Evidence for a Central Origin of the Low-Frequency Oscillation in RR-Interval Variability

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Background—Short-term variability of RR interval and blood pressure occurs predominantly at low frequency (LF; \( \approx 0.1 \) Hz) and high frequency (\( \approx 0.25 \) Hz). The arterial baroreflex is thought to be the predominant determinant of the LF component of RR variability. Patients with severe congestive heart failure (CHF) have an attenuated or absent LF oscillation in RR variability. The left ventricular assist device (LVAD) offers a unique possibility for analysis of spectral oscillations in RR interval independent of any effects of blood pressure that influence these oscillations via the baroreflex.

Methods and Results—We performed spectral analysis of RR, blood pressure, and respiration in 2 patients with CHF before and after LVAD implantation. LF components of the RR-interval and blood pressure variability were absent in both CHF patients before LVAD implantation. After LVAD implantation, spectral analysis of the RR interval showed restoration of a clear and predominant LF oscillation in the native hearts of both patients, with no such oscillation evident in the blood pressure profile.

Conclusions—During total circulatory support with the LVAD, the LF oscillation in RR interval of the native heart, absent in CHF, is restored. This LF oscillation in RR interval occurs in the absence of LF oscillations in blood pressure and thus is unlikely to be explained by baroreflex mechanisms. Hence, the absence of LF oscillation in the RR interval in CHF is functional and is reversible by LVAD circulation. The presence of a predominant LF oscillation in RR interval independent of any oscillation in blood pressure suggests that the LF oscillation is a fundamental property of central autonomic outflow. (Circulation. 1998;98:556-561.)

Key Words: heart failure ■ nervous system, autonomic ■ baroreceptors ■ heart-assist device ■ reflex

Spectral analysis of heart rate variability is a widely used noninvasive technique to assess autonomic indexes of neural cardiac control.1-5 The presence of LF and HF oscillatory rhythms in the variability of the RR interval is well established.3-5 A similar variability profile has also been reported in blood pressure.3 Despite a vast body of literature examining LF and HF oscillations, their genesis remains poorly understood. One model suggests that the LF oscillation in RR interval is produced by a resonance phenomenon (at a frequency of \( \approx 0.1 \) Hz) due to the slow sympathetic control loop of the baroreflex in response to beat-to-beat changes in blood pressure.5-8 Animal studies, however, support the concept of a central oscillator, the rate of which is entrained by the sluggish baroreflex-mediated sympathetic response. Activity of cardiac sympathetic efferent neurons9 and of brain stem neurons involved in the regulation of cardiovascular function10 contains distinct LF and HF oscillatory components. Furthermore, in studies in humans with chronic complete high cervical spinal cord injuries, LF oscillations are evident in both RR-interval and systolic blood pressure spectral powers.11,12

In a closed-loop system, the reflex and mechanical interactions between respiration, blood pressure, and heart rate have confounded attempts to understand RR variability independent of the influence of blood pressure oscillations. Baroreflex responses to LF oscillations in blood pressure contribute to LF oscillations in RR interval. Similarly, LF oscillations in RR interval would augment LF oscillations in blood pressure.

The use of an LVAD has become an accepted therapy as a bridge to cardiac transplantation in cases of hemodynamic deterioration with intractable heart failure.13,14 The LVAD used in the present study obtains oxygenated blood from the native left ventricle and sends it to the arterial circulation. Thus, patients are dependent on the output of the prosthetic heart, which is tightly regulated by the programming mode, for maintenance of blood pressure.
The native heart continues to beat, but the left ventricle has little if any influence on cardiac output. Thus, the oscillatory characteristics of blood pressure variability in these patients are determined primarily by the output programming of the LVAD. The native heart, however, remains innervated and continues to be regulated by the autonomic nervous system. Therefore, blood pressure, which is determined by the output from the LVAD, is dissociated from the effects of any oscillations in RR interval of the native heart. The LVAD, by allowing an uncoupling of the interactions between RR interval and blood pressure, thus allows a unique opportunity to investigate the mechanisms governing neural regulation of RR-interval variability in human subjects.

Recent studies 15–17 suggest that patients with severe heart failure have absent LF oscillations in RR interval, despite high levels of sympathetic activation; this may be secondary to abnormalities in central autonomic regulation. 13 We examined whether improved circulatory homeostasis after LVAD implantation would restore LF oscillation in the native heart and whether this LF oscillation would be present despite the absence of any LF oscillation in blood pressure variability. We studied 2 patients before and after LVAD implantation using spectral analysis of simultaneous measurements of RR interval, blood pressure, and respiration.

Methods

Description of Device

The Thermo Cardiosystems Inc HeartMate left ventricular assist system consists of an implantable pusher-plate blood pump, a percutaneous driveline, and an external power source. The blood system consists of an implantable pusher-plate blood pump, a percutaneous driveline, and an external power source. The blood pump is designed to provide left ventricular support and is connected to the left ventricular apex and ascending aorta by inflow and outflow conduits, respectively. Porcine xenograft valves are located within the woven polyester conduits to ensure a unidirectional flow of blood.

Device implantation is performed through a median sternotomy. The blood pump is located in the left upper quadrant, either beneath the diaphragm or in a preperitoneal position. The inflow conduit passes through the diaphragm and is inserted through the left ventricular apex. The outflow conduit is located beneath the sternum and is attached to the proximal ascending aorta in an end-to-side fashion. The percutaneous driveline connects the blood pump to the external drive unit and passes through the patient’s abdominal wall in the left lower quadrant.

In the patients described in this article, the LVAD functioned in an automatic, full-to-empty mode. During LVAD diastole, blood flows passively from the patient’s left ventricle through the inflow conduit into the LVAD blood chamber. When the blood chamber is 90% full, the pusher plate is activated, compressing the flexible diaphragm. Blood is forced out of the blood chamber during LVAD systole. Blood travels through the outflow conduit into the ascending aorta. Because LVAD rate and output are determined by the rate at which the blood chamber fills, the automatic mode maximizes LVAD output and allows the device to respond to the patient’s physiological need. In contrast, the patient’s native heart continues to be regulated by the autonomic nervous system. Because the patient’s heart is completely decompressed, there is no ejection from the native left ventricle.

Patients and Measurements

Simultaneous measurements of RR interval, respiration (pneumograph), and arterial pressure (Finapres system) were recorded on a Gould 2800 S recorder and a 486 PC during 10 minutes of supine, undisturbed quiet rest before and after LVAD implantation. Before LVAD implantation, both patients were in stable chronic heart failure. Hemodynamic deterioration occurred despite optimal medical therapy, requiring LVAD support as a bridge to cardiac transplantation.

Patient 1

Patient 1 was a 48-year-old man with ischemic cardiomyopathy (LVEF, 20%). The initial study was performed while he was taking isosorbide dinitrate, spironolactone, furosemide, captopril, sodium warfarin, and diltiazem. LVAD support was begun 4 months after the initial study. The study was repeated during LVAD support 15 months after implantation while he was taking aspirin, dipyridamole, and ferrous sulfate.

Patient 2

Patient 2 was a 44-year-old man with idiopathic dilated cardiomyopathy (LVEF, 10%). His initial study was performed while he was taking captopril, digoxin, and furosemide. LVAD support was begun 19 months after the initial study, and a follow-up study was performed 1 month after implantation. At the second study, his medications included aspirin, dipyridamole, diltiazem, and sotalol.

Informed written consent was obtained from both patients. The study was approved by the Institutional Human Subjects Review Committee.

Data Analysis

Analog-to-digital conversion was performed in real time at 600 Hz per channel with a 12-bit converter (Gould). Data were then analyzed off-line with a personal computer (486 PC). The methodology and software for data acquisition and spectral analysis have been described elsewhere. 13 This method allows for spectral analysis of respiration and RR interval as well as beat-to-beat blood pressure. Thus, the coherence and phase relationships of the LF and HF components of these measures can be obtained. In brief, a derivative-threshold algorithm provided the continuous series of RR intervals (tachogram) derived from the ECG. From the arterial pressure signal, beat-to-beat systolic (systogram) and diastolic (diastogram) values were calculated, and the respiratory signal was sampled once every cardiac cycle.

All variability series were analyzed by means of autoregressive parametric spectral and cross-spectral algorithms that automatically provide the number, center frequency, and power of each oscillatory component. Statistical criteria, such as Akaake’s test and Anderson’s test, allowed us to determine the optimal model order (ranging between 8 and 12) fitting the data and enabled us to verify that all information contained in the time series had been extracted in the computation. The power was expressed both in absolute (ms2) and normalized units, which were obtained by dividing the power of each component by total variance, from which the VLF component (0.00 to 0.03 Hz) had been subtracted, and multiplying this value by 100. 13 To better evaluate even minimal aggregations of power in the different frequency bands, variability signals were also analyzed with a fast Fourier transform algorithm. Three frequency bands were predetermined (0 to 0.03, 0.03 to 0.15, and 0.15 to 0.4 Hz). Bivariate autoregressive identification was used to perform cross-spectral analysis 13 and to compute a squared coherence function (ie, the square cross-
spectrum amplitude normalized by the product of the spectra of the 2 signals). Coherence ($K^2$), a measure of the statistical link between 2 variability series at any given frequency, was considered significant if $>0.5$ (coherence is expressed as a number between 1 and 0).

**Results**

**Patient 1**

The mean RR interval and arterial pressure before and after implantation of the LVAD are shown in the Table. Spectral analysis of all variability series before implantation of the LVAD (the Table; Figure 1) showed a bimodal HF component in the RR-interval spectrum (center frequency of major peak, 0.40 Hz) synchronous and highly coherent with the respiratory HF variability and absent LF components in both RR-interval and systolic pressure spectra. Coherence analysis indicated a constant link between all variability profiles in the HF range ($K^2 > 0.7$). A VLF component was present in the variability profiles. The significance of this VLF oscillation is not known and will not be addressed in this article.

After LVAD implantation, the rate of blood pump activation ranged from 102 to 126 beats per minute. Spectral analysis of blood pressure variability showed only an HF oscillatory component. Spectral analysis of the native RR interval (Figure 1), however, showed a clear and predominant LF component that was not evident in the blood pressure profile.

**Patient 2**

The mean RR interval and arterial pressure before and after implantation of the LVAD are shown in the Table. Spectral and coherence analysis of RR interval, systolic pressure, and respiration before implantation of the LVAD showed findings similar to those in patient 1 (the Table; Figure 2). The LF oscillation was again absent in the RR-interval and systolic blood pressure power spectra (Figure 2). HF oscillations in

| RR Interval, Systolic Arterial Pressure, and Their Variabilities in 2 Heart Failure Patients Before and After LVAD Implantation |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Mean Variance Absolute LF Normalized LF Absolute HF Normalized HF |
| RR, ms | SAP, mm Hg | RR, ms$^2$ | SAP, mm Hg$^2$ | RR, ms$^2$ | SAP, mm Hg$^2$ | RR, ms$^2$ | SAP, mm Hg$^2$ | RR, ms$^2$ | SAP, mm Hg$^2$ |
| Patient 1 | | | | | | | | | |
| Pre-LVAD | 803 | 80 | 555 | 45 | Absent | Absent | Absent | Absent | 274 | 14 | 80 | 91 |
| Post-LVAD | 838 | 115 | 328 | 35 | 283 | Absent | Absent | Absent | 88 | 10 | 9 | 28 |
| Patient 2 | | | | | | | | | |
| Pre-LVAD | 963 | 118 | 2796 | 21 | Absent | Absent | Absent | Absent | 745 | 8 | 98 | 94 |
| Post-LVAD | 866 | 121 | 455 | 5 | 229 | Absent | Absent | Absent | 50 | 164 | Absent | 35 | Absent |

RR indicates RR interval; SAP, systolic arterial pressure; and NU, normalized units.

**Figure 1.** Spectral analysis of RR-interval (RR), systolic arterial pressure (SAP), and respiration (Resp) variabilities before and after implantation of LVAD in patient 1. Autoregressive (AR) and fast Fourier transform (FFT) analyses are shown in left and right panels, respectively. There is no LF oscillation evident before LVAD placement. After LVAD placement, the LF oscillation of RR-interval variability is restored and is present even in the absence of LF oscillation in the SAP variability spectrum. a.u. indicates arbitrary units.
RR interval, systolic pressure, and respiration were synchronous and highly coherent ($K^2 > 0.9$).

After LVAD implantation, the rate of blood pump activation was 80 to 96 beats per minute. Spectral analysis of blood pressure variability showed no oscillatory component. Spectral analysis of the native RR interval, however, showed clear LF and HF components (Figure 2). The LF oscillation was not evident in the blood pressure profile. Coherence analysis indicated a constant link between HF oscillations of respiration and RR interval ($K^2 > 0.7$).

**Discussion**

Our data provide unique insight into the fundamental characteristics of oscillatory components of heart rate variability in humans. The novel findings in this study are first, that the absent LF oscillation in RR interval, which is characteristic of severe heart failure, is restored during circulatory support with the LVAD, and second, that the newly restored LF oscillation in RR interval of the native heart is dominant and is evident in the absence of any similar oscillation in blood pressure.

Because of the relative infrequency of LVAD placement, we were able to obtain data in only 2 patients. However, an important strength of this study is that spectral analyses were performed before and after LVAD implantation in the same subjects, providing a powerful basis for comparison of the effects of the LVAD.

Patients with severe heart failure have many biochemical derangements, including profound increases in catecholamines, renin-angiotensin activity, and vasopressin. They also have an attenuated or absent LF oscillation in RR-interval variability. This may be secondary to central mechanisms because the LF oscillations in direct intraneural recordings of sympathetic activity are also absent. Circulatory support with the LVAD is accompanied by marked improvement in neurohumoral measures, with dramatic reductions of $> 70\%$ in catecholamines, renin-angiotensin activity, and vasopressin. Thus, LVAD placement in a patient with heart failure results not only in improvements in indexes of perfusion, such as cardiac output, but also in a marked reduction in the neurohumoral accompaniments of heart failure. Central effects of neurohumoral activation may be implicated in the elimination of the LF neural and circulatory oscillations in heart failure; normalization of neurohumoral activation and restoration of the LF oscillation in RR interval occurs after LVAD implantation. The LF oscillation in RR-interval variability is evident as early as 1 month after initiation of circulatory support with the LVAD.

Although the existence of LF and HF oscillations in RR interval are well established, their origins are unclear. A number of potential mechanisms and interactions may be implicated. One explanation for the presence of HF oscillations in blood pressure variability in normal subjects may be that these RR fluctuations are linked to baroreflex responses to blood pressure changes. Respiratory effects on the intrathoracic low-pressure system and/or cardiac output may produce fluctuations in blood pressure and subsequently in RR interval via the baroreflex. Thus, it is assumed that sinus arrhythmia is caused by respiratory blood pressure waves and not vice versa. This construct has been challenged recently by Akselrod et al in dogs and Taylor and Eckberg in humans. Using fixed-

**Figure 2.** Spectral analysis of RR-interval, systolic arterial pressure, and respiration variabilities before and after LVAD placement in patient 2. Autoregressive and fast Fourier transform analyses are shown in left and right panels, respectively. There is no LF oscillation evident before LVAD placement. After LVAD placement, the LF oscillation of RR-interval variability is restored and is present even in the absence of LF and HF oscillations in the SAP variability spectrum. Abbreviations as in Figure 1.
rate atrial pacing, Taylor and Eckberg\textsuperscript{32} have demonstrated that the HF oscillations in RR interval can actually contribute to HF oscillations in arterial pressure.

Even less is known about the genesis of LF oscillations, which are present in efferent discharge patterns of both sympathetic and vagal neurons.\textsuperscript{31} One construct explains the LF oscillation in RR interval as a result of 2 factors: first, as a baroreflex response to the 0.1-Hz Mayer waves in arterial pressure (the LF blood pressure oscillation); and second, as a consequence of baroreflex buffering of the HF oscillations in blood pressure, resulting in an LF 10-second oscillation because of a resonance phenomenon due to a delay in the sympathetic control loop of the baroreflex.\textsuperscript{6,7,24} Alternatively,\textsuperscript{3,10,34} it has been proposed that the 0.1-Hz oscillations of RR-interval and blood pressure variabilities are due to central rhythmic modulation of neural activity.\textsuperscript{35}

The presence of an LF oscillatory component in blood pressure variability in humans with chronic complete high spinal cord injuries\textsuperscript{1,12} and an LF oscillation in sympathetic nerve discharge and RR-interval variabilities of cats after high cervical spinal section,\textsuperscript{36} strengthens the hypothesis that this LF rhythmicity represents an intrinsic characteristic of the autonomic neural network.

Our data, showing a dominant LF oscillation in RR interval despite the absence of any LF oscillation in blood pressure in patients with an LVAD, contradict any presumed dependence of LF oscillation in RR interval on Mayer wave blood pressure oscillations. In patient 2, for example, the LF oscillation is clear and dominant despite the absence of either LF or HF oscillations in blood pressure.

The power of the HF oscillation in blood pressure is reduced or absent after LVAD placement. Triedman and Saul\textsuperscript{70} have shown that owing to mechanical properties of interposed cardiopulmonary structures (in this article, the LVAD), the influence of respiration-induced changes in central venous pressure, or blood pressure oscillations, is markedly reduced. Thus, the baroreflex response to the HF oscillation, acting through a delay in the sympathetic control loop, is also not essential to generate the dominant LF oscillatory power seen in RR-interval variability.

These findings do not imply that the baroreflex is disengaged from the LF oscillation. Sleight et al\textsuperscript{8} and Piepoli et al\textsuperscript{27} have shown clearly that baroreflex perturbations modulate the RR LF oscillation. Rather, our findings show that a dominant LF oscillation in RR interval can be generated in the absence of a tangible oscillatory baroreflex input. These data support the concept that the LF oscillation in cardiovascular variability represents, in part, a central oscillation in autonomic outflow.

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