constant. While other mathematical models are possible for the curve fitting, the exponential model was chosen, as it provided a good fit for build-up thrombus cases and has been previously used to describe clotting kinetics (16). All analysis of power parameters and exponential curve fitting was performed with a custom Matlab code (The MathWorks, Natick, Massachusetts).

$$\text{Power} = Ae^{B\times t} + C \qquad \text{[Equation 2]}$$

TISSUE PLASMINOGEN ACTIVATOR. Various medications such as heparin, glycoprotein IIb/IIIa antagonists, and tissue plasminogen activator (tPA) are currently being used for the treatment of thrombus and have different clot inhibiting mechanisms. The use of tPA has been shown to have a 50% chance of successfully resolving a device thrombus in an HVAD cohort (7) and so this study was directed toward examining tPA patients. While there was variation between sites for the dose (reported range from 20 to 60 mg) and intravenous versus intraventricular application of treatment, any use of tPA was considered as meeting the criteria for inclusion in this study.

STUDY POPULATION. Patients included in this study were required to have: 1) a clinical record of a pump thrombus event; 2) received at least 1 application of tPA; and 3) a complete log file of the event. In the HeartWare BTT/CAP trial, there were a total of

FIGURE 2 Pump Thrombus With Multiple Treatments



A device thrombus in which the patient received 2 unsuccessful doses of tissue plasminogen activator (on September 29 and October 2) before eventually requiring a pump exchange on October 6.

34 pump thrombus events in 31 patients (8.1% of the total cohort, n = 382) (7). Of the 34 thrombus events, only 16 met this study's criteria of having a tPA treatment, complete log file, and corresponding clinical records. These 16 events occurred in 15 patients with and 1 patient having 2 separate thrombus events, and constituted the algorithm derivation cohort. From the algorithm derivation group, thresholds for growth rate and percent of expected power were qualitatively chosen to include the majority of successful treatments. To validate patterns seen in the algorithm development cohort, several participating sites (including both U.S. and international centers) provided log files, clinical records, and details of tPA treatments for patients with device thrombus. These cases comprised the validation cohort (total of 43 patients with 53 thrombus events) for the power and growth rate analysis.

CLASSIFICATION OF PUMP THROMBUS TREATMENTS. Medical therapy was defined as successful if: 1) a clinical resolution of the pump thrombus was reported; 2) power consumption returned to a normal operating range; and 3) an improvement in biochemical markers of hemolysis was reported. If the patient had a subsequent treatment, pump exchange, urgent/emergency United Network of Organ Sharing status 1A transplant, or death for any reason within 1 month of the tPA treatment, then the medical therapy was considered to be unsuccessful. These definitions of successful and unsuccessful medical therapy follow the classification protocol described by Najjar et al. (7).

ANALYSIS OF MULTIPLE TREATMENTS FOR A SINGLE EVENT. In this study, 10 patients received multiple treatments of tPA for a single occurrence of pump thrombus. In 5 patients, thrombolytics were eventually successful in resolving the event while the other 5 patients eventually required pump exchange. To avoid introducing a statistical bias from analyzing multiple treatments of the same thrombus event, only the log file parameters of the final medical therapy were considered. The final treatment was analyzed because ultimately it was the medical therapy that either successfully or unsuccessfully led to the resolution of the event. As an example (**Figure 2**), the log file analysis would be applied to the last dose of tPA (October 2), which was unsuccessful because an exchange was necessary 4 days later.

STATISTICAL ANALYSIS. The power and exponential fit parameters from the successful and unsuccessful treatments are reported with a mean ± SD and are compared with a Wilcoxon 2-sample test due to the small sample size. The contingency tables are assessed with a Fisher's exact test. In the modified box plots created with MiniTab 15.1.30 software (Minitab Inc., State College, Pennsylvania), the whiskers extend to the smallest/largest observation that are still within the lower/upper limit (Q1 − 1.5 × IQR and Q3 + 1.5 × IQR, respectively). The box denotes the standard Q1, median, and Q3 points and outliers are denoted with an asterisk. All statistical analysis was performed with SAS version 9.2 software (SAS Institute, Cary, North Carolina).

RESULTS

A summary of the log file analysis of the successful and unsuccessful treatments from the validation

group is presented in Table 1. The data from the BTT/CAP treatments was used to propose thresholds to differentiate between successful and unsuccessful treatments (Figure 3A). Threshold values of 1.25 for growth rate and 200% for percent of expected power encapsulated the majority of the successful treatments. There was a 77.7% success rate when the log file parameters were below the 2 thresholds compared to a 42.9% success rate if 1 or more thresholds were exceeded (Figure 3A). However, this difference in medical therapy success rates was not significant due to the low sample size ($p = 0.3$). For the validation group (Figure 3B, Table 2), 81.3% of the treatments that had measurements below both thresholds were successful as compared to a 14.3% (3 of 21) success rate when at least 1 threshold was exceeded; this finding was statistically significant ($p < 0.001$).

There was no difference in the time to treatment or baseline power for the unsuccessful and successful medical therapies. There was a trend for decreased maximum power in the successful treatments (Figure 4A) that did not reach statistical significance. The change in power (Figure 4B) and percent of expected power (Figure 4C) for the successful tPA treatments were significantly lower than the unsuccessful applications of medical therapy. For the exponential fitting, the time constant for the successful treatments was significantly lower than the unsuccessful group (Figure 4D). Of the 15 BTT/CAP patients that received tPA, 2 patients (13.3%) had hemorrhagic cerebral vascular accidents and 1 experienced a gastrointestinal bleed event. The stroke rate of the tPA receiving patients is comparable to the 14.8% overall cerebral vascular accident rate previously published for the BTT/CAP cohort (3). Data of the serious adverse events for the validation cohort was not available.

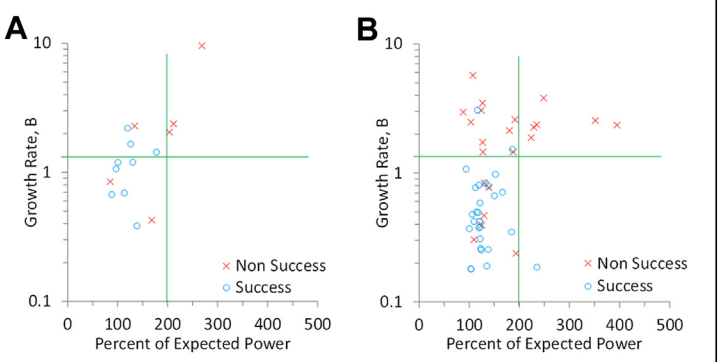
DISCUSSION

We examined the log file patterns and the successfulness of tPA treatments in 58 patients with 69 pump thrombosis events. The overall success rate of tPA-based therapy was 57%, which was comparable to previously reported data (7). For the first time, we identified that the growth rate and percent of expected power are the log file parameters associated with successful tPA treatments. Specifically, tPA-based therapy was successful in 77% of the derivation group and 81% of the validation cohort when the growth rate and power parameters were below thresholds of 1.25 and 200%, respectively.

Pump thrombus is a serious adverse event that can potentially be resolved with thrombolytics although intracranial bleeding is a feared complication in this setting (13–15,17). In a recently published series (17), 24% (4 of 17) of HM II patients had a hemorrhagic stroke after thrombolytic treatment. Thrombolysis is often considered a last resort treatment in HM II patients because clots are generally detected after they are no longer amenable to medical therapy (5,8). The time from the diagnosis of hemolysis until device exchange often exceeded several weeks in a large cohort of HM II patients (18), but early pump exchange strategies in HM II patients have been very successful (19). It is becomingly increasingly clear that the HM II strategies may not be applicable to HVAD patients and that device specific detection of and treatments for thrombosis have to be developed. In this context, our data demonstrates that the use of log files may allow for recognition of thrombus formation in HVAD patients independent of biochemical data and the assessment of the likelihood of tPA success.

Build-up pump thrombus leads to an increase in power because the efficiency of the pump decreases

FIGURE 3 Power and Growth Rate Scatter Plots



Growth rate and percent of expected power from the bridge-to-transplant/continued access protocol (BTT/CAP) group **(A)** and validation group **(B)** with thresholds of 1.25 for growth rate and 200% for power. Note 1 successful BTT/CAP treatment **(A)** had a growth rate of 0.05 and 115.4% power, which is outside the range of the log scale axis.

TABLE 1 Power and Growth Rate Parameters of Successful and Unsuccessful Treatments

	Nonsuccessful Medical Therapy	Successful Medical Therapy	p Value
Time to treatment, days	5.4 ± 5.1	4.7 ± 3.8	0.92
Baseline power, mW	4,049 ± 828	4,161 ± 650	0.80
Maximum power, mW	7,816 ± 4,972	5,414 ± 1,224	0.059
Change in power, mW	3,767 ± 4,858	1,252 ± 1,148	0.0162
% of expected power, %	196.1 ± 136.6	131.0 ± 30.3	0.0155
Coefficient A	2.3 ± 6.0	40.6 ± 77.2	0.0002
Coefficient B	2.87 ± 3.94	0.61 ± 0.56	<0.0001
Coefficient C	4,051 ± 841	4,128 ± 754	0.85

TABLE 2 Rate of Medical Therapy Success Based on GR and Power Thresholds

BTT/CAP	%P ≤200%	%P >200%	Validation	%P ≤200%	%P >200%
GR >1.25	3/4 (75.0)	0/3 (0.0)	GR >1.25	2/13 (15.4)	0/7 (0.0)
GR ≤1.25	7/9 (77.7)	0/0 (0.0)	GR ≤1.25	26/32 (81.3)*	1/1 (100.0)

Values are $n_{success}/n_{total}$ (%). For the validation group, the 81.3% success rate when below both thresholds is significantly greater than the success rate when at least 1 threshold is exceeded. *$p < 0.001$.

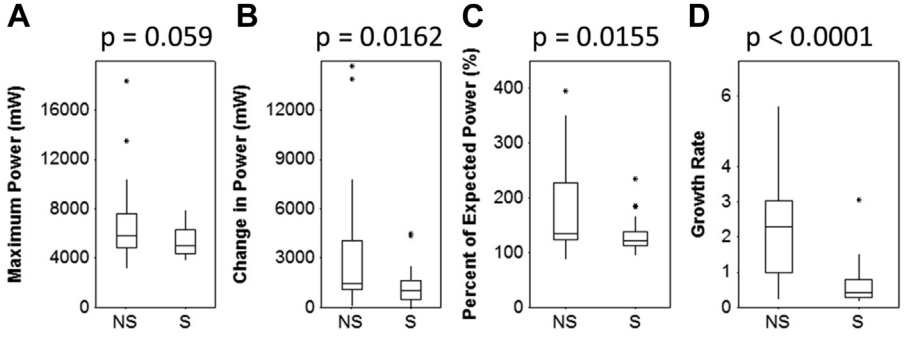
BTT = bridge to transplant; CAP = continued access protocol; GR = growth rate; %P = percent of expected power.

with deposition of material on the impeller. The severity of the thrombus can be related to the magnitude of the power increase according to previous publications (11,20). As a result of device thrombosis, there was a higher peak power and positive change in power (**Figure 4**). For patients with the HVAD system, the consistent power increase during a build-up thrombus could be used for early identification (13,14,21). The growth rate of the power is a previously unused method of gauging the thrombus severity. In this study, medical therapy was most often successful when both the power and growth rate measurements were low (**Figure 3**, **Table 1**) which concurs with the qualitative experiences of single centers (14).

Interestingly, the times to treatment were not different between the successful and unsuccessful medical therapies. For example in **Figure 1**, a successful tPA treatment was administered to resolve a gradual build-up thrombus approximately 4 days after the power had begun to increase. In contrast, the sudden build-up thrombus was treated within 2 days of the high-power alarm but pump exchange was necessary. Previous studies on the HM II device have suggested intensification of routine anticoagulation treatments when there is an early diagnosis of suspected thrombus compared to more aggressive measures when patients appear late in the clinical course (22). While earlier diagnosis and treatment are still preferable (13–15), these results suggest certain types of thrombus may simply be untreatable with thrombolytics. Diagnosis of these types of clots, potentially by identifying high growth rates and power, may enable patients to avoid bleeding risks associated with tPA by proceeding directly to a pump exchange.

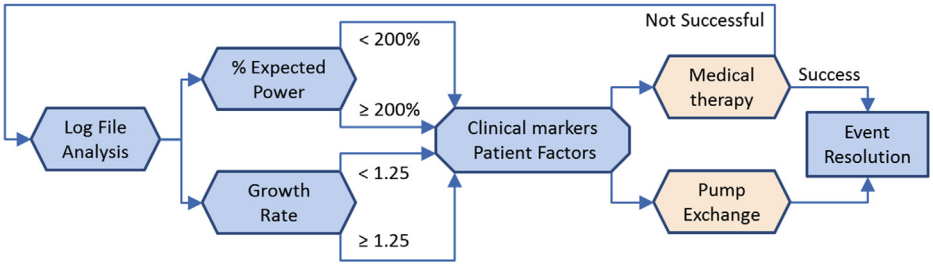
Leading investigators in the field have previously created a guideline for the diagnosis and management of HM II patients with suspected device thrombosis (22). The flow diagram in **Figure 5** is a new potential way of applying log file analysis in the determination of treatment for HVAD patients presenting with signs of thrombus. While this study demonstrates that log file parameters can be an effective predictor of medical therapy results, it is necessary to consider other clinical markers of thrombosis and patient factors. For example, this study does not provide insights on the relevance of and/or specificity of hemolysis (without an elevation of log file power) for HVAD device thrombosis. Evidence of hemolysis is generally associated with pump thrombus (23,24) and a recent study concludes that a certain degree of hemolysis is highly suggestive if not specific for device thrombosis in HM II patients (25). While hemolysis monitoring is important for HM II patients, it is possible that log file monitoring should have a greater emphasis for HVAD patients. This again reaffirms the need for device specific detection and treatment methodologies.

FIGURE 4 Power and Growth Rate Box Plots



Successful (S) medical therapy showed a trend of lower average maximum power **(A)**. The change in power **(B)**, percent of expected power **(C)**, and growth rate **(D)** of successful treatments were significantly lower than the nonsuccessful (NS) group. *Outlier.

FIGURE 5 Log File Algorithm



Consideration of percent of expected power and power growth rate for decision of thrombolytic treatment or pump exchange.

Other clinical measures that should be used in conjunction with the log file analysis include auscultation as pump thrombosis can often be recognized by the different sound that an unbalanced impeller generates (7,9). Imaging methods such as x-rays, computed tomography scans, and echocardiograms can also be used to determine if there is improper positioning of an inflow cannula or other undesirable mechanisms occurring during thrombus (10,26). Using a combination of these clinical indicators along with recognizing log file characteristics could potentially result in improved pump thrombus diagnosis and allow for more effective medical treatment and therefore improved patient safety and outcomes.

STUDY LIMITATIONS. Although patient data was collected from multiple U.S. and worldwide sites, the overall number of patients with clinical records of thrombus and complete log files remains small and it is difficult to make recommendations for clinical practice from this study. As this was not a prospective study and patients without log files were screened from the analysis, there may be a potential selection bias in the tPA-treated patients. However, this is the largest collection of device thrombosis cases to date and prospective collection of a similarly sized cohort would require following nearly 1,000 patients for 1 year given the estimated 0.08 EPPY thrombosis rate. The thresholds of 1.25 for growth rate and 200% for expected power should be adjusted and validated in a larger cohort study. In addition, there is site variability in the medical management of thrombus as the treatment can include any combination of heparin, glycoprotein IIb/IIIa antagonists, and tPA. Even for patients treated with only tPA, sites may use different doses and administer the thrombolytics either intravenously or intraventricularly. These differences in medical therapy protocols could result in varying effectiveness of tPA. Finally, the fitting of occlusion and ingestion thrombi is not ideal as the exponential model is best suited for the slope changes associated with build-up thrombi. Pattern recognition methods that are more applicable to all forms of power signal changes are currently being pursued.

CONCLUSIONS

While pump thrombus events with the HVAD system are uncommon occurrences, they consistently result in a recognizable increase in power consumption. Log file analysis shows that tPA treatments are significantly more likely to be successful if the thrombus has not reached a high percent of expected power and when the thrombus has developed in a gradual manner. In contrast, a sudden appearance of high pump power is unlikely to be successfully managed with tPA. While there is promise in the log file data, conventional clinical markers of thrombus must remain an integral part of diagnosis and management. Increased awareness of the information available from log files and clinical markers will likely allow for improved detection and treatment strategies for device thrombosis and possibly other VAD associated complications as well.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Although uncommon, pump thrombosis is a serious complication for patients with continuous flow left ventricular assist devices.

COMPETENCY IN MEDICAL KNOWLEDGE 2: The application of tissue plasminogen activator can be successful in resolving pump thrombus, but intracranial bleeding is a feared complication in this setting.

TRANSLATIONAL OUTLOOK: When paired with conventional clinical markers, the analysis of the HVAD log files may allow for improved detection of pump thrombus and patient management strategies. Validation studies are needed to develop specific algorithms that can be integrated into clinical practice.

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