Patients With Continuous-Flow Left Ventricular Assist Devices Provide Insight in Human Baroreflex Physiology

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Abstract—The superior clinical outcome of new continuous-flow left ventricular assist devices (LVADs) challenges the physiological dogma that cardiovascular autonomic homeostasis requires pulsatile blood flow and pressure. We tested the hypothesis that continuous-flow LVADs impair baroreflex control of sympathetic nerve traffic, thus further exacerbating sympathetic excitation. We included 9 male heart failure patients (26–61 years; 18.9–28.3 kg/m²) implanted with a continuous-flow LVAD. We recorded ECG, respiration, finger blood pressure, brachial blood pressure, and muscle sympathetic nerve activity. After baseline measurements had been taken, patients underwent autonomic function testing including deep breathing, a Valsalva maneuver, and 15° head-up tilt. Finally, we increased the LVAD speed in 7 patients. Spontaneous sympathetic baroreflex sensitivity was analyzed. Brachial blood pressure was 99±4 mm Hg with 14±2 mm Hg finger pulse pressure. Muscle sympathetic nerve activity bursts showed a normal morphology, were linked to the cardiac cycle, and were suppressed during blood pressure increases. Mean burst frequency was lower compared with age- and body mass index–matched controls in 2 patients, slightly increased in 4 patients, and increased in 2 patients (P=0.11). Muscle sympathetic nerve activity burst latency and the median values of the burst amplitude distribution were similar between groups. Muscle sympathetic nerve activity increased 4±1 bursts per minute with head-up tilt (P<0.0003) and decreased 3±4 bursts per minute (P<0.031) when LVAD speed was raised. The mean sympathetic baroreflex slope was −3.75±0.79%/mm Hg in patients and −3.80±0.55%/mm Hg in controls. We conclude that low pulse pressure levels are sufficient to restrain sympathetic nervous system activity through baroreflex mechanisms.

Key Words: left ventricular assist device ■ continuous flow device ■ pulse pressure ■ muscle sympathetic nerve activity ■ baroreflex sensitivity

More than 5.8 million people in the United States experience end stage systolic heart failure. Of those, 250,000 die each year despite improvements in pharmacotherapy and increasing implantable defibrillator use. Access to cardiac transplantation, which improves symptoms and survival, is limited by donor organ shortage. Initially, left ventricular assist devices (LVADs) served as a short-term bridge to transplantation. Technology refinement and device miniaturization allowed LVAD-treated patients to leave the hospital for months or even years. End-stage heart failure patients equipped with pulsatile LVADs showed 48% reductions in total mortality compared with patients on optimal medical treatment. Earlier pulsatile flow LVADs were bulky and associated with a high risk for infection, thromboembolism, and device failure. Recently developed LVADs produce continuous flow through axial or centrifugal rotary pumps. Compared with pulsatile devices, patients with continuous-flow LVADs fared better in terms of cardiovascular morbidity, reoperations for device repair or replacement, and total mortality. Thus, continuous-flow LVAD use as a bridge to transplantation or as destination therapy is likely to increase. The good clinical outcome challenges the physiological dogma that cardiovascular homeostasis, particularly baroreflex regulation, requires pulsatile blood flow and pressure. Pulsatile pressure minimizes central baroreflex resetting and attenuates efferent sympathetic activity. Conversely, continuous, albeit reduced, baroreceptor discharge with decreased pressure pulsatility could result in sympathetic nervous system escape from baroreflex restraint. The issue is clinically relevant because sympathetic activity is increased in heart failure patients and heralds a poor prognosis. Therefore, we tested the hypothesis that decreased cardiovascular pulsatility in patients with continuous-flow LVADs is associated with profound abnormalities in baroreflex regulation of heart rate and sympathetic nerve activity.
Methods

Patients

We included 9 male end-stage heart failure patients who had been implanted with a continuous-flow LVADs (HeartWare International, Framingham, MA). For each heart failure patient, we assessed baseline recordings from 2 age- and body mass index–matched men. The institutional review board approved the study, and written informed consent was obtained before study entry.

Protocol

We conducted measurements after an overnight fast in the morning hours. ECG, beat-by-beat blood pressure (Finometer Midi, Finapres Medical Systems, Amsterdam, the Netherlands), brachial systolic blood pressure (Doppler ultrasound), and respiration (Niccomo, Medis GmbH, Ilmenau, Germany) were recorded. In addition, we recorded muscle sympathetic nerve activity (MSNA) from the right peroneal nerve (Nerve Traffic Analyzer 662C-3, Biomedical Engineering Department, University of Iowa, Iowa City, IA), as described previously. Briefly, a unipolar tungsten electrode was inserted into the muscle nerve fascicles in the popliteal space. Proper needle positions were verified by the following criteria: (1) tapping on the innervated muscle but not stroking the skin elicits afferent nerve activity; (2) inspiratory breath hold increases the burst frequency; (3) pulse synchrony of the bursts; (4) arousal does not evoke bursts; and (5) internal nerve stimulation causes muscle switches without any paresthesias. Nerve activity was amplified with a total gain of 100,000, bandpass filtered (0.7–2.0 kHz), and integrated using a 0.1-second time constant.

After a ≥15-minute resting period, we obtained baseline measurements for 10 minutes followed by autonomic function testing including deep breathing (respiratory rate of 6 per minute) and a Valsalva maneuver. After connecting the remote control to the LVAD, a second baseline was recorded. LVAD device speed was 2860 rpm. All of the patients were on heart failure medications, including angiotensin-converting enzyme inhibitors (n = 6) or angiotensin II type 1 receptor blockers (n = 1), β-1 adrenoreceptor blockers (n = 6), loop diuretics (n = 3), and oral anticoagulants (n = 9). End stage heart failure resulted from dilated cardiomyopathy (n = 5) or coronary artery disease and myocardial infarction (n = 4). Patients were in New York Heart Association classes II and III. None showed signs or symptoms of left or right ventricular decompensation. Resting left ventricular ejection fraction defined by transthoracic echocardiography increased from 16 ± 1% before implantation to 30 ± 4% after implantation (P < 0.03). We obtained good quality sympathetic nerve recordings in 8 patients. The control group was composed of 16 healthy men (24–62 years; body mass index, 21–28 kg/m²).

Data Analysis

Respiratory sinus arrhythmia was defined as the ratio between the longest and shortest RR interval (distance between R peaks of the ECG in ms) during one deep breathing cycle. The Valsalva ratio was calculated as the ratio between the longest RR interval during phase IV and the shortest RR interval during phase II. Heart rate and blood pressure variabilities, as well as baroreflex heart rate regulation, were assessed using spectral analysis, cross-spectral analysis, and the transfer function between RR intervals and systolic blood pressure. We computed MSNA burst latency (in milliseconds), burst frequency (bursts per minute), burst incidence (bursts per 100 heartbeats), and total activity (area under the bursts per minute as Vs/min). The median value of the normalized burst amplitude distribution was calculated in percentage to characterize possible changes in fiber firing activity. We applied the threshold technique to calculate sympathetic baroreflex slopes between burst incidence and diastolic blood pressure. Diastolic blood pressure values for each cardiac cycle (recorded during the baseline period) were grouped into blood pressure bins (bin size, 1 mm Hg). The percentage of heartbeats associated with a burst in each of these blood pressure bins was calculated. The slope of the relationship between diastolic blood pressure and MSNA was calculated using linear regression. The slope of this relationship has been shown previously to agree with the baroreflex sensitivity calculated during a modified Oxford baroreflex test.

Statistics

All of the data are expressed as mean±SEM. Interindividual and intraindividual differences were compared by Mann-Whitney and Wilcoxon matched pairs tests, respectively. We also applied linear regression analysis. P values <0.05 were considered significant.

Results

Individual patient characteristics are given in Table 1. LVAD had been implanted 7 to 32 months before the study. Mean LVAD speed was 2860±37 rpm. All of the patients were on heart failure medications, including angiotensin-converting enzyme inhibitors (n = 6) or angiotensin II type 1 receptor blockers (n = 1), β-1 adrenoreceptor blockers (n = 6), loop diuretics (n = 3), and oral anticoagulants (n = 9). End stage heart failure resulted from dilated cardiomyopathy (n = 5) or coronary artery disease and myocardial infarction (n = 4). Patients were in New York Heart Association classes II and III. None showed signs or symptoms of left or right ventricular decompensation. Resting left ventricular ejection fraction defined by transthoracic echocardiography increased from 16±1% before implantation to 30±4% after implantation (P < 0.03). We obtained good quality sympathetic nerve recordings in 8 patients. The control group was composed of 16 healthy men (24–62 years; body mass index, 21–28 kg/m²).

Systolic brachial blood pressure was 99±4 mm Hg. Finger blood pressure recordings showed profoundly reduced pulsatility with large interindividual variability. Mean finger pulse pressure was 14±2 mm Hg (range, 4–23 mm Hg). Respira-
Mean MSNA burst latency, burst frequency, burst incidence, and MSNA tracings in a 26-year–old patient. The patient exhibited low pulse pressure and an MSNA burst frequency of 65 bursts per minute, burst incidence ranged from 46 to 88 bursts/100 beats, and burst area ranged from 1.3 to 4.2 Vs/min in LVAD patients. Figure 2 illustrates individual burst frequencies in patients and in control subjects. MSNA was lower compared with age- and body mass index–matched controls in 2 patients, slightly increased in 4 patients, and increased in 2 patients (Figure 2, bottom).

In 6 of 8 patients, we observed a normal negative slope between MSNA burst incidence and diastolic blood pressure (Figure 3). Mean sympathetic baroreflex slope was similar between groups ($P=0.964$; Table 2).

Figure 4 shows finger blood pressure and MSNA tracings for 1 patient at baseline (top) and at highest LVAD speed of 3200 rpm (bottom). Pulse pressure decreased from 15 mm Hg at baseline LVAD speed to 5 mm Hg at maximum speed in this patient. Nevertheless, sympathetic nerve traffic was still suppressed during blood pressure increases. The sympathetic baroreflex slope was $-4.3\%$/mm Hg at baseline and $-3.5\%$/mm Hg at 3200 rpm in this patient. Mean sympathetic baroreflex slope was similar in LVAD patients at increased pump speed ($-3.0\pm0.9\%$/mm Hg) compared with baseline values.

With increased LVAD speed, a slight but statistically not significant diastolic finger blood pressure increase was accompanied by MSNA reduction ($-3\pm4$ bursts per minute; $P=0.031$), although pulse pressure decreased further. One patient showed a different response (Figure 5, top). During head-up tilt, a comparable diastolic blood pressure rise was...
accompanied by a 4±1-bursts per minute MSNA increase ($P=0.0003$; Figure 5, bottom).

## Discussion

The main finding of our study is that, in patients with end-stage systolic heart failure implanted with continuous-flow LVAD, baroreflex MSNA regulation is paradoxically preserved. Moreover, sympathetic activity was surprisingly low in our patients considering the severity of cardiac contractile dysfunction. Only 2 of 8 patients exhibited resting MSNA measurements close to values reported in the literature for patients with severe heart failure.\textsuperscript{14,17} Overall, we only observed a tendency of a higher burst frequency and higher median value of the normalized burst amplitude distribution in LVAD patients compared with control subjects. Burst incidence and the area under the burst were similar between groups. The median of the normalized burst amplitude distribution, thought to be more informative than burst frequency alone, was similar in LVAD patients compared with earlier reported values in healthy controls.\textsuperscript{14} Our findings challenge the idea that normal pressure and flow pulsatility are required to maintain cardiovascular homeostasis. Given the prognostic relevance of baroreflex dysfunction and excessive sympathetic activity in heart failure patients, our findings could translate into clinical outcomes.

In our LVAD-treated patients, pulse pressure was substantially reduced to values as low as 4 mm Hg. If normal pulse pressures were required for baroreflexes to operate, one would expect to observe profound abnormalities in heart rate and MSNA regulation. Baroreceptor activation could be further impeded by the fact that LVAD speed is adjusted such that the aortic valve opens only intermittently.\textsuperscript{18} Baroreflex heart rate regulation was intact at least in part in most of our patients, as evidenced by the heart rate response during the Valsalva maneuver and head-up tilt. However, the mean values of heart rate.

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**Figure 2.** Muscle sympathetic nerve activity (MSNA) in bursts per minute in individual patients compared with age- and body mass index (BMI)-matched healthy controls (top), plotted against systolic finger blood pressure (SBP; middle), and plotted against diastolic finger blood pressure (DBP; bottom).

**Figure 3.** Individual sympathetic baroreflex slopes vs age- and body mass index (BMI)-matched healthy controls.

**Figure 4.** ECG, respiration (Resp), finger blood pressure (FBP), and muscle sympathetic nerve activity (MSNA) tracings for 1 patient at baseline (top) and at 3200 rpm LVAD speed (bottom). Reduction in pulse pressure with increased pump speed did not compromise baroreflex-mediated sympathetic regulation.
rate variability and baroreflex sensitivity of heart rate control were significantly reduced compared with healthy controls. Nevertheless, we recorded abnormal spontaneous baroreflex sensitivities in ≤3 of 8 patients. The observation is unexpected, because parasympathetic heart rate control is severely impaired in heart failure patients. Similar to an earlier study in patients implanted with a HeartMate LVAD, our patients showed reduced but preserved parasympathetic heart rate control assessed by autonomic reflex tests and spectral analysis. In fact, heart rate variability may improve with LVAD treatment. This conclusion remains speculative without measurements of heart rate variability before and after LVAD treatment.

MSNA bursts are governed by baroreflex mechanisms. Loss of afferent baroreceptor input elicits changes in MSNA burst morphology while uncoupling MSNA activity from blood pressure. Our patients showed similar MSNA burst frequency, burst incidence, and area under the burst. Moreover, similar burst latency indicated that MSNA bursts were properly linked to cardiac cycle and blood pressure.

In contrast to baroreflex heart rate control, baroreflex control of sympathetic nerve activity appears to be maintained in heart failure patients. We observed normal sympathetic baroreflex slopes in 6 of 8 LVAD-treated patients.

Increasing LVAD speed was crucial in studying pulse pressure and baroreflex interactions. When we increased LVAD speed, MSNA decreased together with pulse pressure. The reduction in burst incidence as pump rate and diastolic pressure increased is not surprising given that diastolic pressure has a close correlation to sympathetic activity, which is greater than that of either systolic or mean arterial pressures. Overall, our observations indicate that baroreflex control of heart rate and MSNA is maintained in patients with continuous-flow LVAD despite very low pulse pressure values. The finding is important because baroreflexes restrain sympathetic nervous system activity. Severely affected heart failure patients show ≤50-fold increased cardiac norepinephrine spillover. Functional cardiac imaging studies with different tracers suggested that increased global cardiac uptake has a high negative predictive value in terms of cardiac events. MSNA burst rates exceeding 49 bursts per minute were associated with reduced 1-year survival rates in 122 heart failure patients. Our observation that resting MSNA was not profoundly increased compared with matched healthy controls is reassuring and indicates that continuous-flow LVAD therapy might decrease sympathetic drive in heart failure patients. In fact, an earlier study showed reductions in plasma catecholamine concentrations likely through improved cardiac output and tissue perfusion.

The minimal pulse pressure required to induce baroreflex-mediated sympathetic inhibition in humans is unknown. The pulmonary artery pulse pressure is preserved in continuous-flow LVAD patients without right heart failure. Baroreceptors from other receptive fields like cardiopulmonary baroreceptors may compensate for the lack in carotid sinus baroreceptor stimulation. Yet, cardiopulmonary baroreceptors are desensitized in heart failure patients. Increased cardiopulmonary filling pressure can cause pathological sympathetic activation and baroreflex impairment. Relieving the pulmonary circulation through continuous-flow LVAD could elicit an opposite response. The increase in MSNA in response to a mild orthostatic stimulus in our patients suggests this hypothesis. Improvements in physical exercise capacity, reductions in myocardial ischemia, and normalized breathing patterns reducing chemoreflex activation could further improve cardiovascular autonomic control. Because chronic continuous flow may cause aortic thinning, a reduced pulse pressure may be sufficient to elicit baroreceptor excitation. Moreover, data obtained in sinoaortic denervated animals during ganglionic blockade support the hypothesis that cardiac-related bursting of sympathetic nerve activity is not necessary for maintaining normal sympathetic vasoconstrictor tone. Nevertheless, the low pulse pressure accom-
panned by normal MSNA burst morphology in LVAD patients may contradict experimental evidence from animal and human studies.\(^9,20,32\)

One limitation of our study is the relatively low number of patients. Furthermore, because we did not include unstable patients or patients with a complicated postoperative course, our findings have to be interpreted with caution. Moreover, cardiac sympathetic activity cannot be extrapolated from MSNA recorded in peripheral nerves.

**Perspectives**

The low pulse pressure level in patients implanted with continuous-flow LVAD is sufficient to maintain cardiovascular control through baroreflexes. Given the central role of these mechanisms in adjusting heart rate and vascular tone to the requirements of daily life, including standing, our findings are relevant for performance and quality of life in chronically implanted patients. Neurohumoral mechanisms engaged through baroreflex and nonbaroreflex mechanisms have a bearing on long-term cardiovascular outcome. For example, increased baroreceptor activation through electric carotid sinus stimulation is beneficial in experimental heart failure.\(^33\) Recent outcome studies showed improved survival in patients with continuous-flow LVAD.\(^8,34\) Together with improved quality of life.\(^35\) The observation may be explained in part by the fact that technical advantages of continuous-flow LVAD, such as small size and reliability, are not offset by impairments in baroreflex function or sympathetic activation. Our findings provide an impetus to revisit current concepts of human baroreflex physiology in health and disease, including arterial hypertension. Indeed, baroreflex mechanisms contribute to the pathogenesis of arterial hypertension and have been recognized as an important treatment target.\(^12\)

The issue is relevant for patients with arterial hypertension treated with electric carotid stimulators stimulating carotid baroreceptors in a nonpulsatile fashion. A possible implication for the further clinical development of electric carotid sinus stimulators is that continuous stimulation may be sufficient to reduce sympathetic activity and blood pressure. Thus, linking electric discharges to the cardiac cycle in a pulsatile fashion may not be warranted.

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**Disclosures**

M.S. is a consultant to HeartWare.

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**Novelty and Significance**

**What Is New?**

- Sympathetic baroreflex function has not been assessed in patients with continuous-flow LVADs.
- Very low pulse pressure in these patients was sufficient to maintain sympathetic baroreflex function.
- Sympathetic activity was surprisingly low.

**What Is Relevant?**

- Impaired sympathetic baroreflex regulation predisposes to hypertension and cardiovascular damage.

- Our findings are particularly relevant for patients with reduced pulsatile baroreceptor stimulation, including those with LVADs and hypertensive patients treated with electrical carotid sinus stimulators.

**Summary**

Sympathetic baroreflex regulation is maintained in patients with continuous-flow LVADs, suggesting that reduced pressure pulsatility is sufficient for human baroreflexes to operate.
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