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Circadian rhythms in pump parameters of patients on contemporary left ventricular assist device support

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Abstract

Background: Algorithms to monitor pump parameters are needed to further improve outcomes after left ventricular assist device (LVAD) implantation. Previous research showed a restored circadian rhythm in pump parameters in patients on HeartWare (HVAD) support. Circadian patterns in HeartMate3 (HM3) were not studied before, but this is important for the development of LVAD monitoring algorithms. Hence, we aimed to describe circadian patterns in HM3 parameters and their relation to patterns in heart rate (HR).

Methods: 18 HM3 patients were included in this study. HM3 data were retrieved at a high frequency (one sample per 1 or 2 h) for 1–2 weeks. HR was measured using a wearable biosensor. To study overall patterns in HM3 parameters and HR, a heatmap was created. A 24-h cosine was fitted on power and HR separately. The relationship between the amplitude of the fitted cosines of power and HR was calculated using Spearman correlation.

Results: A lower between patient variability was found in power compared with flow and PI. 83% of the patients showed a significant circadian rhythmicity in power ($p < 0.001–0.04$), with a clear morning increase. All patients showed significant circadian rhythmicity in HR ($p < 0.001–0.02$). The amplitudes of the circadian rhythm in power and HR were not correlated (Spearman correlation of 0.32, $p = 0.19$).

Conclusions: A circadian rhythm of pump parameters is present in the majority of HM3 patients. Higher frequency pump parameter data should be collected, to enable early detection of complications in the future development of predictive algorithms.

KEYWORDS
circadian rhythm, left ventricular assist device, LVAD parameters, mechanical circulatory support

1 | PURPOSE

Left ventricular assist device therapy (LVAD) has become an important treatment option for patients with end-stage heart failure. To further improve clinical outcomes after LVAD implantation, early detection of deterioration is key. Several studies were done on early detection of a main complication (pump thrombosis) in patients on HeartWare (HVAD) support by a power-tracking algorithm.[1,2] Despite a disrupted circadian rhythm in blood pressure and heart rate in most patients with severe heart failure,[3] previous research in HeartWare (HVAD) patients suggests that a circadian rhythm in pump parameters is restored within several weeks after LVAD implantation.[4]

Interestingly, circadian rhythmicity is affected in the early stages of pump thrombosis,[5] and similarly, a loss of circadian rhythmicity may also indicate other complications (right heart failure, ventricular tachycardia, outflow graft obstruction). In addition, including the circadian rhythm in algorithms that enable early detection of these complications may improve the sensitivity and specificity of such early prediction tools. Since the withdrawal of HVAD, most patients are implanted with HeartMate 3 (HM3). Circadian patterns in HM3 patients have not been studied before. For the development of prediction algorithms using HM3 pump parameters, it is thus important to describe the circadian rhythm in pump parameters (power and flow) of patients on HM3 support, as the circadian rhythm can be a powerful predictor for early detection of complications. Hence, we aimed to study circadian patterns in HM3 parameters and their relation to circadian patterns in HR.

2 | MATERIALS AND METHODS

This investigator-initiated prospective study was performed at the University Medical Centre Utrecht. The study was approved by the local ethics committee of our center (METC: 20-195). Patients implanted with an HM3 for more than 6 months with two hospital appointments within 14 days were asked for written consent.

2.1 | Study setup

At the first study appointment, HM3's data storage was changed to one sample per 1–2 h instead of two samples per day (which is the standard setting, as data are automatically overwritten after 256 samples). A Philips wearable biosensor was applied to the patient's chest to measure HR with a sampling frequency of 1 Hz. Its data were automatically and securely transferred via Bluetooth to a mobile phone that was provided to the patient. Due to a limited battery life of 4 days, the patient was instructed to replace the sensor at home. During the second study appointment, LVAD and biosensor data were retrieved.

2.2 | Statistics

To compare circadian patterns in HM3 pump parameters (power, flow, pulsatility index (PI)) and the HR between patients, those measures were mean-centered by subtracting the mean of each patient. The amount of available HM3 data and HR data was calculated per patient. HR data were down-sampled to one sample per hour by taking the mean. To study overall patterns, the average mean-centered HM3 pump data and HR were depicted in a heatmap of 24 h. Subsequently, the amplitude of the circadian rhythm in power and HR was studied, as well as their relationship. A 24-h cosine was fitted on the average mean-centered power and HR. The Spearman correlation coefficient between the amplitude of these fitted cosines was calculated. p values were adjusted for multiple testing using the false discovery rate method, and a p value of <0.05 was considered statistically significant. R Version 3.6.3 was used for analysis.

3 | RESULTS

Between June 2021 and December 2022, 18 patients were included in the study after a median of 12 months after primary LVAD implantation. Table 1 shows all

TABLE 1 Baseline characteristics of all patients.

Variable median [IQR] or n (%)	All patients ($n = 18$)
Age (years)	57.5 (24.0)
Male sex n (%)	8 (44)
Etiology—ischemic n (%)	4 (22)
Etiology—dilated n (%)	13 (72.2)
BMI (kg/m^2)	22.1 (4.1)
BSA (m^2)	1.85 (0.27)
INTERMACS n (%)	
1	1 (6)
2	4 (22)
3–7	13 (72)
Preoperative temporary support n (%)	0 (0)
Preoperative eGFR (mL/min/1.73 m^2)	79 (42)
Preoperative bilirubin (μmol/L)	15 (10)
Poor RV function n(%)	1 (6)
Start study (number of months after implantation)	12 (3)

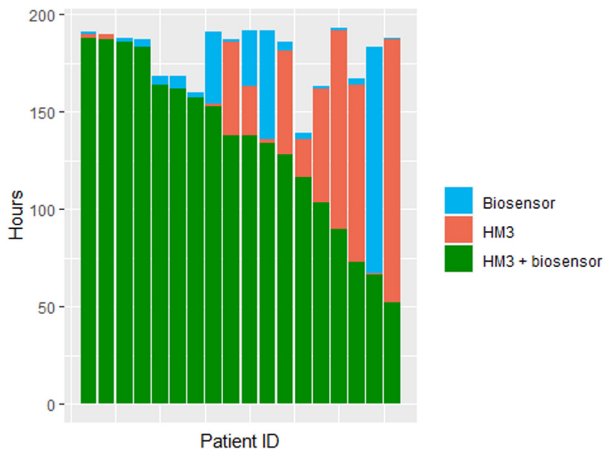

FIGURE 1 Data availability in hours per patient for HeartMate 3 parameters, biosensor, or combined. [Color figure can be viewed at wileyonlinelibrary.com]

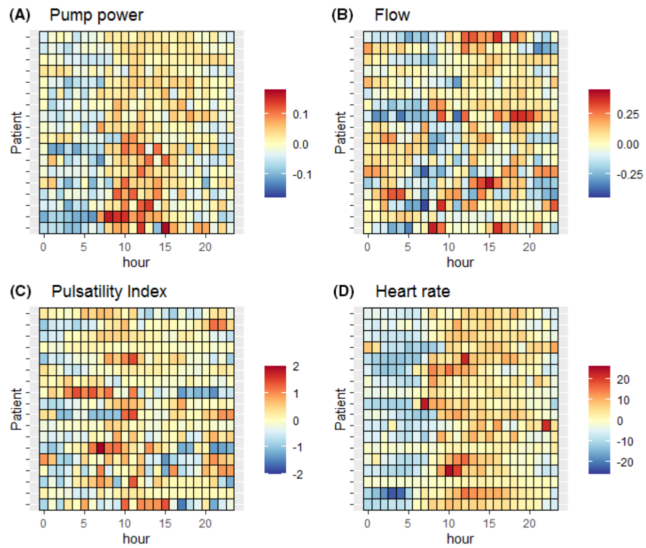

FIGURE 2 Circadian rhythm of pump parameters (power, flow, and pulsatility index) and heart rate. Patients (on the *y*-axis) are sorted on the highest mean-centered average power. [Color figure can be viewed at wileyonlinelibrary.com]

baseline characteristics. The median age was 58 years (IQR: 24 years) and 22% of patients had ischemic etiology. The HM3 speed ranged from 5000 to 5700 rpm and was constant throughout the study. The median time of combined available LVAD and biosensor data was 138 h [IQR: 57 h] per patient, as displayed in Figure 1. Figure 2 depicts a heatmap of all average mean-centered values of power, flow, and PI for all patients. All patients demonstrated a clear increase in power in the morning. Visually, a higher between-patient variability was found in the circadian rhythm of flow and PI compared with power. 15 out of 18 patients (83%) showed a significant circadian rhythmicity in power (p values ranging from <0.001 to 0.04). For flow, 10 out of 18 patients (56%) showed a significant circadian rhythmicity (p values ranging from <0.001 to 0.03, whereas for PI 12 out of 18 patients (72%) showed a significant circadian rhythmicity. For HR, all patients showed a significant circadian rhythmicity (p values ranging from <0.001 to 0.02). Figures S1 and S2 display the individual circadian rhythm and fitted cosine of power and HR. The Spearman correlation between the amplitude of the fitted cosine on power and HR was 0.32 ($p = 0.19$), so the degree of the circadian rhythm in power and HR was not correlated. Nevertheless, the time of the onset of the increase in power and HR seems to be congruent in both parameters.

4 | DISCUSSION

We aimed to study the circadian rhythm in HM3 parameters and its relationship with the circadian pattern in HR. The majority of the patients on HM3 LVAD support (83%) showed a circadian rhythm in power, with an increase in the morning. Although with a variable degree, all patients showed a circadian rhythm in HR with decreased values at night. The amplitude of the circadian rhythm in power and HR was not correlated.

In contrast to the constant HM3 speed, pump parameters fluctuate throughout the day. Those pump parameters (power, flow, and PI) are affected by the preload and afterload of the heart, which can be affected by alterations in, for example, medication, fluid balance, activity, or adverse events. For example, Consolo et al. showed that at the early stages of pump thrombosis, the circadian rhythm in power is disrupted.[5] In our study, three patients did not demonstrate a significant circadian rhythm in power. One of these patients was admitted due to septic arthritis in the knee 1 week after the study, which may have affected the circadian rhythm of the pump parameters. However, a causal relation cannot be proven.

No correlation between the strength (amplitude) of the circadian rhythm in power and HR was demonstrated. HR, preload, and afterload follow complex interrelationships and influence pump parameters, which may have led to the absent correlation between circadian amplitude in HR and power and contributes to the interindividual variation in the circadian rhythm of pump parameters. Alternatively, no significant relationship was found due to sample size. Likely, other aspects have a higher impact on power and flow, which conceal the effect of variation in HR throughout the day. Intrinsic factors such as systemic vascular resistance may play an important role. Additionally, power measures can be affected by voltage-dependent motor efficiency, which varies throughout the day because of battery changes.

In contrast to our results, Castagna et al. found that only 4 out of 29 (14%) of their patients on HeartMate II support showed a nocturnal reduction in HR, defined as a reduction of >10% in HR during the night.[6] These differences may be explained by the different methods used or due to different patient populations. Moreover, intrinsic differences between HMII and HM3 may play a role. 90% of their LVAD patients were prescribed a beta-blocker, which may partly be responsible for the reduced circadian rhythmicity in HR. Both patient populations are relatively small, so a larger cohort is needed to confirm these findings.

The current study is limited by several factors. Some patients had missing data because of an error in data transmission of the biosensor or automatic overwriting of the HM3 data. However, in all patients, a minimum of 52 h was available, which was considered to be sufficient for the current analysis. Although our cohort was small, in concordance with previous studies on circadian rhythms in LVAD, our findings are relevant as it is the first description of circadian rhythm in HM3 pump parameters. Last, the current study was not designed to investigate the degree of the effect on the circadian rhythm of each individual contributing factor, including voltage-dependent motor efficiency and vascular resistance. Hence, future studies should point this out.

Since the withdrawal of HVAD from the global market in June 2021,[7] HM3 is the most commonly implanted LVAD. Current study findings are relevant for the development of algorithms to (remotely) monitor HM3 parameters to early identify deterioration.[8] Variation in pump parameters due to the circadian rhythm could lead to unnecessary false alarms or late detection of specific pump parameter trends. Therefore, algorithms should on one hand adjust for the circadian rhythm, for example, with higher patient-specific alarm thresholds for power/flow during the day compared with the night. On the other hand, the circadian rhythm itself can be included as a predictor. Last, these findings are potentially relevant for clinical practice.

Concluding, a circadian rhythm of pump parameters, especially power, is present in the majority of the patients on HM3. Therefore, it is suggested to collect pump parameter data at a higher frequency, to facilitate the development of algorithms to monitor pump parameters that consider its circadian rhythm.

AUTHOR CONTRIBUTIONS

L. Numan: Concept/design, data analysis/interpretation, drafting article, data collection, approval of the article. **M. Wösten:** Data analysis/interpretation, critical revision of article, data collection, approval of the article. **M. Moazeni:** Data analysis/interpretation, critical revision of the article, approval of the article. **E. Aarts:** Concept/design, Data analysis/interpretation, critical revision of the article, statistics, approval of the article. **N. P. Van der Kaaij:** Critical revision of the article, approval of the article. **L. Fresiello:** Critical revision of the article, approval of the article. **F. W. Asselbergs:** Concept/design, critical revision of the article, funding secured by, approval of the article. **L. W. Van Laake:** Concept/design, critical revision of the article, funding secured by, approval of the article.

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CONFLICT OF INTEREST STATEMENT

L.N., M.W., M.M., E.A., N.P.v.d.K., L.F., and F.W.A. have no conflict of interest. L.W.L received consultancy fees from Medtronic, Abbott, Vifor, and Novartis, outside the submitted work.

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REFERENCES

1. Slaughter MS, Schlöglhofer T, Rich JD, Brown MC, Kadrolkar A, Ramos V, et al. A power tracking algorithm for early detection of centrifugal flow pump thrombosis. ASAIO J. 2021;67:1018–25. https://doi.org/10.1097/MAT.0000000000001509
2. Gross C, Dimitrov K, Riebandt J, Wiedemann D, Laufer G, Schima H, et al. Validation of intrinsic left ventricular assist device data tracking algorithm for early recognition of centrifugal flow pump thrombosis. Life. 2022;12(4):563. https://doi.org/10.3390/life12040563
3. Crnko S, Printezi M, Zwetsloot PP, Leiteris L, Lumley AI, Zhang L, et al. The circadian clock remains intact, but with dampened hormonal output in heart failure. eBioMedicine. 2023;91:104556.
4. Slaughter MS, Ising MS, Tamez D, O'Driscoll G, Voskoboynikov N, Bartoli CR, et al. Increase in circadian variation after continuous-flow ventricular assist device implantation. J Heart Lung Transplant. 2010;29(6):695–7. https://doi.org/10.1016/j.healun.2009.12.006
5. 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(10):1077–86. https://doi.org/10.1016/j.healun.2019.04.008
6. Castagna F, McDonnell BJ, Mondellini GM, Gaudig A, Pinsino A, McEniery C, et al. Twenty-four-hour blood pressure and heart rate variability are reduced in patients on left ventricular assist device support. J Heart Lung Transplant. 2022;41:802–9. https://doi.org/10.1016/j.healun.2022.02.016
7. Medtronic. Left ventricular assist device (LVAD) for advanced heart failure still walking beside you. Published 2021. [cited

2021 Nov 2]. Available from: https://www.medtronic.com/us-en/patients/treatments-therapies/ventricular-assist-device.html

8. Numan L, Moazeni M, Oerlemans MIFJ, Aarts E, van der Kaaij NP, Asselbergs FW, et al. Data-driven monitoring in patients on left ventricular assist device support. Expert Rev Med Devices. 2022;19(9):677–85. https://doi.org/10.1080/17434440.2022.2132147

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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