Central and Peripheral Blood Flow During Exercise

with a Continuous-Flow Left Ventricular Assist-Device:

Constant vs. Increasing Pump Speed. A Pilot Study

Brassard et al: LVAD Pump Speed During Exercise

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Abstract

Background—End-stage heart failure is associated with impaired cardiac output (CO) and organ blood flow. We determined whether CO and peripheral perfusion are maintained during exercise in patients with an axial-flow left ventricular assist device (LVAD) and whether an increase in LVAD pump speed with work rate would increase organ blood flow.

Methods and Results—Invasively determined CO and leg blood flow and Doppler-determined cerebral perfusion were measured during two incremental cycle exercise tests on the same day in eight patients provided with a HeartMate II® LVAD. In random order, patients exercised both with a constant (~9775 rpm) and with an increasing pump speed (+400 rpm per exercise stage). At 60 Watts, the elevation in CO was more pronounced with increased pump speed (8.7±0.6 vs. 8.1±1.1 L min⁻¹; mean±SD; P=0.05), but at maximal exercise, increases in CO (from 7.0±0.9 to 13.6±2.5 L min⁻¹; P<0.01) and leg blood flow (0.7 (0.5-0.8) to 4.4 (3.9-4.8) L min⁻¹ per leg; median (range); P<0.001) were similar with both pumping modes. Normally middle cerebral artery mean flow velocity increases from ~50 to ~65 cm sec⁻¹ during exercise, but in LVAD patients with a constant pump speed it was low at rest (39±14 cm sec⁻¹) and remained unchanged during exercise, whereas in patients with increasing pump speed, it increased by 5.2±2.8 cm sec⁻¹ at 60 Watts (P<0.01).

Conclusions—With maximal exercise, the axial-flow LVAD supports near-normal increments in cardiac output and leg perfusion, but cerebral perfusion is poor. Increased pump speed augments cerebral perfusion during exercise.

Key Words: heart failure, cerebrovascular circulation, cardiac output, left ventricular assist device
Left ventricular assist device (LVAD) is superior to medical treatment for management of end-stage heart failure \(^1\), and patients with a LVAD have an actuarial survival rate of more than 70% at 18 months \(^2\). Although pulsatile and continuous flow LVADs are comparable with respect to resting cardiac output (CO) and exercise capacity \(^3\)-\(^6\), axial-flow LVAD is preferred to the pulsatile LVAD due to its longer life span, lower incidence of stroke, and similar or better performance in terms of improvement in quality of life and functional capacity \(^1,2,5\). A LVAD is used as a bridge to recovery or transplantation \(^7\), and increasingly as destination therapy making it important how well the LVAD serves the demands of a physically active life.

Pulsatile LVAD works in an automatic mode with the pulsating rate responding to an increase in pump filling, and by forwarding an increased venous return, thus providing for a substantial increase in CO during exercise \(^4\). In contrast, axial-flow LVAD usually works in a continuous mode with a fixed pump speed (\(\sim 9,000-10,000\) rpm) set from determinations of the highest delivery of blood from the left ventricle (LV) when the patient is resting. The fixed pump speed is chosen as the speed which is high enough to ensure effective unloading of the LV yet low enough to avoid excessive emptying of the ventricle resulting in arterial hypotensive episodes (“suction”) \(^8\). With a continuous (or axial) flow device an increase in CO is seen with increasing venous return even if the pump speed is fixed, but modeling studies have suggested that pump outflow can be further increased with increasing pump speed (increased rotary frequency) \(^9,10\) and we therefore considered that it might be an advantage if the continuous flow LVAD, like the pulsatile LVAD, increased pump speed during exercise. The initial increase in CO established following implantation of a fixed speed LVAD supports a continuous
improvement in exercise capacity and general re-conditioning of the patient. However, patients with a LVAD are still often working at the limits of their exercise capacity and even a small improvement in the ability to increase CO during exercise may be important since CO is the main determinant of maximal oxygen uptake in normal subjects.

Accordingly, we evaluated whether increased pump speed improves exercise capacity and if it elevates CO during exercise and improves perfusion of two important organs, i.e. the exercising legs and the brain. In addition, we assessed if LVAD pump speed can be increased without causing episodes of arterial hypotension (“suction”).

Methods

Eight end-stage heart failure patients provided with a HeartMate II 
LVAD (Thoratec Corp., CA), who had been clinically stable for more than four weeks prior to the study participated in the trial. The patients provided informed consent as approved by the Ethics Committee of Copenhagen (07-041) in accordance with the Helsinki declaration. The patients were treated with angiotensin-converting enzyme inhibitors (6/8 pts.), beta-blockers (8/8 pts.), spironolactone (8/8 pts.), and warfarin (8/8 pts.). The patients’ INR, normally maintained between 2.0 and 3.0, was kept between 2.0 and 2.2 on the study day to minimize the risk of bleeding in response to the invasive procedures. Exclusion criteria included LVAD implantation less than three months before the study, age < 18 yrs, and significant co-morbidities. The LVAD pump speed was adjusted using echocardiographic guidance no more than four weeks prior to the study, and the appropriateness of this setting was assured on the test day by increasing and decreasing this pump speed by 1000 rpm. Increasing pump speed did not change the LV diameter, but lowering pump speed provided
for an increase in the LV diameter.

**Study design**

The patients performed two progressive maximal exercise tests on the same day, i.e. one with a fixed pump speed and the other with the pump speed increased in parallel with the intensity of exercise. A paired randomization procedure resulted in four patients starting with exercise at constant pump speed, while the others started with exercise at increasing pump speed. Neither the patients nor the directly participating investigators were aware of the LVAD pump speed, since it was set by a nurse who was not otherwise involved in the study. When increased, the increment of the pump speed was 400 rpm per exercise stage. This specific increase in pump speed was chosen on the basis of patient-specific sensitivity in LV dimensions to increments in LVAD pump speed at rest and on changes needed to increase CO in model studies. The progressive exercise protocol included 30-Watt stages of 2 min on a modified semi-supine cycling ergometer at a pedaling rate of 60 rpm as dictated by a metronome with the first stage chosen to be 60 Watts. Perceived exertion was rated from 6 (easy) to 20 (strenuous). Before the first exercise protocol, patients were allowed a 30-min semi-supine rest, and the two maximal exercise protocols were separated by at least 60 min, in order for the patients to recover from the initial exercise test and to allow venous lactate concentrations to return to the resting value.

**Instrumentation and measurements**

Following local anesthesia (2% lidocaine) and guided by ultrasound and pressure tracings, a 5F Swan-Ganz catheter (Baxter Healthcare Corp., Irvine, CA) was placed in the
pulmonary artery via the right internal jugular vein. Central vascular pressures were referenced to atmospheric pressure via uni-flow pressure transducers (Baxter Healthcare Corp.) zeroed below the sternal angle and connected to a pressure monitoring system (Dialogue-2000; IBC-Danica, Copenhagen, Denmark). At each stage, the CO was determined in triplicate using boluses of ice-cooled 0.9% saline (Viridia CMS M1167/77A, Hewlett-Packard, Andover, MA). Three patients agreed to have right leg blood flow, primarily reflecting exercising skeletal muscle blood flow, determined. A catheter was inserted into the right femoral vein and the tip of the catheter was advanced to a position 2 cm proximal to the inguinal ligament. A thermistor (Edslab, T.D. Probe, 94-030-2.5F, Baxter A/S, Allerød, Denmark) was advanced 8 cm beyond the tip of the catheter and leg blood flow was measured by the constant infusion thermodilution technique. Briefly, venous and infusate temperatures were monitored before and during ice-cold saline infusion (10-15 sec) at a rate of 120 ml min\(^{-1}\) to establish a decrease in venous blood temperature of 0.6-2.0 °C. Resting blood flow measurements were performed at an infusion rate of ~30 ml min\(^{-1}\) for 30-45 sec. Infusate temperature (0-4 °C) was measured at the site of entry of the catheter (Edslab flow-through thermister). Venous blood temperature and saline infusate temperatures were recorded at a 400 Hz analog-to-digital sampling rate (Powerlab 16 s data acquisition system, Chart v4.13 software, ADInstruments, Sydney, Australia) onto the hard drive of a computer. Also, blood samples were obtained from both the femoral vein and the pulmonary artery during the last 30 sec before transition to the next exercise level, and immediately analyzed for oxygen content and lactate concentration (ABL-745, Radiometer Medical, Copenhagen, Denmark). Heart rate was determined by three-lead electrocardiography and arterial oxygen saturation.
(SaO₂) was monitored by pulse oximetry. Echocardiographic interrogation of the LV was performed at rest and at the end of each exercise stage (IE33 Ultrasound machine, Philips, Netherlands). LV dimensions were determined and fractional shortening calculated from end-systolic and end-diastolic 2D frames obtained in the parasternal long-axis window. We focused on mobility of the aortic valve and signs of suction (sudden reduction in LV size).

To determine cerebral perfusion, middle cerebral artery mean flow velocity (MCA Vₘₑᵃⁿ) was followed beat-to-beat by transcranial Doppler through the temporal ultrasound window with a 2-MHz probe (Multidop X, DWL, Sipplingen, Germany; Figure 1)¹⁹, ²⁰. After obtaining the optimal signal-to-noise ratio, the probe position was secured with a headband and adhesive probe ultrasonic gel (Tensive, Parker Laboratories, Orange, NJ). MCA Vₘₑᵃⁿ reflects cerebral blood flow if the arterial diameter remains constant, and changes in MCA pulsation relative to Vₘₑᵃⁿ were assessed by the pulsatility index ²⁰. For healthy resting human subjects MCA Vₘₑᵃⁿ is ³⁵¹ (range 36-55) cm s⁻¹ ²⁰. Cerebral tissue hemoglobin oxygen saturation of the frontal lobe (ScO₂) was determined by dual-wavelength near-infrared spectrophotometry with the sensor placed on the forehead above the frontal sinus (INVOS Cerebral Oximeter, Somanetics, Troy, MI). By spatial resolution, the INVOS spectrophotometer determines changes in the absorption of light at 808 and 750 nm and reports the ScO₂ with small or negligible influence from diploë and subcutaneous tissue ²¹. The normal resting value is ³⁷5 (range 59-91)%, and a clinically significant decrease in cerebral perfusion is associated with a decrease in ScO₂ of ³⁷10%-15%. ²¹-²³ Another optode was placed over the left rectus femoris muscle for detection of the exercising skeletal muscle oxygen saturation [SmO₂; normal resting value ³⁷~75 (range 70-87)]% ²¹-²³.
Statistical analysis

One-way analysis of variance for repeated measures was used to evaluate changes between and within conditions. Changes from rest to light exercise (60 Watts, considered to correspond to everyday living) and from rest to maximal exercise were analyzed. Paired data were compared with Holm-Sidak’s test if normally distributed and by Dunn’s test if this was not the case. Data are presented as mean ± SD or, if not normally distributed, as medians with range. A P-value < 0.05 was considered statistically significant. Pre-study values for changes in CO and exercise capacity for patients provided with a HeartMate device were not available and, accordingly, a calculation of statistical power was not performed.

Results

Baseline characteristics of the patients are presented in Table 1. The resting pump speed was 9,775 (range 9,400 – 10,200) rpm. The pump speed remained unchanged at the resting value in one exercise bout, and the pump speed was increased stepwise to a maximum of 11,500 (11,300-11,700) rpm [7 (16-21)%] in the other exercise bout. No patient was pacemaker-dependent for the increase in heart rate. With the fixed pump speed, the aortic valve was closed during the entire cardiac cycle in six patients, whereas two patients demonstrated intermittent opening of the valve without any detectable flow across the valve. No cases of LV suction, or any other potential adverse reactions, were noted during exercise, either with constant or with increasing pump speed. At the highest workload, patients expressed an exertion rate of 19 (19-20). Five patients were exhausted
after having completed four stages (150 Watts) and three patients after having completed five stages (180 Watts) without differences between exercise conditions. Exercise time was similar between conditions (698±270 sec for the increased pump speed vs. 700±300 sec for the constant pump speed; p=0.94).

Constant pump speed

*Light exercise (60 Watts)*

At rest the aortic valve was open in only two patients. The results documented normal flows and anaerobic metabolism (pH and lactate) during rest but a low cerebral perfusion with a MCA $V_{\text{mean}}$ of 39±14 cm sec$^{-1}$ (~80% of normal; Table 2). From rest to the first stage of exercise (60 Watts), the number of patients with aortic valve opening increased from two to five, but we did not observe any changes in LV dimensions or fractional shortening (Table 2). Systemic hemodynamics, CO, MCA $V_{\text{mean}}$, ScO$_2$, central venous pressure and LV diameters did not change from rest to 60 Watts (Table 2). Leg blood flow increased, whereas total central venous oxygen saturation and skeletal muscle saturation decreased (all p<0.05).

*Maximal exercise*

During maximal exercise, the aortic valve opened in seven patients, but LV dimensions and fractional shortening were unchanged (Table 2). From rest to maximal exercise, CO, heart rate, mean (all p<0.001) and systolic pulmonary artery pressures (p<0.01) increased (Figure 2; Table 2), whereas diastolic pulmonary artery pressure was unchanged. SaO$_2$ remained unchanged whereas venous pH decreased to 7.21 (7.17-7.24).
and venous lactate increased to 8.1 (7.3-8.4) mmol L⁻¹. Total central venous oxygen saturation decreased to 23 (20-29)%. Similarly leg blood flow increased to 4.4 (3.9-4.8) L min⁻¹ and rectus femoris SmO₂ decreased to 58 (47-68)%. MCA V_mean decreased (p<0.05) without affecting ScO₂. The pulsatility index increased two-fold (p<0.001).

**Increasing pump speed**

*Light exercise (60 Watts)*

At 60 Watts, CO reached a higher value with increasing pump speed compared to constant pump speed (8.7±0.6 vs. 8.1±1.1 L min⁻¹; p=0.051; Figure 2), and the MCA V_mean increased by 5.2±2.8 cm s⁻¹ (13% increase from rest; p<0.001 vs. rest and constant pump speed). Compared to rest, ScO₂ was reduced but by less than what is considered clinically meaningful. Changes to all other variables were similar to those seen during exercise with constant pump speed.

*Maximal exercise*

With increasing pump speed, MCA V_mean decreased to the resting value, but MCA V_mean was still significantly higher than the value attained with the fixed pump speed (Table 2). Compared to rest, ScO₂ was reduced but by less than what is considered clinically meaningful. Changes in all other variables were similar to those for the exercise condition with constant pump speed.

**Discussion**

This study examined CO and leg and cerebral perfusion in patients with systolic heart
failure supported by an axial-flow LVAD before and during strenuous dynamic exercise, and evaluated if increments in LVAD pump speed corresponding to the increase in exercise level might influence these blood flows. Even if the LVAD pump speed was constant at the level set at rest, CO and leg blood flow increased significantly during strenuous cycling exercise. Cerebral perfusion, however, was only ~80% of the perfusion observed in normal subjects at rest, and it did not increase with exercise. A moderate increase in LVAD pump speed during exercise was well tolerated by the patients, but did not improve exercise tolerance. The increase in pump speed, however, was associated with an elevated CO during light exercise, and perhaps more importantly with an improved cerebral perfusion: thus, the otherwise low cerebral perfusion now increased to a small extent with exercise.

A LVAD relieves the LV by continuously forwarding blood from the LV apex to the aorta, repositioning the otherwise up- and right-shifted LV pressure-volume loop towards normal values (i.e. a left- and downwards shift). We thus expected the increasing pump speed to shift the LV pressure-volume loop further down- and leftwards. Flow and pressure across the LVAD co-vary with pump speed along with influences from blood volume, blood viscosity, baroreflex adjustments, and LV contractility. In an axial-flow LVAD, pump flow (and if the aortic valve remains closed also the CO) is non-linearly related to pump speed. Model data suggest that an increment of 400 rpm above the pump speed already unloading the LV results in a ~400 mL min⁻¹ increase in trans-pump blood flow and hence CO. In line with these predictions, we did observe a ~400 mL min⁻¹ increase in CO from rest to the first stage of exercise with a 400 rpm increment in pump speed, and it is likely that further increments in pump speed would increase CO to a greater
extent. If further improvements are to be seen with exercise-related increments in LVAD pump speed, it is important to first demonstrate that moderate increments are possible without the risk of inadequate filling of the LV and arterial hypotension. With the chosen increments in pump speed, we did not observe any episodes of suction, and the echocardiography evaluation did not demonstrate any lowering in LV diameter. Accordingly, we consider that pump speed could be safely increased further.

The LVAD achieved significant increments in CO during exercise, even with the constant pump speed. Thus, with strenuous exercise and a fixed pump speed, CO increased by 9.0 L min⁻¹ (precisely corresponding to the increase in leg blood flow), and the 17% augmentation in LVAD pump speed did not provide any further increment in maximal CO or a further reduction in anaerobic metabolism (as shown by unchanged plasma pH and lactate levels). The increase in CO (to 8.1 and 13.6 L min⁻¹ at 90 and 150 Watts, respectively) remains far below what is seen in normal subjects (~19 L min⁻¹ at 145 Watts with a similar protocol) 26, but the changes in CO and lactate are not far from what is seen in heart failure patients with relatively better LV systolic function (LVEF 0.40; NYHA I-II; ~11 L min⁻¹ at 90 Watts) 27. We hypothesized that CO would increase to a greater extent with higher pump speed, but were unable to demonstrate such an elevation, possibly because CO had already been significantly increased by insertion of the HeartMate and because we routinely set a high resting pump speed (9,400-10,200 vs. 8,600-9,800 rpm reported in other patients 8). Unchanged LV diameters during exercise suggest that pump speed can be increased further, and we speculate that further increments in pump speed would translate into more pronounced elevations in CO compared to what was observed in our patients at 60 Watts. With augmented CO and cerebral perfusion, we speculated that
exercise tolerance would improve, but it did not. This demonstrates that the ability to improve cerebral perfusion is only one determinant of what limits exercise performance in patients with severe heart failure, who have already improved their exercise capacity considerably by having a LVAD inserted, and who are now capable of carrying out quite strenuous exercise. In healthy individuals, cardiopulmonary function plays an important role in exercise performance, whereas in patients with chronic heart failure the relationship is less clear. 

We used transcranial Doppler with insonation of the MCA to determine cerebral perfusion. Transcranial Doppler is a well validated measure of cerebral perfusion in normal subjects and heart failure patients, and the increase in pulsatile flow velocity with exercise intensity indicates that cerebral perfusion by transcranial Doppler is a valid measure of cerebral blood flow also in LVAD patients. In normal subjects, MCA $V_{\text{mean}}$ increases from ~50 to 65 cm sec$^{-1}$, and ScO$_2$ also tends to increase during dynamic exercise. In our patients, the LVAD secured a normal resting CO that allowed for a near-normal exercise tolerance, but cerebral perfusion was low even at rest, and it was negatively impacted by exercise when the LVAD pump speed was kept constant. On the other hand, cerebral perfusion was increased during light exercise, and although cerebral perfusion did not increase to levels reached in normal subjects at maximal exercise level, cerebral perfusion remained elevated with increasing pump speed.

The increase in cerebral perfusion with increasing pump speed is probably related to a small increment in CO perhaps in combination with an increase in arterial blood pressure. At rest, cerebral perfusion is autoregulated and influenced mainly by the arterial carbon dioxide tension, but during exercise cerebral perfusion is also related to CO.
demonstrated in normal subjects in response to beta1-blockade and in patients with heart failure or atrial fibrillation \textsuperscript{33-35}. Since the change in leg blood flow accounted for most, if not all, of the increase in CO, the improvement in cerebral perfusion induced by an augmentation of pump speed represents not only a redistribution of an elevated CO but perhaps also an elevation in arterial pressure. Simulation data \textsuperscript{14} suggest that in our patients, an increase in pump speed is associated with an increase in mean arterial pressure of \textasciitilde5 mmHg. It is likely that further increments in LVAD pump speed will increase CO and arterial pressure to the extent that cerebral perfusion can reach normal values and cerebral tissue oxygenation will increase, as is the case in normal subjects.

New generations of LVADs have focused on becoming mechanically simpler with trans-cutaneous delivery of energy, but this study supports also maintaining interest in improving automaticity of LVADs. To conform to the Frank-Starling law of the heart, pump speed should be increased in parallel with LV volume or filling pressure. While quite impressive values for resting and exercise-induced increments in CO and leg blood flow were seen with a constant LVAD pump speed, cerebral perfusion was low in comparison with what is seen in normal subjects. Although, we applied slightly higher pump speeds than the often reported 8,600-9,800 rpm \textsuperscript{8}, cerebral perfusion did not increase in response to exercise if the pump speed was kept constant. However, a further 17\% increase in LVAD pump speed with exercise provided for an increase and hence a partial normalization of an otherwise poor cerebral perfusion.
Acknowledgments

Heidi Kjeldgaard performed the randomization procedure and controlled the HeartMate II® console during the study.

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Disclosures

Finn Gustafsson reports consulting fees for Thoratec Inc. The remaining authors have no conflicts to disclose.
References


Table 1. Baseline characteristics of patients

<table>
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<tr>
<th>Subjects</th>
<th>Age</th>
<th>Sex</th>
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<th>Days with LVAD</th>
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</tbody>
</table>

Mean±SD 39±18 329±190 9775±311

LVAD, left ventricular assist device; DM, diabetes mellitus; RPM, revolutions per minute
Table 2. Middle cerebral artery mean velocity (MCA \( V_{\text{mean}} \)), frontal lobe oxygenation, cardiac output, heart rate, central venous pressures and left ventricle diameters for the periods of interest in the experimental and control exercise protocols

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>60 Watts</th>
<th>Maximal exercise</th>
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<tbody>
<tr>
<td><strong>Constant pump-speed (average 9,775 rpm)</strong></td>
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<tr>
<td>MCA ( V_{\text{mean}} ), cm sec(^{-1} )</td>
<td>41±12</td>
<td>41±13</td>
<td>37±12( \dagger )</td>
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<td>Cerebral pulsatility index</td>
<td>0.5±0.2</td>
<td>0.7±0.3</td>
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<td>Frontal lobe oxygenation, %</td>
<td>63±7</td>
<td>61±10</td>
<td>59±10</td>
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<td>Cardiac output, L min(^{-1} )</td>
<td>7.0±0.9</td>
<td>8.1±0.6</td>
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<td>Heart rate, bpm</td>
<td>75±12</td>
<td>85±9</td>
<td>129±24( ^* )</td>
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<td>Systolic pulmonary artery pressure, mmHg</td>
<td>24±9</td>
<td>33±15</td>
<td>40±14( ^* )</td>
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<tr>
<td>Diastolic pulmonary artery pressure, mmHg</td>
<td>14±7</td>
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<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>20±7</td>
<td>24±13</td>
<td>29±12( ^\dagger )</td>
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<td>LV end-diastolic diameter, mm</td>
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<td>Fractional shortening</td>
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</table>

|                         |            |            |                  |
| **Increasing pump-speed (+400 rpm per stage)** |            |            |                  |
| MCA \( V_{\text{mean}} \), cm sec\(^{-1} \) | 39±14      | 45±14\( ^* \) | 40±15\( ^\dagger \) |
| Cerebral pulsatility index | 0.5±0.2   | 0.7±0.3   | 1.1±0.7\( ^\dagger \) |
| Frontal lobe oxygenation, \% | 66±11      | 62±12\( ^\dagger \) | 59±12\( ^* \) |
| Cardiac output, L min\(^{-1} \) | 6.0±2.1    | 8.7±1.1\( ^\dagger \) | 12.1±3.6\( ^* \) |
| Heart rate, bpm          | 76±7       | 88±10     | 129±25\( ^* \) |
| Systolic pulmonary artery pressure, mmHg | 24±5      | 35±11     | 42±14\( ^* \) |
| Diastolic pulmonary artery pressure, mmHg | 11±8      | 14±11     | 16±14            |
| Mean pulmonary artery pressure, mmHg | 18±8      | 23±12     | 29±14\( ^* \) |
| LV end-diastolic diameter, mm | 59±9       | 59±10     | 59±11            |
| LV end-systolic diameter, mm | 53±10      | 54±7      | 53±10            |
Fractional shortening

<table>
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<tr>
<th></th>
<th>0.07±0.07</th>
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</table>

Data are mean±SD for normally distributed data. * p<0.001 vs. rest, † p<0.01 vs. rest, ‡ p<0.05 vs. rest, # p<0.05 vs. other exercise condition.
Figure Legends

**Figure 1.** Original recordings of the transcranial Doppler determined middle cerebral artery mean flow velocities in a resting normal subject (top panel), and two tracings from a heart failure patient provided with an axial-flow continuous left ventricular assist device (Heart Mate II®) representing rest and light exercise, respectively (middle and bottom panels). Note the appreciably lower absolute blood velocities encountered in the heart failure patient and the increase seen with exercise if the pump speed of the assist device is increased.

**Figure 2.** Changes in cardiac output, middle cerebral artery mean flow velocity (MCA $V_{mean}$), total central venous oxygen saturation, heart rate, leg blood flow, and skeletal muscle oxygen saturation in eight heart failure patients provided with an axial-flow continuous left ventricular assist device (HeartMate II®) during two maximal cycling exercise tests with fixed (mean 9,775 rpm; open circles) and constantly increasing left ventricular assist device pump speed (+400 rpm per stage; filled circles) performed on the same day.

The horizontal broken lines inserted in the cardiac output, total central venous oxygen saturation (Pawelczyk et al., 1992; reference #26) and MCA $V_{mean}$ (Jorgensen et al., 1992; reference #20) plots represent delta values seen during exercise in normal subjects. Plots are means ± standard error of mean. * $p<0.001$ vs. rest, † $p<0.05$ vs. rest, ‡ $p<0.01$ vs. other condition, § $p<0.05$ vs. other condition.
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