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REVIEW ARTICLE

Reviewing the clinical utility of ventricular assist device log files

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Abstract

Background Ventricular assist devices (VADs) have provided a temporising solution to many individuals with refractory heart failure (HF) while awaiting a suitable donor for heart transplantation which remains the gold standard in treatment. Many of the discussions around VADs involve ongoing morbidity; however, one aspect of VADs that is often overlooked is the utility of their log files. We decided to review the literature for mentions of the clinical utility of VAD log files.

Methods A keyword search was utilised on PUBMED using the terms 'Ventricular Assist Device' and 'Log files'. Perhaps unsurprisingly, this search only yielded 4 results with further articles being discovered through the bibliography of these publications.

Results The 4 identified articles provided basic information on log files, particularly with reference to the HVAD. Logs can be categorised into three types—data (pump parameters), events (changes in parameters) and alarms (abnormal function). Using a combination of these logs, we can readily identify abnormal pump operation such as the development and progression of pump thrombosis, suction events and gastrointestinal bleeding. However, the research potential of log files was not discussed in these publications, particularly as it pertains to areas such as studying speed modulation and pulsatility in VADs.

Conclusions VADs are an important staple in the treatment of patients with refractory HF. Log files provide a treasure-trove of information and knowledge that can be utilised for clinical benefit. Furthermore, log files provide an excellent tool for conducting research into device functionality. Current literature on the clinical utility of log files is sparse with much untapped potential.

Keywords Ventricular assist device log files

LVADs background

Advancements in medical technology and emerging treatments have led to a significant decline in cardiovascular mortality; however, heart failure (HF) has emerged as a growing epidemic in the twenty-first century. Despite optimal medical management, HF mortality remains high with an aggregate 50% 5-year survival rate and similar 1-year survival rates in those with advanced refractory HF [1–3].

Orthotopic heart transplantation remains the gold standard of treatment in patients with advanced refractory HF. Thanks to modern improvements, 1- and 5-year survival rates of 86% and 79%, respectively, are expected in recipients [4–6]. Despite favourable outcomes, heart transplantation is restricted due to the limitation of available organs. This, in combination with an increasing proportion of the population suffering from HF, has put this unique patient group in a difficult position [5, 7]. To overcome these limitations, left-sided ventricular assist devices (VADs) were created to either bridge patients with HF till an organ is available or to alternatively control symptoms and provide a better quality of life if they are not candidates for transplantation [8–10].

In an attempt to replicate native human physiology, first-generation VADs were pulsatile in nature; however this in itself posed a number of problems including device size and device failure rates due to multiple moving components [11]. To remedy the mechanical failings of first-generation pulsatile-flow LVADs (PF-LVAD), newer models adopted a continuous flow design enabling device miniaturisation and reduction of moving parts. Current third-generation centrifugal continuous-flow LVADs (CF-LVADs), such as the Medtronic (formerly HeartWare) HVAD (Medtronic,

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Minneapolis, MA, USA), have 1- and 2-year survival rates of 81% and 70% which are comparable to heart transplantation, establishing LVAD support as an appropriate treatment alternative [12, 13].

As a result of the improved design, newer VADs have pushed the boundaries of their use in individuals with HF. In addition to being able to keep individuals alive for longer, with fewer comorbidities, while they await to be transplanted, they have also been used as destination therapy. In this select patient cohort, VADs provide a means of permanent support as these patients do not meet the criteria to be listed for a heart transplant [14]. Despite being a life-saving treatment, there are still many challenges complicating long-term CF-LVAD therapy [13]. In particular, the continuous flow design augments a circulatory environment with significantly diminished arterial pulsatility, potentially precipitating device-related complications.

Log files

One of the more unique aspects of VADs that is often overlooked is their log files. These files not only shed light on ongoing VAD function but also aid in the management of these devices. In our institution, these files are downloaded every time a patient with an LVAD presents for a follow-up appointment and no less often than every 3 months. To better understand the usefulness of these file, we decided to conduct a literature search as a starting point. Due to limitations of a MeSH term search, namely, not capturing 'log files' as a recognised term, a keyword search was instead utilised on PubMed. The keywords were 'Ventricular Assist Device' and 'Log files'. Perhaps unsurprisingly, this search only yielded 4 results [15–18]. These articles provided some foundational information with other articles being discovered through the bibliography of the aforementioned publications.

Before progressing any further with discussing the usefulness of log files, we feel that it is important to expound on what VAD log files are. For this description, we will be using the Medtronic HVAD as an example. The controller of this device has three different types of logs:

Data: Data logs record average VAD parameters – namely, rotational speed, power consumption and estimated VAD flow. The word 'estimated' is key in this consideration, as the device does not have a sensor to detect actual flow; instead, this flow is approximated from power consumption and motor speed; hence the estimated flow is at the level of the pump. This data is recorded every 15 minutes.

Events: These logs record operating parameters, for example, set speed, blood viscosity and alarm limit set points. Unlike data logs, this type of log is recorded at time of occurrence.

Alarms: These types of logs record activated and cleared alarms of medium and high priority, for example, high wattage, low flow, suction, VAD disconnect electrical fault, and controller failure. Like event logs, this is recorded at the time of occurrence.

Normal pump operation – according to log files

A pump is said to be operating normally when there are no reported adverse events and parameters are within the therapeutic range as demonstrated by Fig. 1. Some of the early analyses that examined VAD log files demonstrated circadian variation of VAD flow [19, 20]. It is postulated that this cycle is a result of activity levels as body position changes [21]. In fact, some of the information uncovered through analysis of log files provided impetus to the claim that CF-LVAD flows were significantly affected by these aforementioned position changes through altered loading conditions and not heart rate [22].

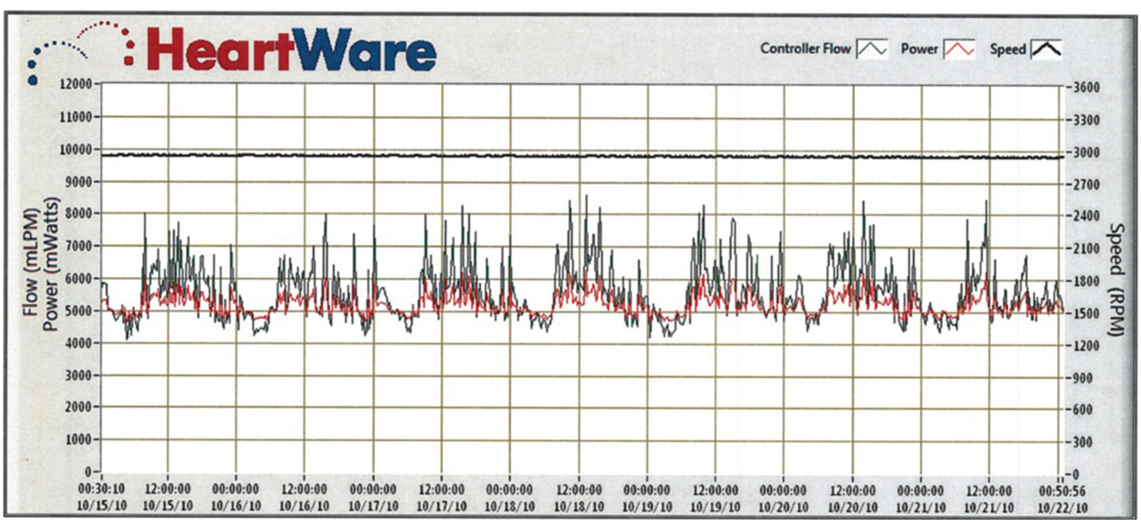

Fig. 1 LVAD log file demonstrating normal operation [18]

Abnormal pump operation demonstrated from log files

Thrombosis

VADs are not fully biocompatible. As a result, thrombosis has been a well-documented and potentially catastrophic comorbidity associated with device use. One of the biggest dangers associated with VAD thrombus is the possibility of dislodgement and potential embolic stroke [23, 24]. Much like the evolution of VADs over time from larger (pulsatile) devices to smaller (continuous) devices, so too has the morphology of pump thrombus. In the past, thrombus was small relative to the larger VAD – it was therefore difficult to thrombose the entire pump. The current-generation VADs, on the other hand, have smaller gaps between the pump components. These smaller gaps predispose a large section of the pump to thrombus, which may result in static clot and pump failure [25].

Thrombosis can be classified as pre-pump, intra-pump and post-pump. In each instance, deposition of clot can result in pump power and flow changes. Similarly, it should be stated that thrombotic events may be acute or chronic or clot ingestion may occur (Fig. 2a and b). This in turn causes increased power consumption and reduced pump efficiency that is proportional to the severity of the thrombus [18].

VAD log files can help provide a great deal of information about pump thrombosis. For example, Jorde et al. [16] extracted log file data for VAD patients and, with some mathematical modelling, were able to obtain an average VAD power during normal operation. This in turn allowed them to describe what

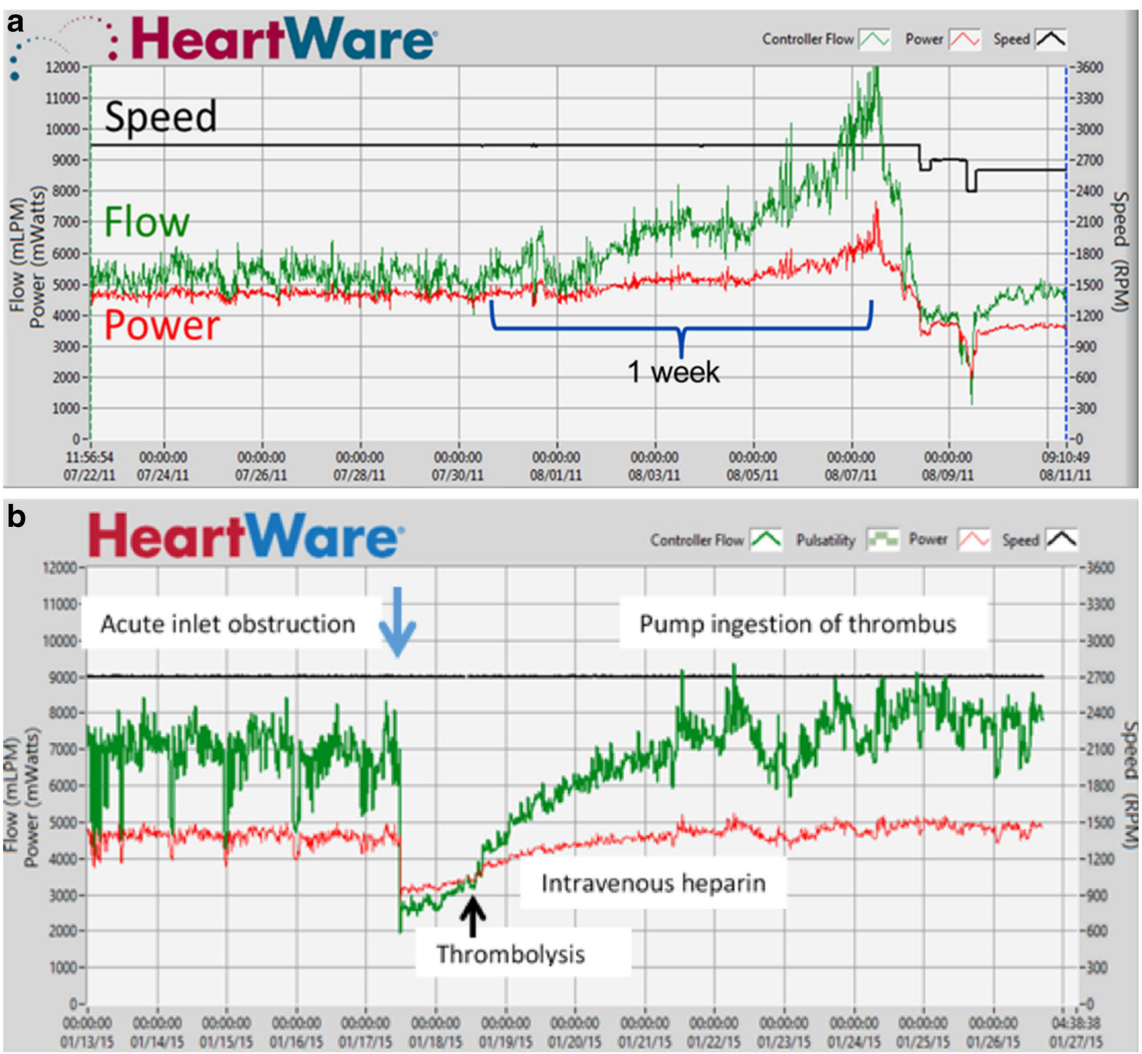

Fig. 2 **a** Demonstrating a gradual increase in pump power to maintain pump speed and overcome the resistance of a pump thrombus. Eventually, as the thrombus increases in size, this compensatory mechanism begins to fail, and so does pump speed. It is worthy to note that although flow appears to increase, it is only an estimated flow (derived from the increased power) and does not reflect actual flow in this scenario. **b** Demonstrating acute LVAD inlet obstruction secondary to a thrombus as illustrated by the rapid decline in power and therefore rapid decline in estimated flow with subsequent thrombolysis restoring normal flow

VAD power is likely to look like during a thrombus event. In this definition, pump thrombosis was defined as the period when power changed by over 3 standard deviations from baseline for at least 1.5 hours.

While defining a thrombosis event is helpful, a further benefit of VAD log files is the ability to look at the actual impact of thrombus on power consumption within the pump. For example, maximum power reached during the event could be investigated; secondly, a change in power between maximum and baseline can be used, and thirdly, a measure of interpatient variability around pump speed and power, termed 'expected value' of power consumption, could be investigated to assess the impact of thrombus on power [16].

Additionally, log files are useful in mapping out the progression of a thrombus event. For example, clot formation may be gradual or sudden; similarly the clot may be ingested which can then cause pump conclusion. All of this can be obtained from power data. A gradual build-up of clot will be demonstrated by power gradually going up and then declining, whereas a sudden build-up can be demonstrated by excess power consumption occurring suddenly; ingestion may be a combination of sudden power increase, followed by a return to baseline, and pump occlusion may be demonstrated by a sudden reduction in power [16] (Fig. 3).

In fact, Jorde et al. [16] went so far as to model the growth of thrombi using log files to generate an equation that tracked the exponential nature of growth. See below for model:

$$\text{Power} = Ae^{B\times t} + C$$

In this formula, the coefficient B is a time constant corresponding to the rate of power consumption increase, whereas coefficients *A* and *C* are a power stretch factor and power shift, noting that these are mathematical models and do not carry biological significance of the time constant. According to the authors of this study, the model provided the best fit for thrombus build-up [16].

Going further still, the treatment of pump thrombus can also be monitored with the aid of log files. Jorde et al. used this as a co-criteria for clot resolution in their study such that when patients with pump thrombi were treated, resolution of the thrombus was partly contingent on the power parameter returning to a normal operating range, in addition to clinical and biochemical resolution of the clot.

Consolo et al. (2019) used log files to demonstrate that the circadian rhythm developed in VAD patients has important implications for the development of pump thrombosis. In this study, log files for patients who experienced thrombotic adverse events were analysed and compared to patients with normal function. They

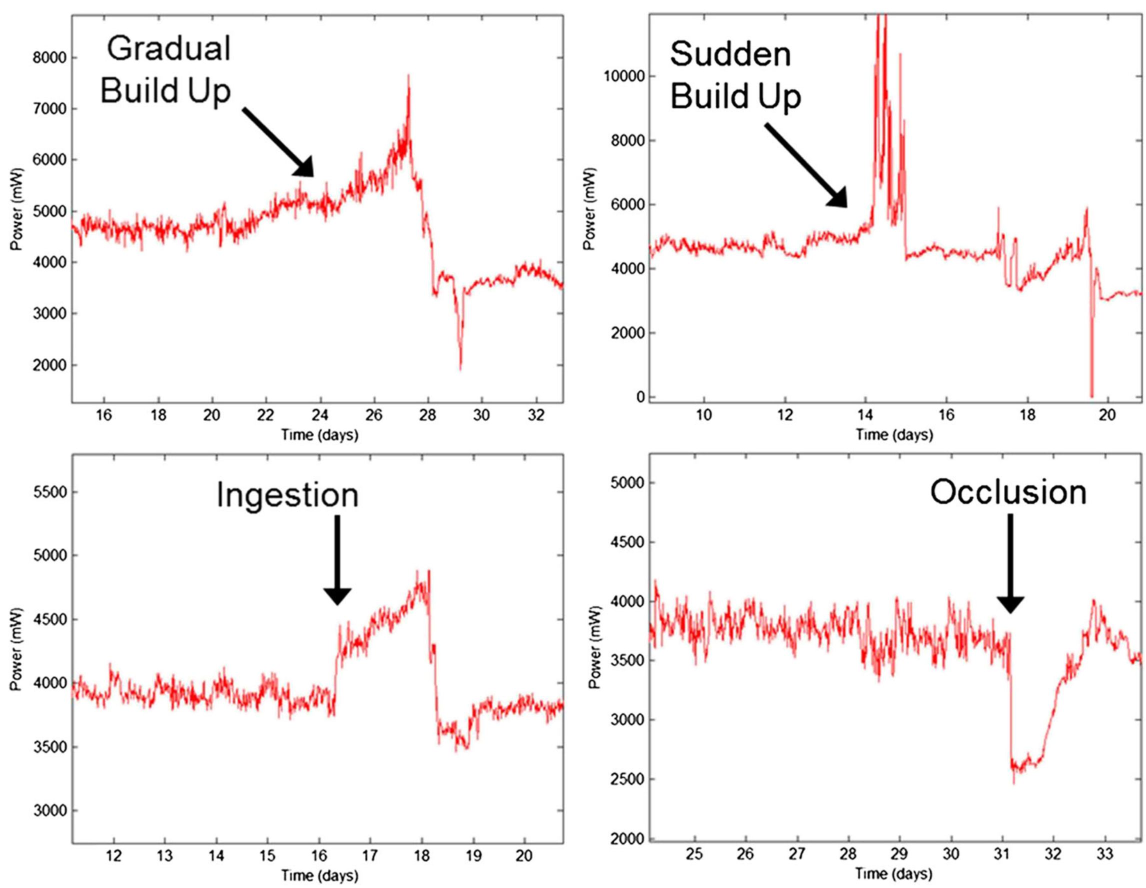

Fig. 3 Demonstrating power changes in the pump during thrombus development [16]

found that the early stages of pump thrombosis alters circadian variability and as such may act as an early marker of pump thrombosis (see Fig. 4). Similarly, resolution of thrombotic events tends to restore the stable circadian variability. This allowed the authors to develop a new tool to analyse the time-frequency of HVAD log files in order to facilitate early identification of pump thrombosis.

Uncovering device malfunction

New and emerging technology tends to go hand in hand with a steep learning curve; as such, initial implants of new devices may uncover device malfunction. Fortunately, this can often be diagnosed using log files. One recent example of this is the twisting

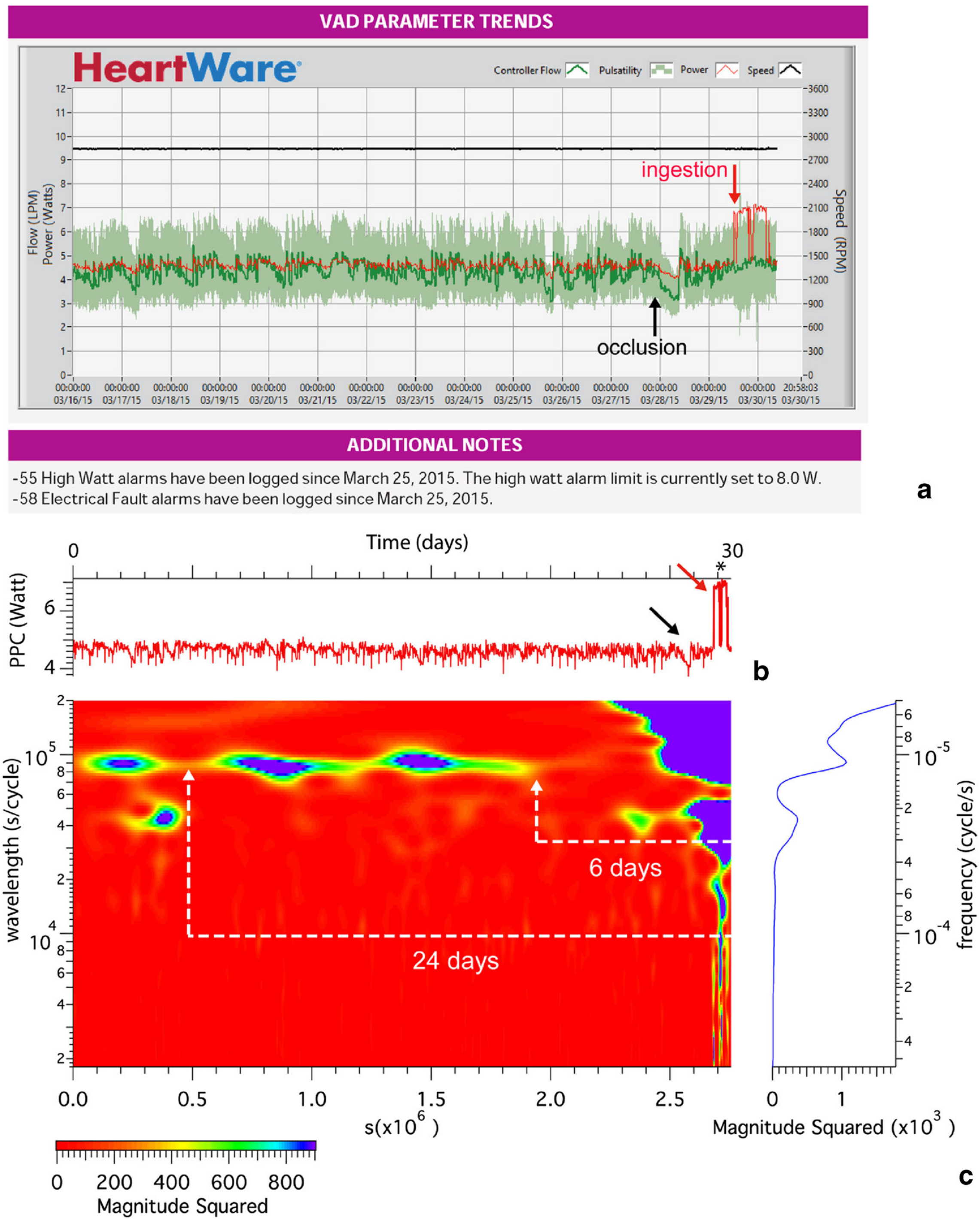

Fig. 4 Instability of circadian rhythm 24 days prior to development of thrombosis event (C) with (B) demonstrating the peak power consumption of the pump at the time of thrombosis (black arrow), which produces the inflow cannula occlusion and subsequent reduced flow reflected by the black arrow (A)

outflow graft associated with early HeartMate 3 models. It was postulated that the main mechanism behind this is the new design of the HeartMate 3 outflow graft containing a metallic swivel joint which was allowed to freely rotate post-implant and intended to allow the implanting surgeon to avoid twisting when implanting the pump. This mechanism unfortunately had the unintended consequence of allowing the outflow graft to rotate in either direction sporadically, which can contribute to twist. This twisting manifested itself in reduced pump parameters on log files – namely, reduced pump flow (median 1.6 L/min, ranging from 0.7 to 3.6 L/min) [26].

Another paper by Posada et al. [27] assessed cases of outflow graft occlusion of the new HeartMate 3 device. In this case series, the authors identified 2 patients who developed extrinsic occlusion of the outflow graft. In both patients, log files were useful in demonstrating steadily declining flows over time [27].

One other interesting case of potential device malfunction is power spikes observed in some HeartMate II pumps. In a study published by Salerno et al. [28], pump power and speed measurements were analysed post pump implant. In this study, they defined early power elevations as power spikes of > 10 W within the first post-operative days. Patients were then split into two groups depending on whether they experienced a power spike with subsequent follow-up. Interestingly, no association was found between early power spikes and deleterious outcomes such as stroke and pump thrombus [28].

A further study by Tibrewala et al. (2015) contends that early power spikes in the HeartMate II devices were in fact associated with increased rates of pump thrombosis [29]. Log files clearly play an important role in this area, with the ability to regularly monitor power output, assessing for the presence of early power elevation as well as closely following up the patient cohort who demonstrated early power elevation to ensure that they do not experience adverse outcomes at an increased rate – particularly pump thrombosis.

Suction events

Continuous flow LVADs are subject to suction due to the current design of constant impeller speed in both systole and diastole. Suction can be caused by a number of reasons, for example, suboptimal inflow cannula positioning or repositioning of the inflow cannula as a result of left ventricular underfilling [18]. Left ventricular underfilling may in turn result from a number of events which includes hypovolemia, RV failure or cardiac tamponade. Arrhythmias and suction have an interesting relationship in that arrhythmias may cause suction events due to left ventricular dysfunction; however, the inverse is also true in that the mechanical action of suction may precipitate arrhythmias [30].

Suction events can happen intermittently or continuously; as an example of intermittent suction, please (see Fig. 5). Immediately post-systole is the period in the cardiac cycle where the VAD inflow cannula is most susceptible to suction events. The reason for this is purely mechanical in that during systole the ventricular free wall or septum is closer in proximity to the inflow cannula. In instances of intermittent suction, the flow periodically and sharply deflects towards either very low flow (1–2 L/min) or even approaching 0 L/min during systole [18]. This poses a sharp contrast in that under normal conditions, flow increases through systole [30]. Diagnosing continuous suction events proves more challenging due to the inability to discriminate systole from diastole on VAD waveforms.

Cardiac dysfunction

VAD log files are surprisingly useful when it comes to uncovering multiple examples of cardiac dysfunction. Right HF can be diagnosed with a combination of clinical signs and

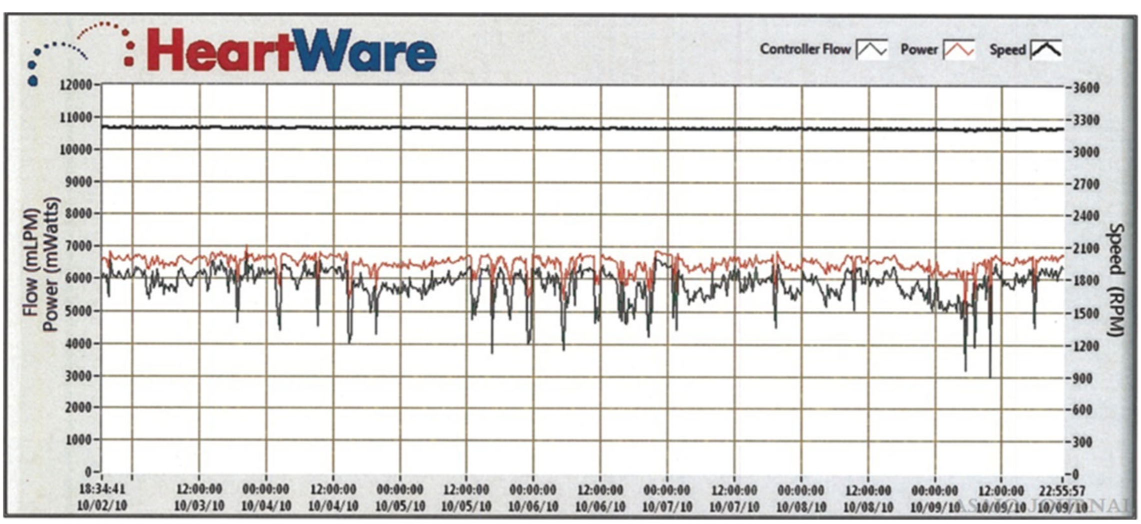

Fig. 5 Demonstrating intermittent suction [18]

VAD log information. Right HF can mimic severe hypovolemia with severely reduced pump flow.

This is due to left ventricular underfilling [30] which can then precipitate suction. As shown in the recent study by Consolo et al. [15], there may be a particular signature in the analysis of log file data associated with right heart failure. Further study is required in this area. Aortic regurgitation is another condition that may be identified using VAD log files – a regurgitant aortic valve is characterised by high peak and mean trough flows combined with low pulsatility [30].

Other uses for VAD log files

Optimising volume status

Changes in volume status are common in patients with VADs. Many reasons can affect fluid balance in this patient cohort which includes, but is not limited to, blood loss, diuretic, fluid infusion and medication. In hypervolemic states, left ventricular filling is increased, which results in higher diastolic and systolic pressures; this in turn results in reducing pressure gradients across the pump and consequently higher pump flows. Conversely, the same holds true for a hypovolemic state [30]. Changes in flow are apparent when reviewing VAD log files, and they can therefore aid long-term volume monitoring.

Trends in power and flow due to gastrointestinal bleeding

One of the important uses in log files is in the trends available on immediate review. A useful pattern to recognise in outpatient care is a gradual decrease in estimated pump flows. As seen in Fig. 6a, despite unchanged activity, there is a decrease in flows over a 2–3 day period. On further clinical review, gastrointestinal bleeding was diagnosed. This may be explained by the decrease in haematocrit associated with significant bleeding states, resulting in decreased power consumption requirements by the pump and therefore decreased estimated flows. That this is not due to hypovolaemia is evident

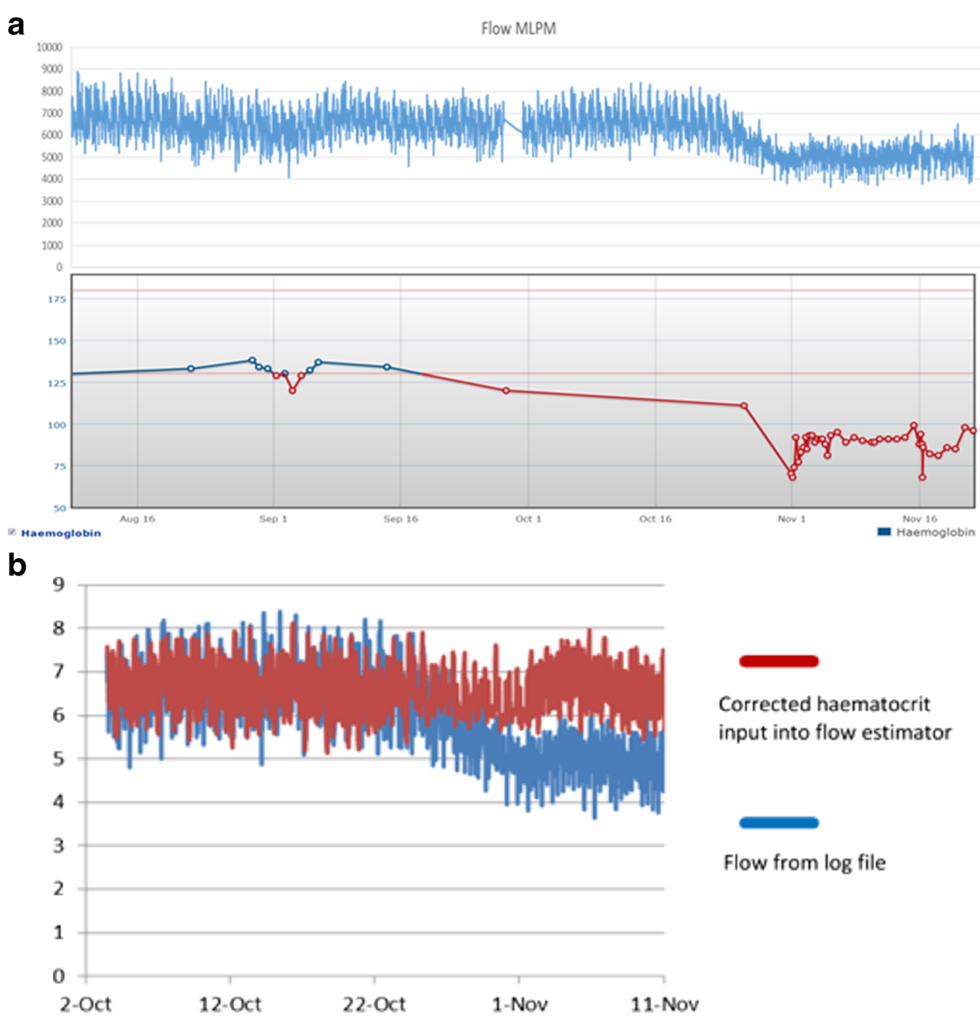

Fig. 6 **a** Reduction in haemoglobin mirrored by reduction in estimated pump flow. **b** Corrected estimated pump flow based on accurate haematocrit in bleeding event compared to actual flow

by recalculating the pump flows from the power and updating the haematocrit on a daily basis (Fig. 6b).

Future direction

Studying pulsatility

Most studies that investigate the association between pulsatility and outcomes do so through comparison of older-generation PF-LVADs with newer CF-LVADs. In this way, pulsatility is analysed as a binary variable; that is, flow is either pulsatile or non-pulsatile. It has become apparent that some level of pulsatility still exists within CF-LVAD pumps. Therefore, consideration of pulsatility as continuous within a spectrum may be more appropriate in adequately determining how pulsatility affects outcomes.

We propose that log files can be utilised to better understand the degree of pulsatility as well as its impact on patients with VADs. An example of this can include assessing the impact of high pulsatility on mean flow, peak flow and trough flows and its resultant impact on pump thrombosis, stroke and gastrointestinal bleeding events. From our experience with the HVAD, we feel that familiarity with this pump, as well as the ability to extract log files for flow, would be ideal for further study.

Automated pump speed modulation, such as the Lavare cycle, serves as a washout of the pump and may enact a degree of pseudo-pulsation. By studying the log files of VAD patients with the Lavare cycle on and off, we would be able to make some conclusion about whether it makes a significant impact on pulsatility. This also requires further assessment, with early retrospective data suggesting improved outcomes with automated pump speed modulation activated [31]. In our experience, the Lavare cycle does not induce a meaningful degree of artificial pulsatility; however, a study will need to evaluate this in detail before a firm conclusion can be drawn.

Machine learning and log files

The APOGEE trial, a HeartWare HVAD Destination Product Surveillance Registry (PSR) Platform, will be a key trial in assessing the clinical benefits of log files. This trial will seek to further understand the impact of implant procedure, blood pressure management and anticoagulation therapy in patients receiving an HVAD. The trial will be prospective and observational, and patients will be followed up for up to 12 months. At the time of writing this paper, the Apogee trial is recruiting for the study [32]. Collecting data prospectively may allow future studies into automated assessment of pump function using log file analysis in real time. This will need to be confirmed with the appropriate outcome assessments.

Conclusion

VADs are an important staple in the treatment of patients with refractory HF. Log files which are recorded for these devices provide a treasure trove of information and knowledge that can be utilised for clinical benefit. Specific examples of this include diagnosing problems such as pump thrombosis, gastrointestinal bleeding and suction. Furthermore, log files provide an excellent tool for conducting research into device functionality. Going forward, a greater emphasis on the utility of log files in clinical management and ongoing research is warranted.

Compliance with ethical standards CSH is a consultant for Medtronic and Abbott and has received research funds from Medtronic. Informed consent, an ethical statement and human/animal rights considerations were not applicable given this was a review article.

References

1. Norton C, Georgiopoulou VV, Kalogeropoulos AP, Butler J. Epidemiology and Cost of Advanced Heart Failure. Prog Cardiovasc Dis. 2011;54:78–85.
2. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139:e56–e528.
3. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Eng J Med. 2001;345:1435–43.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137–61.
5. Kadakia S, Moore R, Ambur V, Toyoda Y. Current status of the implantable LVAD. Gen Thorac Cardiovasc Surg. 2016;64:501–8.
6. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report—2014; focus theme: retransplantation. J Heart Lung Transplant. 2014;33:996–1008.
7. Mehra MR. Guidelines for Listing Candidates for Heart Transplant: A 10-Year Update. JAMA Cardiol. 2017;2:98–9.
8. Lim HS, Howell N, Ranasinghe A. The physiology of continuous-flow left ventricular assist devices. J Card Fail. 2017;23:169–80.
9. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Eng J Med. 2009;361:2241–51.
10. Aaronson KD, Slaughter MS, Miller LW, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation. 2012;125:3191–200.
11. Rigatelli G, Santini F, Faggian G. Past and present of cardiocirculatory assist devices: a comprehensive critical review. J Geriatr Cardiol. 2012;9:389–400.
12. Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. N Eng J Med. 2017;376:451–60.
13. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant. 2017;36:1080–6.

14. Silva EJ. Mechanical circulatory support: current status and future directions. Prog Cardiovasc Dis. 2016;58:444–54.
15. Consolo F, Esposti F, Gustar A, De Bonis M, Pappalardo F. Log files analysis and evaluation of circadian patterns for the early diagnosis of pump thrombosis with a centrifugal continuous-flow left ventricular assist device. J Heart Lung Transplant. 2019;38:1077–86.
16. Jorde UP, Aaronson KD, Najjar SS, et al. Identification and management of pump thrombus in the heartware left ventricular assist device system: a novel approach using log file analysis. JACC: Heart Fail. 2015;3:849–56.
17. Rame JE, Birati EY. HeartWare left ventricular assist device pump thrombosis: a shift away from ramp. JACC Heart Fail. 2015;3:857–9.
18. Chorpenning K, Brown MC, Voskoboynikov N, Reyes C, Dierlam AE, Tamez D. HeartWare controller logs a diagnostic tool and clinical management aid for the HVAD pump. ASAIO J. 2014;60:115–8.
19. Slaughter MS, Ising MS, Tamez D, et al. Increase in circadian variation after continuous-flow ventricular assist device implantation. J Heart Lung Transplant. 2010;29:695–7.
20. Suzuki K, Nishinaka T, Miyamoto T, Ichihara Y, Yamazaki K. Circadian variation of motor current observed in fixed rotation speed continuous-flow left ventricular assist device support. J Artif Organs. 2014;17:157–61.
21. Hu SX, Keogh AM, Macdonald PS, et al. Interaction between physical activity and continuous-flow left ventricular assist device function in outpatients. J Card Fail. 2013;19:169–75.
22. Muthiah K, Gupta S, Otton J, et al. Body position and activity, but not heart rate, affect pump flows in patients with continuous-flow left ventricular assist devices. JACC Heart Fail. 2014;2:323–30.
23. Akin S, Soliman OI, Constantinescu AA, et al. Haemolysis as a first sign of thromboembolic event and acute pump thrombosis in patients with the continuous-flow left ventricular assist device HeartMate II. Neth Heart J. 2016;24:134–42.
24. Dang G, Epperla N, Muppidi V, et al. Medical management of pump-related thrombosis in patients with continuous-flow left ventricular assist devices:a systematic review and meta-analysis. ASAIO J. 2017;63:373–85.
25. Tchantchaleishvili V, Sagebin F, Ross RE, Hallinan W, Schwarz KQ, Massey HT. Evaluation and treatment of pump thrombosis and hemolysis. Ann Cardiothorac Surg. 2014;3:490–5.
26. Mehra MR, Salerno C, Naka Y, et al. A tale of the twist in the outflow graft: An analysis from the MOMENTUM 3 trial. J Heart Lung Transplant. 2018;37:1281–4.
27. Duero Posada JG, Moayedi Y, Alhussein M, et al. Outflow graft occlusion of the HeartMate 3 left ventricular assist device. Circ Heart Fail. 2017;10:pii.e004275.
28. Salerno CT, Sundareswaran KS, Schleeter TP, Moanie SL, Farrar DJ, Walsh MN. Early elevations in pump power with the HeartMate II left ventricular assist device do not predict late adverse events. J Heart Lung Transplant. 2014;33:809–15.
29. Tibrewala A, Nassif M, Raymer D, et al. Early elevated pump power and associated hemolysis amongst HeartMate II left ventricular assist devices. J Cardiac Fail. 2015;21:S39–40.
30. Rich JD, Burkhoff D. HVAD flow waveform morphologies: theoretical foundation and implications for clinical practice. ASAIO J. 2017;63:526–35.
31. Zimpfer D, Strueber M, Aigner P, et al. Evaluation of the HeartWare ventricular assist device Lavare cycle in a particle image velocimetry model and in clinical practice. Eur J Cardiothorac Surg. 2016;50:839–48.
32. Investigators, A.S. Apogee, A HeartWare HVAD Destination Product Surveillance Registry (PSR) Platform. 2019; Available from: https://clinicaltrials.gov/ct2/show/NCT03697980.