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Increase in circadian variation after continuous-flow ventricular assist device implantation

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The circadian rhythm of varying blood pressure and heart rate is attenuated or absent in patients with severe heart failure. In 28 patients supported by a left ventricular assist device (LVAD) for at least 30 days, a restoration of the circadian rhythm was demonstrated by a consistent nocturnal decrease, and then increase, of the LVAD flow while at a constant LVAD speed. The return of the circadian rhythm has implications for cardiac recovery, and the observation indicates that the continuous-flow LVAD has an intrinsic automatic response to physiologic demands.
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Cardiovascular circadian variations, characterized by a diurnal increase and a nocturnal decrease in heart rate and blood pressure, have been observed in normotensive and hypertensive patients. These circadian rhythms are attributed to variations in the modulation of the cardiovascular system by the sympathetic and parasympathetic nervous systems. The circadian rhythm of the nocturnal decrease in blood pressure and heart rate is attenuated or absent in patients with severe heart failure.[1–3] In heart allograft recipients, this cardiovascular circadian rhythm is absent in the short-term due to denervation of the transplanted heart and the impairment of the cardiopulmonary baroreflex.[1,4] Months after heart transplantation, however, partial or complete restoration of the cardiovascular circadian rhythm has been reported in heart failure patients.[5]

Restoration of the cardiovascular circadian rhythms may signal an increase in vasomotor tone, cardiac conduction, and overall cardiovascular end-organ health. However, the diurnal variation of blood flow in patients implanted with a left ventricular assist device (LVAD) may have important implications in characterizing myocardial and vasomotor recovery. This study describes the diurnal variation in LVAD flow observed in 28 heart failure patients during a 30-day period.

Methods

This study was approved by the Institutional Review Board at each participating institution in the United States or an equivalent authority at each participating institution in Europe and Australia. An informed consent was obtained from all participating patients.

Patients and inclusion criteria

This was a retrospective study of 28 patients (24 men, 4 women) with New York Heart Association (NYHA) class IV heart failure who were being supported by a HeartWare HVAD (HeartWare, Miami Lakes, FL) for bridge to

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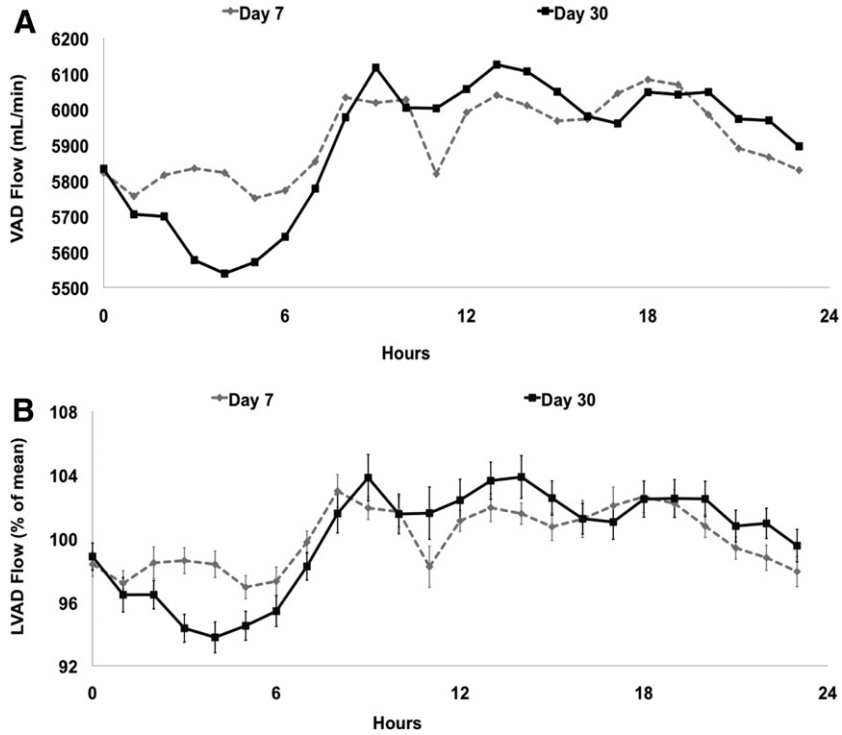


Figure 1 Hourly values of left ventricular assist device (LVAD) (A) flow and (B) the mean percentage change are shown on Day 7 (gray line) and Day 30 (black line). Hour 0 corresponds to midnight and Hour 23 corresponds to 11:00 PM. These data show that the circadian variation in LVAD flow is significantly higher on Day 30 than on Day 7, indicating a restoration of the circadian rhythm. The error bars designate the standard error of the mean.

transplantation. Patients were 47.0 ± 2.6 years old, weighed 81 ± 3 kg, and had a body surface area (BSA) of 1.94 ± 0.04 m^2. The etiology for heart failure was ischemic in 11 patients, idiopathic in 14, viral in 2, and familial cardiomyopathy in 1. A BSA of 1.2 m^2 or higher was required for clinical trial inclusion. The study excluded patients with acute myocardial infarction within 14 days or cardiothoracic surgery 30 days before LVAD implant. To eliminate bias due to variations in LVAD motor speed, only 28 patients whose LVAD speed was maintained within a 20 rpm range during the 30-day study period were included.

Data collection and analysis

The HeartWare HVAD flow (liters/min), motor speed (rpm), and power (watts) data were collected every 15 minutes after device implantation using the HeartWare system controller. Data were downloaded during clinical visits and de-identified before data analysis.

The diurnal variations in LVAD flow, motor speed, and power were analyzed using LabVIEW software (National Instruments Corp, Austin, TX). The LVAD flow, speed, and power values were averaged by the hour for each patient. For the study, the first post-operative day was designated as Day 1 for all patients. Post-implantation Day 7 was considered as the baseline to eliminate any bias in diurnal variation due to post-operative stress, hemodynamic instability, and medications. Statistical evaluations were made hourly between patients using a paired 2-tailed *t*-test with a values of $p \leq 0.05$ considered statistically significant.

Results

The average LVAD flow (5.9 ± 0.1 liters/min) and motor speed (2750 ± 40 rpm) at Day 7 were statistically similar to LVAD flow (0.9 ± 0.2 liters/min) and speed (2740 ± 40 rpm) at Day 30. All patients showed an increased diurnal variation in LVAD flow on Day 30 compared with Day 7 (Figure 1). The nocturnal decline, defined as the decrease in LVAD flow and power between midnight (Hour 0) to 4:00 AM (Hour 4), was 27% greater on Day 30 than on Day 7 ($p < 0.002$; Table 1). In addition, the morning increase, defined as the increase in LVAD flow and power between 4:00 AM (Hour 4) and 9:00 AM (Hour 9), was 33% greater on day 30 than on Day 7 ($p < 0.002$). The LVAD pump speed was maintained at a constant value throughout the day (LVAD speed variation ≤10 rpm). The average diurnal variation in LVAD flow was significantly higher ($p < 0.01$) on Day 30 than on Day 7, indicating a restoration of the circadian rhythm.

Discussion

This study demonstrated that LVAD support with the HeartWare HVAD restores at least some of the normal cardiovascular circadian rhythm that is often abolished in heart failure and that the LVAD flow is automatically adjusted in response to physiologic changes. Although our study did not measure blood pressure and heart rate, as have some other studies on cardiovascular circadian rhythms, the ob-

Table 1 Average Nocturnal Decline and the Morning Increase in Left Ventricular Assist Device Variables

Variable	Day 7	Day 30
Flow		
24-hour liters/min	5.9 ± 0.1	5.9 ± 0.2
Nocturnal decline, %	12.3 ± 0.9	17.5 ± 1.5[a]
Morning increase, %	13.1 ± 0.2	18.6 ± 1.9[a]
Speed		
24-hour rpm	2,750 ± 40	2,740 ± 40
Nocturnal decline, %	1.3 ± 0.2	1.1 ± 0.2
Morning increase, %	1.0 ± 0.2	1.1 ± 0.2
Power		
24-hour KW	4.7 ± 0.2	4.6 ± 0.2
Nocturnal decline, %	6.4 ± .0.7	7.3 ± 0.6
Morning increase, %	6.0 ± 0.5	7.5 ± 0.7

[a]The average flow, speed, and power on Days 7 and 30 were not statistically significant, but the nocturnal decrease and morning increase in left ventricular assist device variables are statistically significant ($p < 0.002$).

served changes in LVAD flow showed the same circadian pattern seen in healthy individuals.

It is unclear whether the loss of a cardiovascular circadian rhythm in heart failure patients is a cause or an effect, but there is evidence that its return would have beneficial effects on cardiac function.[6] The cardiovascular circadian rhythm has been observed as a nocturnal decrease in the blood pressure and heart rate, which is mainly due to a conversion of sympathetic to parasympathetic nervous system control during sleep time. These changes in blood pressure and heart rate are largely responsive to hormonal control, but there are also molecular rhythms within cardiomyocytes that control gene expression that are responsible for vascular integrity, metabolism, and myocardial growth and remodeling.[7] Cardiomyocyte repair and regeneration occurs during the circadian phase of lowered physiologic stress and is believed to be necessary for maintenance of general cardiovascular health. In fact, its absence is considered a risk factor for developing heart failure.[8]

The nocturnal decrease of LVAD flow while at a constant pump speed indicates that continuous-flow pumps have an intrinsic response to physiologic changes. Because the LVAD flow rate is dependent on differential pressure (pre-load to after-load) when the motor speed is constant, the circadian changes observed reflect changes in left ventricular pressure (LVP) and systemic vascular resistance (SVR). Under normal operating conditions, a decreased LVAD flow results from an increase in the SVR or a decrease in LVP. Therefore, the nocturnal decrease in LVAD flow is a response to a decreased LVP, and the SVR is likely to remain constant or may decrease due to the normal parasympathetic response. The precise hemodynamic circadian changes during LVAD support have not been studied.

The loss of the cardiovascular circadian rhythm in heart failure patients is not well understood, but numerous internal and external factors are involved. The restoration of a circadian rhythm during LVAD support is likely related to a reduction in cardiovascular stress and the sympathetic response. Further studies are needed to better define the mechanisms of the loss and return of cardiovascular circadian rhythms. An extended temporal investigation to quantify the effects of LVAD support on circadian rhythm 6 months after implantation is currently underway.

Disclosure statement

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References

1. Idema RN, van den Meiracker AH, Balk AH, Bos E, Schalekamp MA, Man in 't Veld AJ. Abnormal diurnal variation of blood pressure, cardiac output, and vascular resistance in cardiac transplant recipients. Circulation 1994;90:2797-803.
2. Lombardi F, Sandrone G, Mortara A, et al. Circadian variation of spectral indices of heart rate variability after myocardial infarction. Am Heart J 1992;123:1521-9.
3. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllyla VV. Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. Stroke 1997;28:2150-4.
4. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733-43.
5. van de Borne P, Leeman M, Primo G, Degaute JP. Reappearance of a normal circadian rhythm of blood pressure after cardiac transplantation. Am J Cardiol 1992;69:794-801.
6. Hermida RC, Ayala DE, Portaluppi F. Circadian variation of blood pressure: the basis for the chronotherapy of hypertension. Adv Drug Deliv Rev 2007;59:904-22.
7. Sole MJ, Martino TA. Diurnal physiology: core principles with application to the pathogenesis, diagnosis, prevention and treatment of myocardial hypertrophy and failure. J Appl Physiol 2009;107:1318-27.
8. Plante GE. Sleep and vascular disorders. Metabolism 2006;55:S45-9.