Sympathetic Neural and Hemodynamic Responses to Upright Tilt in Patients With Pulsatile and Nonpulsatile Left Ventricular Assist Devices

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Background—Left ventricular assist devices (LVADs) are now widely accepted as an option for patients with advanced heart failure. First-generation devices were pulsatile, but they had poor longevity and durability. Newer generation devices are nonpulsatile and more durable, but remain associated with an increased risk of stroke and hypertension. Moreover, little is understood about the physiological effects of the chronic absence of pulsatile flow in humans.

Methods and Results—We evaluated patients with pulsatile (n=6) and nonpulsatile (n=11) LVADs and healthy controls (n=9) during head-up tilt while measuring hemodynamics and muscle sympathetic nerve activity. Patients with nonpulsatile devices had markedly elevated supine and upright muscle sympathetic nerve activity (mean±SD, 43±15 supine and 60±21 bursts/min at 60° head-up tilt) compared with patients with pulsatile devices (24±7 and 35±8 bursts/min; P<0.01) and controls (11±6 and 31±6 bursts/min; P<0.01); however, muscle sympathetic nerve activity was not different between patients with pulsatile flow and controls (P=0.34). Heart rate, mean arterial pressure, and total peripheral resistance were greater, whereas cardiac output was smaller, in LVAD patients compared with controls in both supine and upright postures. However, these hemodynamic variables were not significantly different between patients with pulsatile and nonpulsatile flow.

Conclusions—Heart failure patients with continuous, nonpulsatile LVADs have marked sympathetic activation, which is likely due, at least in part, to baroreceptor unloading. We speculate that such chronic sympathetic activation may contribute to, or worsen end-organ diseases, and reduce the possibility of ventricular recovery. Strategies to provide some degree of arterial pulsatility, even in continuous flow LVADs may be necessary to achieve optimal outcomes in these patients. (Circ Heart Fail. 2013;6:293-299.)

Key Words: assist device ■ baroreceptors ■ heart failure ■ nonpulsatility ■ pulsatility

Clinical Perspective on p 299

Vasomotor sympathetic activity plays an important role in arterial pressure regulation via the baroreflex in humans.5 The carotid baroreceptors respond to pulsatile pressures because the deformation of baroreceptors is required to promote neural firing. With reduced pulsatility, less deformation of baroreceptors may lead to lower rates of baroreceptor afferent discharge, causing less inhibition of sympathetic nerve activity (SNA). Indeed, it was previously found in dogs that for the same mean carotid sinus pressure, pulsatile pressure caused significantly greater inhibition of SNA than static/nonpulsatile pressure.6,7

The primary objective of this study was to evaluate and compare sympathetic neural control in patients with pulsatile and nonpulsatile LVADs. This comparison not only may be sympathetic activation because of the absence of arterial pulsatility in patients with continuous flow devices.
important clinically, but also provides a unique opportunity to study fundamental human cardiovascular physiology. Our hypothesis was that patients with nonpulsatile LVADs would have a greater SNA compared with patients with pulsatile devices. To accomplish this objective, we measured muscle SNA (MSNA) and hemodynamics in these patients at rest and during orthostasis. Data were also compared with those obtained from healthy controls.

**Methods**

**Subjects**

Seventeen patients with LV AD were enrolled in the study (6 pulsatile and 11 nonpulsatile). Patients were recruited from the Advanced Heart Failure Management Clinic at University Hospital St. Paul, and the Heart Failure Clinic at Baylor University Medical Center, a collaboration with the University of Texas Southwestern Medical Center. Nine healthy, normotensive subjects served as controls. Table 1 describes the characteristics of each of the groups. All patients with LVAD had fully recovered from the surgical placement of the assist device and were currently ambulatory outpatients. Five pulsatile patients had a HeartMate I pump (Thoratec, Pleasanton, CA), and 1 patient had a Thoratec PVAD. Ten nonpulsatile patients had a HeartMate II pump, and 1 patient had a HeartWare pump (Thoratec). The patients did not take any medications that could affect the function of the autonomic nervous system, such as β-blockers, the morning of the study. All other medicines were continued during the study. All subjects gave written informed consent, approved by the institutional review boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas.

**Measurements**

**Heart Rate and BP**

Heart rate (HR) was monitored from lead II of the ECG (Hewlett-Packard, Andover, MA), and beat-to-beat arterial pressure was derived by finger plethysmography (Nexfin, Amsterdam, The Netherlands). Arm cuff BP was measured at the level of the brachial artery using a sphygmomanometer (SunTech, Morrisville, NC) in pulsatile patients and by using a Doppler and sphygmomanometer in the nonpulsatile patients (onset of flow representing mean arterial pressure [MAP]).

**Cardiac Output**

Cardiac output (Qc) was measured with the foreign gas rebreathing technique. Qc was calculated from the disappearance rate of acetylene in expired air, measured with a mass spectrometer (model MGA1100, Marquette, Milwaukee, WI) after adequate mixing in the lung had been confirmed by a stable helium concentration. This technique has been well validated as a measure of effective pulmonary blood flow (blood flow to ventilated lung) in healthy individuals and patients with cardiovascular disease. Total peripheral resistance was calculated as the quotient of MAP and Qc, multiplied by 80 (expressed as dyn·s·cm⁻²). MAP was calculated as ([SBP–DBP]/3)+DBP, where SBP and DBP are arm cuff systolic and diastolic BP measured during rebreathing, respectively.

**Muscle Sympathetic Nerve Activity**

MSNA signals were obtained with the microneurographic technique. Briefly, a recording electrode was placed in the peroneal nerve at the popliteal fossa, and a reference electrode was placed subcutaneously 2 to 3 cm from the recording electrode. The nerve signals were amplified (gain, 70,000–160,000), band-pass filtered (700–2000 Hz), full-wave rectified, and integrated with a resistance-capacitance circuit (time constant, 0.1 second). Criteria for adequate MSNA recording included the following: (1) pulse synchrony in patients with pulsatile devices and controls; (2) facilitation during the hypotensive phase of the Valsalva maneuver, and suppression during the hypertensive overshoot after release; (3) increases in response to breath holding; and (4) insensitivity to emotional stimuli. Measurement of MSNA in humans represents integrated sympathetic outflow from a variety of inputs, including carotid and cardiopulmonary baroreceptors.

**Blood Samples**

Blood samples were drawn from an intravenous catheter placed in an antecubital vein. Plasma catecholamine was measured with high-precision liquid chromatography.

**Table 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients With LVAD</th>
<th></th>
<th>Healthy Controls (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulsatile (n=6)</td>
<td>Nonpulsatile (n=11)</td>
<td></td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>5/1</td>
<td>9/2</td>
<td>5/4</td>
</tr>
<tr>
<td>Age, y</td>
<td>50±13</td>
<td>48±12</td>
<td>37±9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172±9</td>
<td>178±12</td>
<td>170±10</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86±25</td>
<td>98±26</td>
<td>66±13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.8±7.2</td>
<td>30.6±6.3</td>
<td>22.9±2.5</td>
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<tr>
<td>LVAD time, mo</td>
<td>9±4</td>
<td>3±2</td>
<td>...</td>
</tr>
<tr>
<td>β-Blocker, %</td>
<td>100</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>83</td>
<td>82</td>
<td>...</td>
</tr>
<tr>
<td>ARB, %</td>
<td>0</td>
<td>9</td>
<td>...</td>
</tr>
<tr>
<td>Diuretic, %</td>
<td>83</td>
<td>64</td>
<td>...</td>
</tr>
<tr>
<td>Aldo antagonist,%</td>
<td>33</td>
<td>55</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mean±SD.
ACE indicates angiotensin converting enzyme; Aldo, aldosterone; ARB, angiotensin II AT1 receptor blocker; BMI, body mass index; and LVAD, left ventricular assist device.
Protocol
The experiment was performed starting in the morning after a light breakfast and no caffeinated beverages within 12 hours in a quiet, environmentally controlled laboratory with an ambient temperature of ≥25°C. After at least 20 minutes of quiet rest in the supine position, baseline hemodynamic variables were measured. At least 10 minutes after acceptable nerve recordings were obtained, baseline MSNA, BP, and HR data were collected for 3 minutes. The subject was then tilted passively to 30° and 60° head-up tilt (HUT) for 10 minutes each. A belt was placed across the subjects’ waist to make sure they would not fall. A bicycle saddle was used to support approximately two-thirds of the body weight while the subject stood on a plate at the end of the tilt bed on one leg, allowing the other leg to be relaxed for microneurography.14 HR, BP, and MSNA were recorded continuously during tilting. Qc measurement was repeated after 5 minutes of each tilting stage, and the blood sample was taken when supine and at the end of 60° tilt. After HUT, the subject was returned to the supine position for recovery.

Data Analysis
MSNA signals were obtained and analyzed by an experienced microneurographer. MSNA was expressed as the number of bursts per minute (burst frequency). Baseline data were averaged for 3 minutes. Data during tilting were collected from the second to the fifth minute, and averaged for 3 minutes.

Statistical Analysis
Data are expressed as mean±SD. Changes in MSNA and hemodynamics because of HUT were analyzed by 2-way repeated measures ANOVA. The Holm–Sidak method was used post hoc for multiple comparisons. All statistical analyses were performed with a personal computer–based analysis program (SigmaPlot, version 12, San Jose, CA). P<0.05 was considered statistically significant.

Results
MSNA and Hemodynamic Responses to Head-up Tilt
Figure 1 shows representative tracings of MSNA from 1 pulsatile and 1 nonpulsatile LVAD patient. In all patients with pulsatile devices, MSNA was synchronized with the arterial pulse waveform generated by the LVAD, independent of the intrinsic HR; for nonpulsatile patients, MSNA was generally not synchronized with the arterial pressure waveform, though in a few patients with some degree of function of the native heart, and a quantifiable pulse pressure, there seemed to be some degree of pulse synchronization. Burst frequencies during HUT for all groups are compared in Figure 2. Patients with nonpulsatile LVADs had markedly elevated MSNA in the supine position and with HUT compared with patients with pulsatile devices (P<0.01) and controls (P<0.01). MSNA was not significantly different between pulsatile patients and healthy controls (P=0.34).

Hemodynamic data during HUT are shown in Table 2. With HUT, MAP (P=0.57), HR (P=0.54), Qc (P=0.53), and total peripheral resistance (P=0.84) did not differ significantly between the LVAD groups. However, MAP, HR, and total peripheral resistance were greater, whereas Qc was lower, in both groups of patients with LVAD compared with controls (all P<0.05).

Catecholamine Levels During Head-up Tilt
Plasma norepinephrine for the patients with nonpulsatile devices was substantially and clearly greater than controls in both the supine and tilted positions (P<0.001); the patients with the pulsatile devices had norepinephrine levels that were midway between both other groups and not clearly distinguishable from either statistically (P=0.18; Table 3). Norepinephrine increased in all groups with tilting and was highest in the nonpulsatile group. Epinephrine levels were low and did not change significantly in any group. There were no significant interactions between groups and positions.

Discussion
The major finding of this study was that patients with nonpulsatile LVADs have higher MSNA than patients with pulsatile LVADs or healthy controls in both the supine and upright positions. This marked sympathetic activation occurred despite similar global hemodynamics (mean BP, Qc, and total peripheral resistance) and medical therapy for heart failure, and thus is highly likely to be secondary to the nonpulsatile nature of the devices.

Mechanisms for Sympathetic Activation With Nonpulsatile Flow
There are several potential mechanisms for these observations. First, the most obvious explanation is that nonpulsatile LVADs do not stimulate the arterial baroreceptors to a similar degree as pulsatile devices or normal controls. For example, previous elegant animal studies have suggested that at the same mean pressure, pulsatile pressure as compared with static pressure leads to much greater carotid baroreceptor afferent nerve firing, and greater centrally mediated suppression of efferent SNA.7,15 Furthermore, exposure of baroreceptors to elevated levels of static pressure causes a rapid resetting or desensitization of the receptors within minutes,16 which does not happen in the setting of normal pulsatility. This alteration in baroreflex function may be compounded by alterations in endothelial function in patients with nonpulsatile flow. For
example, reduced pulsatility at the same mean flow leads to reduced shear stress, which may reduce nitric oxide (NO) production and impair endothelial function. Not only will reduced NO decrease endothelial vasodilation, but it also has been shown to increase sympathetic activity in humans.

Third, humoral factors (ie, angiotensin II, aldosterone, etc.) may be involved in sympathetic activation in nonpulsatile patients, especially in the chronic state. Although we did not measure renal-adrenal hormones in this study, a recent report showed that both plasma renin activity and aldosterone were much greater in patients with nonpulsatile than pulsatile LVADs. The greater plasma renin activity leads to a greater level of angiotensin II in patients with nonpulsatile devices, which in animal research contributes substantially to background SNA. Furthermore, a chronic increase in aldosterone has a similar sympathoexcitatory action, such as observed in patients with primary hyperaldosteronism in whom MSNA is markedly elevated. It is possible that chronic exposure to a higher concentration of renin, angiotensin II, and aldosterone may also contribute to sympathetic activation in patients with nonpulsatile LVADs.

It is also important to emphasize that regulation of sympathetic activity in patients with heart failure is complex and represents input from multiple sources. For example, a review...
sympathetic innervation after LV AD implantation. Although with conflicting results. Earlier studies suggested no change, although a more normal pulsatile flow seems to have much less sympathetic activation compared with patients with nonpulsatile LVADs, it may be that the presence of nonpulsatile flow could be another factor that might be added to the model of contributors to sympathetic activation in these patients.

Clinical Implications of Hyperadrenergic State With Nonpulsatile Flow

Cardiovascular risk increases with higher levels of sympathetic activity. Especially in heart failure, sympathetic activation may contribute to disease progression and outcomes, which has been the primary pathophysiology driving the modern use of β-blockers in patients with heart failure. The level of sympathetic activation demonstrated in this study of patients with nonpulsatile LVADs is quite dramatic, similar to those observed from patients with decompensated congestive heart failure and end-stage renal disease, despite the near normalization of hemodynamics. Conversely, patients with more normal pulsatile flow seem to have much less sympathetic activation compared with patients with nonpulsatile flow, especially during orthostasis. Two previous studies used iodine 123-meta-iodobenzylguanidine (123I-mIBG) scintigraphy in an attempt to image cardiac sympathetic innervation with conflicting results. Earlier studies suggested no change, although more recent studies suggested an increase in cardiac sympathetic innervation after LVAD implantation. Although the distribution of pulsatile and nonpulsatile devices differed between these 2 studies, the hemodynamic unloading was much more dramatic in the recent experience regardless of device type. Perhaps, most importantly, the restoration of normal pulsatile sympathetic innervation seemed to be a marker of functional recovery after LVAD implantation, although a direct comparison between pulsatile and nonpulsatile devices has not been made. To our knowledge, there have not been any previous studies reporting direct measurement of sympathetic outflow to the vasomotor regions in skeletal muscle in either pulsatile or nonpulsatile LVADs. Further studies using this high resolution technique and addressing clinically meaningful outcomes seems warranted, especially in patients being considered for device explantation (ie, bridge to recovery).

Sympathetic activation may not only prevent functional myocyte recovery after reverse remodeling, but also higher sympathetic activity could lead to other adverse cardiovascular events in these patients over time, such as acute coronary syndromes, stroke, uncontrolled hypertension, and adverse renal effects. Other frequent adverse effects in these patients are also potentially related to this unique physiology and hypertension (ie, gastrointestinal bleeding). The stroke rate (ischemic and hemorrhagic) in patients with LVAD has been high, including a previous report of stroke incidence of 19% in destination patients with a HeartMate II. More recent data suggest that with added experience with implantation and management of these devices, stroke rates are now lower (particularly hemorrhagic stroke). These physiological and clinical events could directly relate to high sympathetic activation in these patients, but of course longer term follow-up is needed in this patient population. Serial hemodynamic analyses in patients with LVAD are currently lacking. This type of assessment is going to be particularly important in older destination therapy patients who may have these devices for many years and will be an important factor for the design and management of nonpulsatile devices in the future.

This study provides insight into important clinical implications for LVADs and perhaps points toward novel approaches to improve LVAD design. For instance, devices could be designed that have inherent pulsatility, even using modern durable, continuous flow technology. How best to implement such pulsatility, whether by doing so, sympathetic activation can be reduced, and whether such an approach would improve clinical outcomes, including rates of recovery are questions for future studies.

Limitations

There are several limitations of this study that must be acknowledged. First, the sample size was small (though similar to other studies examining the pathophysiology of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Supine Pulsatile</th>
<th>Supine Nonpulsatile</th>
<th>Healthy Controls</th>
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</thead>
<tbody>
<tr>
<td>Epinephrine (pg/mL)</td>
<td>35±21</td>
<td>26±27</td>
<td>41±41</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>385±134</td>
<td>536±333*</td>
<td>205±53</td>
</tr>
<tr>
<td>Dopamine (pg/mL)</td>
<td>21±3</td>
<td>24±12</td>
<td>...</td>
</tr>
</tbody>
</table>

HUT indicates head-up tilt; and LVAD, left ventricular assist device.

*P<0.001 compared with healthy controls.
with LVADs); however, the data were consistent and statistically significant with regard to the increased MSNA. Because pulsatile LVADs are rarely used in the current era and because their durability is not as great as nonpulsatile pumps, only a few pulsatile patients could be included in this study. Second, microneurography only measures SNA to vasomotor regions of skeletal muscle. It may be that there are regional differences in SNA in patients with LVADs that are clinically meaningful. Third, we only requested patients to withhold β-blockers but not other medications. Moreover, for safety reasons, the β-blockers were only held for a short period of time to prevent the acute effects of β-blockers on hemodynamics at the time of our study. We recognize that the chronic effects of β-blockade are not eliminated by this approach and cannot exclude an effect either of their chronic use or even acute withdrawal on the outcomes of this study. Other medications may have affected MSNA responses in these patients, although we would expect a medication effect to have been present in both groups of patients because their use of other heart failure therapies were equal in both groups. Finally, there were different time intervals since LVAD placement for the patients. In this regard, however, it is important to note that all study patients were stable, ambulatory, and asymptomatic (NYHA 1 [New York Heart Association class 1]) at the time of the study procedures. Although we cannot rule out unknown differences regarding this time interval, all patients were hemodynamically and functionally similar, and we think this is quite unlikely to cause any differences in MSNA measurement or response to HUT.

This study demonstrates that patients with nonpulsatile LVADs have increases in sympathetic activity, presumably because of baroreceptor unloading, but likely compounded by impaired baroreflex function, endothelial dysfunction, and changes in circulating levels of humoral factors related to the renin-angiotensin-aldosterone system. Further work is needed to characterize and address the clinical implications of this persistent and chronic sympathetic activation in these patients with nonpulsatile assist devices, and also how to best optimize pump speed, BP, and the device’s role in exercise performance.

Acknowledgments

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Disclosures

None.

References


CLINICAL PERSPECTIVE

The major finding of this study was that patients with nonpulsatile left ventricular assist devices have higher muscle sympathetic nerve activity than patients with pulsatile left ventricular assist devices or healthy controls in both the supine and upright positions. This marked sympathetic activation is likely to be secondary to the nonpulsatile nature of the devices (ie, baroreceptor unloading). We speculate that it is conceivable such chronic sympathetic activation could contribute to, or worsen end-organ dysfunction over time, and potentially reduce the possibility of ventricular recovery. Studies evaluating this hypothesis should be performed, as strategies to provide some degree of arterial pulsatility, even in continuous flow left ventricular assist devices, may be necessary to achieve optimal outcomes in these patients.
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