Log files analysis and evaluation of circadian patterns for the early diagnosis of pump thrombosis with a centrifugal continuous-flow left ventricular assist device

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BACKGROUND: No clinical standardized methods exist to identify the early stage of the development of pump thrombosis in the setting of HVAD (Medtronic Inc., USA) implantation. We aimed at developing a clinically relevant tool to evaluate HVAD operation during long-term support and at identifying a new reliable marker for the early diagnosis of pump thrombosis reflecting altered patient-pump physiological interplay.

METHODS: We developed a novel algorithm based on time-frequency analysis of the HVAD log files allowing the detection of the intrinsic circadian rhythmicity of the pump power consumption. With this tool, we retrospectively evaluated (1) post-operative restoration of circadian rhythm (n = 14 patients), (2) long-term stability of circadian rhythmicity in patients with no reported adverse events (n = 12), and (3) alteration of circadian fluctuations in patients who suffered from pump thrombosis (n = 19).

RESULTS: We demonstrate (1) progressive development of circadian rhythm following post-operative recovery (93% of the patients, 23 ± 15 days after implantation), (2) long-term stability of circadian rhythmicity in patients with no thrombotic complications (92% of the patients; 962 (445–1447) days of support), and (3) severe instability and loss of circadian fluctuations before the thrombotic event (89% of the patients, 12 ± 6 days ahead of the clinical manifestation of overt pump thrombosis). Furthermore, we provide the first clinical evidence of recovery of circadian rhythmicity following non-surgical resolution of pump thrombosis.

CONCLUSIONS: Time-frequency analysis of the HVAD log files provides a new tool for the early diagnosis of pump thrombosis. Loss of circadian rhythmicity might trigger medical evaluation, improving the results of medical management of pump thrombosis, and decreasing the need for pump exchange.

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KEYWORDS: left ventricular assist device; pump thrombosis; log files; circadian rhythm; time-frequency analysis

Introduction

Pump thrombosis (PT) is a severe complication of continuous-flow Left Ventricular Assist Devices (LVADs),1–3 which is driven by patient- and/or device-specific characteristics that synergize with systemic factors to the development of
the thrombotic event. PT can occur because of in-pump thrombus build up or ingestion of a mobilized thrombus. Treatment is based on intravenous anticoagulation and/or thrombolytic therapy. Its success rate is the highest at an early stage of PT and decreases in the case of late diagnosis. In case of treatment failure or severe cardiac insufficiency, emergency pump exchange remains the only therapeutic option, which, however, is associated with a significant drop in survival, and high costs.

Diagnosis of PT is based on the analysis of the system log files, as the event is typically preceded by changes in pump power consumption (PPC) associated with modifications of the pump workload. Detection of hemolysis is also pursued to confirm the diagnosis. Previous studies have suggested the value of log files analysis of the HeartWare HVAD Ventricular Assist Device (Medtronic Inc, USA) and of early recognition of the changes in PPC to resolve the event. In addition, specific patterns of PPC changes have been identified and correlated to in-pump thrombus build up, suction of a mobilized thrombus, or pre-pump flow obstruction caused by a thrombus occluding the inflow cannula. Despite this, the HVAD thrombus alarm is unable to provide early diagnosis of PT. In the case of in-pump thrombus, the alarm is triggered following high-Watt power spikes (1–2 Watts above the average value), which are indicative of major device malfunctioning due to a huge thrombus already formed in the pump. In the case of pre-pump obstruction, the low flow alarm is triggered following major decrease of the LVAD flow (1–2 L/min), which is associated with the acute, clinically overt phase of the event.

Kauffman et al. have suggested analysis of the acoustic spectrum of the pump (i.e., analysis of third harmonics) to detect PT. However, acoustic analysis is usually performed following the first diagnosis of a suspected PT, to increase the diagnostic precision. As a result, to date no clinical standardized methods exist to detect the early phase of PT. Its development might have enormous clinical value in limiting the progression of the thrombotic event and associated complications.

Slaughter et al. suggested that continuous-flow pumps have an intrinsic response to the patient’s physiological circadian rhythmicity. The authors described circadian fluctuations in LVAD flow and PPC in patients with no reported adverse clinical events and LVAD parameters within the therapeutic range. In this study, we hypothesized that patients who develop gradual in-pump thrombus build up or pre-pump inflow cannula occlusion might experience instability of the circadian variability (CV) of PPC because of changes of the pressure gradient across the pump head and flow obstructions that alter the “physiological” intrinsic interactions between the pump and the native circulation. Accordingly, we developed a novel algorithm able to detect circadian variation of the PPC of the HVAD, and evaluated if altered non-circadian trends of PPC might be identified before overt PT.

Methods

Study design and patient population

This study was performed at San Raffaele Scientific Institute in Milan, Italy, and was conducted in patients implanted with the HVAD. The controller of the HVAD uniquely allows for downloading and post-processing of the log files, where PPC is iteratively recorded every 15 minutes and stored over 30 consecutive days of pump operation. All the log files analyzed in this study were provided by Medtronic, Inc. following the deidentification and anonymization of Medtronic proprietary data.

We analyzed 3 different sets of data. First, we retrospectively analyzed the log files of HVAD patients with sinus rhythm and stable clinical conditions in the early post-operative period (30-to-60 post-operative days) to verify that our tool was able to identify the restoration of circadian rhythm as previously described. Second, we retrospectively analyzed the log files of patients with no reported events of PT over the long-term to evaluate the effective stability of circadian rhythmicity. Third, we retrospectively analyzed the log files of HVAD patients who suffered from PT. The data were analyzed over 30 day-period that preceded clinical manifestation of the thrombotic event. For each patient, the time at which the algorithm detected a significant alteration in CV of the PPC was recorded, and the prognostic power of our algorithm was compared with that of the HVAD high-Watt alarm. The clinical manifestation of PT was identified from the log files as the date at which the peak of PPC was reached. Full details of the time-frequency analysis are reported as Supplementary Material.

Results

Analysis of post-operative recovery of circadian rhythmicity

Log files of 14 patients in the 30-to-60 post-operative days were provided and analyzed. We observed effective restoration of the CV of the PPC in 13 out of 14 (93%) patients following 23 ± 15 days of HVAD support. The restoration of the CV was consistent with a significant increase in magnitude (i.e., power) of the PPC in the circadian frequency band. Representative data are shown in Figure 1: in the case presented, while CV of the PPC was strongly unstable or totally absent (magnitude = 0, red colored in Figure 1) over the first 15 days of support, the power in the circadian band increased significantly starting from day 16 (magnitude >0; Figure 1). Then, it progressively increased in magnitude and remained stable over the 16-to-30 post-operative days, indicating the establishment of optimized pump operation.

Analysis of long-term circadian rhythmicity in patients with no diagnosed adverse events

Log files of 12 patients with no reported thrombotic adverse events were provided and analyzed. The median time of support was 962 (445–1447) days. We observed long-term stability of the CV of the PPC in 11 out of 12 (92%) patients, consistent with the measured magnitude (i.e., power) of the PPC in the circadian frequency band (Figure 2). Pronounced instability of the CV was recorded in one patient with severe right ventricular dysfunction (Supplementary Figure 1). In addition, our data suggest that variation of the pump speed dictated by clinical needs is unlikely to induce disruption of the CV, as it was observed in one patient in this cohort (Supplementary Figure 2), and
further corroborate the reliability of our tool to recognize the variations of circadian rhythmicity associated with clinical events.

Analysis of circadian rhythmicity in patients with diagnosed PT

Log files of 19 thrombotic events were provided and analyzed, specifically, 14 events of in-pump thrombus build up and 5 events of pre-pump inflow cannula occlusions and thrombus ingestions. All the data originate from clinical cases of confirmed PT diagnosed according to INTERMACS criteria. Thrombotic events were adjudicated according to the specific morphology of the log files, as described previously.

We observed loss of the CV in the PPC in 17 out of 19 patients (89%) 12 ± 6 days before clinical manifestation of the thrombotic event (Table 1). A comparison of the predictive power of our method (detection of loss of CV) with that of in-built standard HVAD alarm (high-watt power spikes) indicates enhanced prognostic capability and significant improvement of early diagnosis of our algorithm (Table 1; \(p < 0.0001\)). In the case of build-up PT, the algorithm detected loss of CV in 12 out of 14 patients (86%) 12 ± 7 days before clinical manifestation of the event (Table 1; \(p < 0.0001\) vs HVAD alarm); in the case of thrombus ingestion, the algorithm detected loss of CV in all 5 events (100%) 11 ± 5 days before clinically overt PT (Table 1; \(p = 0.008\) vs HVAD alarm). Representative data of time-frequency analysis of build-up PT and thrombus ingestion events are shown in Figures 3 and 4, respectively. Loss of CV was consistent with a sudden decrease of the magnitude (i.e., power) in the circadian frequency band of the PPC. In the presented cases, power in the circadian frequency band progressively decreased until it was completely absent 7 days before the clinical manifestation of the build-up PT (Figure 3) and 6 days before thrombus ingestion (Figure 4), respectively. In both cases, a first significant instability of PPC circadian rhythmicity was recorded 20 (Figure 3) and 24 (Figure 4) days before overt PT, respectively.

In Figure 5, the results of the analysis of the CV of the PPC performed in a patient who suffered from recurrent PT are shown (\(n = 2\) in-pump build-up thrombosis), further enlightening the robustness and reliability of our method for the early detection of loss of CV and early diagnosis of...
Representative data of long-term stability of the CV of the pump power consumption (PPC) in patients with no diagnosed adverse events. In the presented case, log files were analyzed following 690 days of support. (A) Log files analysis provided by HeartWare (Medtronic Inc.). (B) Left: Wavelet time-frequency analysis of the PPC: a stable CV was observed over 30 days of pump operation, consistent with the recorded magnitude (i.e., power) of the PPC signal in the circadian frequency band. Right: Fourier analysis of the PPC signal demonstrates the stability of the circadian rhythm, consistent with the peak of power concentration in the $1.16 \pm 0.3 \times 10^{-5}$ Hz circadian frequency band.

Table 1  Early Loss of Circadian Variability (CV) of the Pump Power Consumption (PPC) in Patients with Clinically Diagnosed Pump Thrombosis (PT)

<table>
<thead>
<tr>
<th></th>
<th>All PTs</th>
<th>Build-up PT</th>
<th>Thrombus ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>19</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Early loss of CV</td>
<td>17 (89%)</td>
<td>12 (86%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Loss of CV (days before the thrombotic event)</td>
<td>12 ± 6</td>
<td>12 ± 7</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>Triggering of the HVAD high-Watt alarm (days before the thrombotic event)</td>
<td>1.6 ± 1.7</td>
<td>1.8 ± 1.8</td>
<td>1.2 ± 1.6</td>
</tr>
</tbody>
</table>
In the case presented, we observed a stable CV of the PPC (1) 12 months (Figure 5A) and (2) 6 months (Figure 5B) ahead the first thrombotic event. Conversely, a loss of CV was detected 11 days before clinical manifestation of the first PT (Figure 5C). In addition, our data indicate the restoration of CV following the resolution of the first event (18 days after the event, Figure 5D). Later loss of CV was again detected, which anticipated the

**Figure 3** Representative data showing early loss of the CV of the pump power consumption (PPC). (A) Log files analysis provided by HeartWare (Medtronic Inc.) indicates gradual in-pump thrombus build up and shows progressive increase of PPC and pump flow over time; the red arrow indicates triggering of the high-Watt alarm. (B) The PPC signal is depicted over 30 consecutive days of support as retrieved from the HVAD log files; the red arrow indicates triggering of the high-Watt alarm (corresponding to the red arrow in A); * indicates clinical manifestation of the thrombotic event (peak of PPC). (C) Left: Wavelet time-frequency analysis of the PPC: the white arrows indicate (1) a first instability of circadian rhythmicity recorded 20 days prior to the thrombotic event, consistent with significant decrease of magnitude in the circadian frequency band, and (2) loss of CV 7 days before clinical manifestation of the event. Right: Fourier analysis of the PPC signal shows the peak of power concentration in the $1.16 \pm 0.3 \times 10^{-5}$ Hz circadian frequency band.
second thrombotic event (13 days before its clinical manifestation; Figure 5D).

**Discussion**

This study describes a novel tool for the evaluation of HVAD pump operation during long-term support and highlights its value for the early identification of PT. The tool is based on the analysis of the system log files. Specifically, the algorithm we developed allows characterization of the presence (or absence) of the intrinsic CV of the PPC. Indeed, we show that HVAD patients gain circadian rhythm following post-operative recovery (Figure 1). Circadian rhythmicity consists of reproducible changes of PPC and flow over daytime and is detected by our algorithm via time-frequency Wavelet decomposition analysis as the magnitude of the PPC signal in the circadian frequency band, and (2) loss of CV 6 days before clinical manifestation of the event. Right: Fourier analysis of the PPC time signal shows the peak of power concentration in the $1.16 \pm 0.3 \times 10^{-5}$ Hz circadian frequency band.

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**Figure 4** Representative data showing early loss of CV of the pump power consumption (PPC). (A) Log files analysis provided by HeartWare (Medtronic Inc.) indicates a first significant reduction of PPC and pump flow (black arrow, occlusion of the inflow cannula) followed by sudden increase in PPC (red arrow, thrombus ingestion). (B) The PPC signal is depicted over 30 consecutive days of support as retrieved from the HVAD log files; the black arrow indicates triggering of the low flow alarm; the red arrow indicates triggering of the high-Watt alarm; * indicates clinical manifestation of the thrombotic event (peak of PPC). (C) Left: Wavelet time-frequency analysis of the PPC: the white arrows indicate (1) a first instability of circadian rhythmicity 24 days prior to the development of the thrombotic event, consistent with significant decrease of magnitude in the circadian frequency band, and (2) loss of CV 6 days before clinical manifestation of the event. Right: Fourier analysis of the PPC time signal shows the peak of power concentration in the $1.16 \pm 0.3 \times 10^{-5}$ Hz circadian frequency band.
Figure 5  Analysis of CV of the pump power consumption (PPC) in a HVAD patient who suffered from recurrent pump thrombosis (PT). A stable CV was observed over 30 days of pump operation 12 months (A) and 6 months (B) before the development of the first PT. A loss of CV was recorded 11 days prior to clinical manifestation of the first thrombotic event (C). Recovery of the CV was recorded 18 days following resolution of the event (green arrow in C), which remained stable until 13 days before the second thrombotic event (D). (C) and (D) depict consecutive time-windows. Red arrows in (C) and (D) indicate triggering of the HVAD high-Watt alarm. * indicates clinical manifestation of the thrombotic event (peak of PPC).
might produce abnormal changes of the PPC before clinical evidence or triggering of the high-power alarm. As such, the potential to discriminate between physiological (circadian) and pathological (non-circadian) patterns of the PPC might turn into a clinically relevant tool for the early identification of PT.

Though recognized as a valuable diagnostic tool of an ongoing clinical event, the HVAD alarm of high-Watt power spikes does not have the acuity to trigger medical interventions before overt thrombosis. Indeed, the analysis of high-Watt power spikes prevents recognition of frequency oscillations of the PPC baseline. Further refinements of this approach are unlikely to increase early sensitivity upon thrombotic events: lowering the threshold for high-Watt spikes (1) would trigger false alarms because of (low) PPC oscillations associated with physiological circadian variations, (2) would negatively affect the quality of life of the patients because of recurring false alarms, and (3) might trigger unnecessary medical interventions.

Our approach moves standard analysis of the power spikes of the PPC toward the evaluation of its intrinsic variability in the frequency domain. Indeed, we do not look at power spikes; instead, the analysis is based on the recognition of intrinsic fluctuations of the signal baseline. Importantly, alterations of the CV appear evident when high-Watt power spikes are still absent.

Time-frequency analysis is performed on log files retrieved from the HVAD controller. As such, PPC values corresponding to the Lavare cycle might be randomly stored in the time series. However, since these PPC values are characterized by much higher frequency components than those of the CV, it is highly unlikely that this would influence recognition of the CV pattern.

Time-frequency analysis of the PPC achieved unprecedented early sensitivity to abnormal pump operating dysfunctions, which correlate with the initial stage of the thrombotic event (Table 1). With our approach, we can characterize not only the presence of CV at single time points (i.e., single days of support), but also the presence of repetitive CV over time (i.e., over consecutive days of support). Thanks to these peculiar characteristics, time-frequency analysis allowed us to quantify (1) the recovery of the CV following post-operative recovery, (2) long-term stability of the CV in patients with no reported adverse events, (3) the alteration of the CV that precedes clinical manifestations of a thrombotic event, and iv) the recovery of the CV following the event resolution. Our algorithm is able to identify not only in-pump early thrombus build up (sensitivity: 86%, 12 days before on average; Table 1) but also occlusions of the inflow cannula prior to thrombus ingestion, with apparent superior predictive capability (sensitivity: 100%, 11 days before on average; Table 1).

With this background, we envision the potential for the development of a miniaturized central processing unit to be integrated into the HVAD external controller allowing real-time analysis of the CV of the PPC and equipped with ad-hoc alarm signals driven by the algorithm output data. Furthermore, this external unit might be equipped with remote data transmission systems allowing continuous/on-demand evaluation of the CV by physicians. Such a system might forewarn of major thrombotic complications and enhance prompt medical management, thus reducing their progression, associated morbidity, and costs related to their treatment. Early detection of thrombotic complications might immediately translate into earlier readmission, evaluation, and prompt initiation of inherent therapies. As such, it might enhance the success of medical therapy. Indeed, the success of any non-surgical treatment of PT (IV heparin/thrombolytics) is strongly dependent on the time of event recognition.8,14,15

We emphasize the value of this technology in the perspective of acceptable quality of life of the patients, as the proposed miniaturized central processing unit system would not increase the weight or dimensions of the system, nor worsen wearability of the bag that holds the controller.

In addition, we envision a potential for our method to optimize the intensity and duration of lytics to reduce drug-related side-effects (bleeding) associated with unnecessary drug administration: indeed, our approach allows detecting the recovery of the CV following the initiation of lytics (Figure 5) that we hypothesize to be indicative of event resolution associated with restoration of normal pump operation. We also envision the translatability of our method to other LVAD systems (either centrifugal or axial pumps), as well as other clinical settings, for example, temporary mechanical circulatory support systems, such as the Impella (Abiomed Inc., USA). For this aim, further studies aimed at testing the reliability of our tool against axial rotary blood pumps are warranted. In addition, although LVAD systems that abated the incidence of PT are now commercially available, these are not free from thromboembolic events (stroke). These events are often triggered by the propulsion of small in-pump thrombi downstream of the pump itself. In particular, the increased clearance gap between the housing and the blades of the HeartMate 3 LVAD (Abbott Laboratories, USA), as well as flow features associated with the artificial pulse, might facilitate the expulsion of small thrombi before their growth, thus leading to thromboembolic events. Since high-Watt power spikes are not triggered until formation of large thrombi and major impairment of the pump operation, these phenomena remain unnoticed and might evolve into clinically relevant adverse events. Alternatively, the early stages of these phenomena might be characterized by alterations of the CV of the PPC. This is consistent with the results of this study, where major alterations of the CV were identified earlier than high-Watt power spikes. In addition, long-term analysis of the CV in HeartMate 3 patients might be of particular value to validate the specificity of the proposed tool, since this device has a very limited incidence of PT.

**Study limitations**

Analysis of the CV was not correlated to pre- and/or post-operative patient characteristics and hemodynamic profile, such as the function of the right ventricle, cardiac rhythm, aortic/mitral insufficiency and/or left ventricle residual contractility. Blood flow through the LVADs is dependent...
upon a pressure gradient across the pump head, and centrifugal pumps are highly sensitive to pre-load and afterload changes. PPC directly reflects this hemodynamic status, and therefore, might be influenced by the aforementioned factors. However, the presence of the circadian rhythm is the preliminary step allowing the identification of altered PPC patterns by our algorithm, and regardless of any intrinsic/extrinsic factors working on the hemodynamics, a loss of circadian rhythm should be interpreted as indicative of pump dysfunction. Alternatively, according to our results (Supplementary Figure 1), further investigation focused at evaluating the potential/effectiveness of our tool to recognize and predict onset of progressive right ventricular dysfunctions and to discriminate between these phenomena and the early stage of actual PT events would be of particular importance to validate our tool. Furthermore, we acknowledge that there might be patients who do not recover a circadian rhythm following LVAD implantation. In addition, the sensitivity of our tool is not 100% and should be validated in a larger cohort; likely, the tool should be prospectively validated to evaluate its value as far as the therapeutic intervention is concerned. Finally, the predictive capability of our tool might be compared to that associated with specific clinical states that predispose to PT events or biological markers predicting PT (e.g., inflammation, infections, decompensation, and hemolysis).

Conclusion

We developed a new tool based on time-frequency analysis of the HVAD log files to early identify PT. We demonstrated, for the first time, that (1) HVAD patients gain circadian rhythmicity following post-operative recovery; (2) circadian rhythmicity remains stable in the long-term; (3) the early stage of PT alters circadian variability and offers the potential to early identify the thrombotic event prior to any clinical manifestation; and (4) resolution of the thrombotic event is accompanied by the recovery of a stable circadian variability. With this tool we achieved an unprecedented enhanced predictive capability of thrombotic complications. This study also suggests the potential value of the systematic monitoring of circadian rhythm in HVAD patients to provide a comprehensive clinical and value of the systematic monitoring of circadian rhythm in botic complications. This study also suggests the potential of circadian variability. With this tool we achieved an

Acknowledgments

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Conflicts of interest

FC, FE and FP are coinventors of the algorithm used in the study that is the object of a European Patent Application.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2019.04.008.

SUPPLEMENTARY METHODS

Time-frequency analysis of circadian variation of pump power consumption

Log files were downloaded from the HVAD controller, and time-frequency analysis was performed to highlight the presence of repetitive circadian variation (CV) of the pump power consumption (PPC) signal over time. Time-frequency analysis allows the detection of the presence of different frequency components in a time series, at single time points, as well as over their temporal evolution. Accordingly, time-frequency analysis allowed quantifying the presence of the frequency of interest over the 30-day log-file time series, that is the frequency component associated with daily circadian rhythmicity of the PPC. The CV was identified consistent with the power (i.e., the magnitude) of the PPC signal within the circadian frequency band (1.16 ± 0.3 × 10⁻⁵ Hz, corresponding to 1/24 hours ±30 minutes).

We performed time-frequency analysis of the PPC signal via custom-made and in-built IgorPro6 (Wavemetrics) procedures; in particular, we employed Wavelet decomposition with Morlet mother wavelet in the scale range 5 × 10⁻⁶-5.5 × 10⁻⁴ Hz (HVAD sampling frequency: 1.11 × 10⁻³ Hz). In this procedure, we measured power in the frequency band associated with CV. CV was defined as prevalent at a specific time point if the power in the circadian band was >50% of the total signal power at the same time point subtracted by its DC component; the CV was defined as stable if it remained prevalent for at least 5 days in a row.

Statistical analysis

The data in Table 1 are presented as mean and standard deviation. Normality of the distribution was assessed via the Shapiro-Wilk test. The Student’s t-test was used to evaluate differences between the groups (loss of circadian rhythmicity vs HVAD high-Watt alert). A p-value < 0.05 was assumed to be statistically significant.

References


