Sympathetic Neural and Hemodynamic Responses to Upright Tilt in Patients with Pulsatile and Non-Pulsatile Left Ventricular Assist Devices

Markham et al: MSNA Responses to Orthostasis in LVAD Patients

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Abstract

**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 non-pulsatile 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 non-pulsatile (n=11) LVADs and healthy controls (n=9) during head-up tilt (HUT) while measuring hemodynamics and muscle sympathetic nerve activity (MSNA). Patients with non-pulsatile devices had markedly elevated supine and upright MSNA (mean± SD: 43±15 supine and 60±21 bursts/min at 60° HUT) compared to 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, MSNA was not different between patients with pulsatile flow and controls (P=0.34). Heart rate, mean arterial pressure, and total peripheral resistance were greater, while cardiac output was smaller, in LVAD patients compared to controls in both supine and upright postures. However, these hemodynamic variables were not significantly different between patients with pulsatile and non-pulsatile flow.

**Conclusions**—Heart failure patients with continuous, non-pulsatile 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.

**Key Words:** assist device, heart failure, baroreceptors, pulsatility, non-pulsatility
Left ventricular assist devices (LVADs) are now a standard option for patients with advanced heart failure. These devices are used with increasing frequency for patients who require hemodynamic stabilization, either as a bridge to transplantation or destination therapy. First generation devices were large, pulsatile, and had limited durability. The newer generation devices, which have mostly replaced the earlier ones, are non-pulsatile, continuous flow, and have improved durability and better outcomes. Nevertheless, it is quite difficult to measure blood pressure (BP) in these patients with no pulse, and there is an increased risk of uncontrolled hypertension and possibly stroke. Moreover, some patients may fail to recover myocyte contractile function despite apparent improvements in cardiac morphology (reverse remodeling) after chronic unloading with a LVAD reducing the number of patients who can potentially be explanted. One potential mechanism for this failure may be persistent or even enhanced sympathetic activation due to the absence of arterial pulsatility in patients with continuous flow devices.

Vasomotor sympathetic activity plays an important role in arterial pressure regulation via the baroreflex in humans. The carotid baroreceptors respond to pulsatile pressures, since 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/non-pulsatile pressure.

The primary objective of this study was to evaluate and compare sympathetic neural control in patients with pulsatile and non-pulsatile LVADs. This comparison not only may be important clinically, but also provides a unique opportunity to study fundamental human
cardiovascular physiology. Our hypothesis was that patients with non-pulsatile LVADs would have a greater SNA compared to 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 LVAD patients were enrolled in the study (6 pulsatile and 11 non-pulsatile). 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 LVAD patients had fully recovered from the surgical placement of the assist device and were currently ambulatory outpatients. Five pulsatile patients had a HeartMate I pump, and 1 patient had a Thoratec PVAD. Ten non-pulsatile patients had a HeartMate II pump, and 1 patient had a HeartWare pump. The patients held any medications that could affect the function of the autonomic nervous system, such as beta-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 Blood Pressure
Heart rate (HR) was monitored from lead II of the ECG (Hewlett-Packard), and beat-to-beat arterial pressure was derived by finger plethysmography (Nexfin). Arm cuff BP was measured at the level of the brachial artery using a sphygmomanometer (SunTech) in pulsatile patients, and by using a Doppler and sphygmomanometer in the non-pulsatile patients (onset of flow representing mean arterial pressure).

Cardiac Output

Cardiac output (Qc) was measured with the foreign gas re-breathing technique.\(^8\) Qc was calculated from the disappearance rate of acetylene in expired air, measured with a mass spectrometer (model MGA1100, Marquette) 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.\(^9\) and patients with cardiovascular disease.\(^10\) Total peripheral resistance (TPR) was calculated as the quotient of mean arterial pressure (MAP) and Qc, multiplied by 80 (expressed as dyn·s·cm\(^{-5}\)). MAP was calculated as \([\text{SBP-DBP}/3]+\text{DBP}\), where SBP and DBP are arm cuff systolic and diastolic BP measured during re-breathing, respectively.

Muscle Sympathetic Nerve Activity

MSNA signals were obtained with the microneurographic technique.\(^11\) 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 to 160 000), band-pass filtered (700 to 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.

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 approximately 25° C. After at least 20 minutes of quiet rest in the supine position, baseline hemodynamic variables were measured. At least 10 min 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 subject’s waist to make sure he or she 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. 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 2nd to the 5th minute, and averaged for 3 minutes.

**Statistical Analysis**

Data are expressed as mean ± standard deviation. Changes in MSNA and hemodynamics due to HUT were analyzed by two-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). A probability value of <0.05 was considered statistically significant.

**Results**

**MSNA and Hemodynamic Responses to Head-up Tilt**

Figure 1 shows representative tracings of MSNA from one pulsatile and one non-pulsatile 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 non-pulsatile 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...
appeared to be some degree of pulse synchronization. Burst frequencies during HUT for all
groups are compared in Figure 2. Patients with non-pulsatile LVADs had markedly elevated
MSNA in the supine position and with HUT compared to 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 TPR (p=0.84) did not differ significantly between the LVAD groups.
However, MAP, HR, and TPR were greater, while Qc was lower, in both groups of LVAD
patients compared to controls (all p<0.05).

**Catecholamine Levels during Head-up Tilt (Table 3)**
Plasma norepinephrine (NE) for the patients with non-pulsatile 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 NE levels that were midway between both other groups and not clearly
distinguishable from either statistically (p=0.18). NE increased in all groups with tilting, and was
highest in the non-pulsatile 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 non-pulsatile LVADs have higher muscle
sympathetic nerve activity 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 TPR) and medical therapy for heart failure, and thus is highly likely to be secondary to the non-pulsatile nature of the devices.

**Mechanisms for Sympathetic Activation with Non-pulsatile Flow**

There are several potential mechanisms for these observations. First, the most obvious explanation is that non-pulsatile 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 to static pressure leads to much greater carotid baroreceptor afferent nerve firing, and greater centrally mediated suppression of efferent sympathetic nerve activity. Furthermore, exposure of baroreceptors to elevated levels of static pressure causes a rapid resetting or desensitization of the receptors within minutes 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 non-pulsatile 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.

Thirdly, humoral factors (i.e., angiotensin II, aldosterone, etc.) may be involved in sympathetic activation in non-pulsatile patients, especially in the chronic state. Although we did not measure renal-adrenal hormones in this study, one recent report showed that both plasma renin activity and aldosterone were much greater in patients with non-pulsatile than pulsatile LVADs. The greater plasma renin activity leads to a greater level of angiotensin II in patients with non-pulsatile devices, which in animal research contributes substantially to background sympathetic
nerve activity. Moreover, 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 non-pulsatile 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, in an elegant review article by John Floras, he emphasizes that not only ventricular dysfunction and baroreflex unloading, but impaired cardiopulmonary modulation of baroreflex activity due to elevated filling pressures, a generalized sympathetic activation from pulmonary congestion and elevated intracardiac pressures, concomitant sleep apnea and/or obesity, and alterations in feedback from skeletal muscle may all contribute to sympathetic activation. It must be emphasized that the patients in this study were NOT in heart failure and had been well compensated for months with the assistance of mechanical support. Given the increased numbers of patients with heart failure who are now receiving LVADs, it may be that the presence of non-pulsatile 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 Non-pulsatile 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 beta blockers in patients with heart failure. The level of sympathetic activation demonstrated in this study of patients with non-pulsatile LVADs is quite dramatic, similar to those observed from patients with decompensated...
congestive heart failure and/or end-stage renal disease, despite the near-normalization of hemodynamics.\textsuperscript{26, 27} Conversely, patients with more normal pulsatile flow appear to have much less sympathetic activation compared to patients with non-pulsatile 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\textsuperscript{28} though more recent studies suggested an increase in cardiac sympathetic innervation after LVAD implantation.\textsuperscript{29} Although the distribution of pulsatile and non pulsatile devices differed between these two studies, the hemodynamic unloading was much more dramatic in the recent experience regardless of device type. Perhaps most importantly, the restoration of normal cardiac sympathetic innervation seemed to be a marker of functional recovery after LVAD implantation,\textsuperscript{29} though a direct comparison between pulsatile and non-pulsatile 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 non-pulsatile LVADs. Further studies using this high resolution technique and addressing clinically meaningful outcomes seems warranted, especially in patients being considered for device explantation (i.e. “bridge to recovery”).\textsuperscript{30}

Not only may sympathetic activation prevent functional myocyte recovery after reverse remodeling, but 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 (i.e. GI bleeding). The stroke rate (ischemic and hemorrhagic) in LVAD patients has been high, including a previous report of stroke incidence of approximately 19\% in destination patients with a HeartMate II.\textsuperscript{3} 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 LVAD patients 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 non-pulsatile devices in the future.

This study provides insight into important clinical implications for LVADs and perhaps points towards 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. One, the sample size was small (though similar to other studies examining the pathophysiology of patients with LVADs); however, the data were consistent and statistically significant with regard to the increased MSNA. Since pulsatile LVADs are rarely used in the current era and since their durability is not as great as non-pulsatile pumps, only a few pulsatile patients could be included in this study. Two, microneurography only measures sympathetic nerve activity to vasomotor regions of skeletal muscle. It may be that there are regional differences in sympathetic nerve activity in patients with LVADs that are clinically meaningful. Three, we only requested patients to withhold beta-
blockers but not other medications. Moreover, for safety reasons, the beta blockers were only held for a short period of time to prevent the acute effects of beta blockers on hemodynamics at the time of our study. We recognize that the chronic effects of beta 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, though we would expect a medication effect to have been present in both groups of patients since their use of other heart failure therapies were equal in both groups. Lastly, there were different time intervals since LVAD placement for the groups. In this regard, however, it is important to note that all study patients were stable, ambulatory, and asymptomatic (NYHA 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 feel this is quite unlikely to cause any differences in MSNA measurement or response to HUT.

In conclusion, this study demonstrates that patients with non-pulsatile left ventricular assist devices have increases in sympathetic activity, presumably due to baroreceptor unloading, but likely compounded by impaired baroreflex function, endothelial dysfunction, and/or 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 non-pulsatile assist devices, and also how to best optimize pump speed, blood pressure, and the device’s role in exercise performance.
Acknowledgements

The time and effort put forth by the subjects is greatly appreciated.

Sources of Funding

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Disclosures

None.

References


### Table 1. Subject characteristics

<table>
<thead>
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<th>Variables</th>
<th>Patients with LVAD</th>
<th>Healthy Controls</th>
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<tbody>
<tr>
<td></td>
<td>Pulsatile (n=6)</td>
<td>Non-pulsatile (n=11)</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>5/1</td>
<td>9/2</td>
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<tr>
<td>Age (yrs)</td>
<td>50 ± 13</td>
<td>48 ± 12</td>
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<td>Height (cm)</td>
<td>172 ± 9</td>
<td>178 ± 12</td>
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<tr>
<td>Weight (kg)</td>
<td>86 ± 25</td>
<td>98 ± 26</td>
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<td>BMI (kg/m²)</td>
<td>30.8 ± 7.2</td>
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<tr>
<td>LVAD time (mo)</td>
<td>9 ± 4</td>
<td>3 ± 2</td>
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<tr>
<td>Beta-blocker (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>83</td>
<td>82</td>
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<tr>
<td>ARB (%)</td>
<td>0</td>
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</tr>
<tr>
<td>Diuretic (%)</td>
<td>83</td>
<td>64</td>
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<tr>
<td>Aldo antagonist (%)</td>
<td>33</td>
<td>55</td>
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Values are mean ± standard deviation. LVAD, left ventricular assist device. BMI, body mass index. ACE, angiotensin converting enzyme. ARB, angiotensin II AT1 receptor blocker. Aldo, aldosterone.
### Table 2. Hemodynamic responses to HUT

<table>
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<tr>
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<td>Pulsatile</td>
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<td>HR (bpm)</td>
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<td>Supine</td>
<td>86 ± 7</td>
<td>87 ± 7**</td>
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<tr>
<td>30° HUT</td>
<td>87 ± 11</td>
<td>88 ± 5**</td>
</tr>
<tr>
<td>60° HUT</td>
<td>89 ± 7</td>
<td>92 ± 9**</td>
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<td>Qc (L/min)</td>
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<tr>
<td>Supine</td>
<td>4.88 ± 1.2*</td>
<td>5.19 ± 1.2</td>
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<tr>
<td>30° HUT</td>
<td>4.20 ± 1.3*</td>
<td>4.59 ± 1.2</td>
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<tr>
<td>60° HUT</td>
<td>3.71 ± 1.5*</td>
<td>4.26 ± 1.5</td>
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<td>MAP (mmHg)</td>
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<tr>
<td>Supine</td>
<td>90 ± 14</td>
<td>94 ± 15*</td>
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<tr>
<td>30° HUT</td>
<td>94 ± 19</td>
<td>103 ± 14*</td>
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<tr>
<td>60° HUT</td>
<td>103 ± 25</td>
<td>105 ± 15*</td>
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<td>TPR (dyn-s-cm(^{-5}))</td>
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<tr>
<td>Supine</td>
<td>1577 ± 529*</td>
<td>1567 ± 625</td>
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<tr>
<td>30° HUT</td>
<td>2041 ± 1029*</td>
<td>2010 ± 756</td>
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<tr>
<td>60° HUT</td>
<td>2698 ± 1583*</td>
<td>2482 ± 1510</td>
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Values are mean ± standard deviation. HUT, head-up tilt. LVAD, left ventricular assist device.

HR, heart rate. Qc, cardiac output. MAP, mean arterial pressure. TPR, total peripheral resistance.

*P<0.05 and **P<0.01 compared to healthy control
### Table 3. Catecholamine responses to HUT

<table>
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<tr>
<td>Supine</td>
<td></td>
<td></td>
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<tr>
<td>Dopamine (pg/mL)</td>
<td>21 ± 3</td>
<td>24 ± 12</td>
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<tr>
<td>Norepinephrine (pg/mL)</td>
<td>385 ± 134</td>
<td>536 ± 333**</td>
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<tr>
<td>Epinephrine (pg/mL)</td>
<td>35 ± 21</td>
<td>26 ± 27</td>
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<tr>
<td>60° HUT</td>
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<td></td>
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<tr>
<td>Dopamine (pg/mL)</td>
<td>26 ± 8</td>
<td>22 ± 3</td>
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<tr>
<td>Norepinephrine (pg/mL)</td>
<td>421 ± 40</td>
<td>610 ± 242**</td>
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<tr>
<td>Epinephrine (pg/mL)</td>
<td>24 ± 10</td>
<td>41 ± 28</td>
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Values are mean ± standard deviation. HUT, head-up tilt. LVAD, left ventricular assist device.

**P<0.001 compared to healthy controls.
Figure Legends

Figure 1. Representative individual ECG, MSNA, and blood pressure recordings from patients with non-pulsatile (A) and pulsatile (B) LVADs in the supine and 60 degree head-up tilt (HUT) positions.

Figure 2. Individual and mean MSNA burst frequencies in healthy controls and patients with pulsatile and non-pulsatile LVADs in the supine position and during upright tilt. Values are mean ± standard deviation. *P<0.05 compared to the supine position.
Figure 1

A
Non-pulsatile LVAD patient

ECG

10 s

MSNA

Supine 60° HUT

BP (mmHg)

180
160
140
120
100
80
60
40

B
Pulsatile LVAD patient

Supine 60° HUT

ECG

10 s

MSNA

BP (mmHg)

180
160
140
120
100
80
60
40
Figure 2

ANOVA
Pulsatile vs. controls p=0.34
Non-pulsatile vs. controls p<0.01
Pulsatile vs. non-pulsatile p<0.01
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