Central and Peripheral Blood Flow During Exercise With a Continuous-Flow Left Ventricular Assist Device 
Constant Versus Increasing Pump Speed: A Pilot Study

Patrice Brassard, PhD; Annette S. Jensen, MD; Nikolai Nordborg, PhD; Finn Gustafsson, MD, DMSc; Jacob E. Møller, MD, DMSc; Christian Hassager, MD, DMSc; Søren Boesgaard, MD, DMSc; Peter Bo Hansen, MD; Peter Skov Olsen, MD, DMSc; Kåre Sander, MD, DMSc; Niels H. Secher, MD, DMSc; Per Lav Madsen, MD, DMSc

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 2 incremental cycle exercise tests on the same day in 8 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 W, the elevation in CO was more pronounced with increased pump speed (8.7±0.6 versus 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 to 0.8) to 4.4 (3.9 to 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·s⁻¹ during exercise, but in LVAD patients with a constant pump speed it was low at rest (39±14 cm·s⁻¹) and remained unchanged during exercise, whereas in patients with increasing pump speed, it increased by 5.2±2.8 cm·s⁻¹ at 60 W (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. (Circ Heart Fail. 2011;4:554-560.)

Key Words: heart failure ■ cerebrovascular circulation ■ cardiac output ■ left ventricular assist device

The left ventricular assist device (LVAD) is superior to medical treatment for management of end-stage heart failure,¹ and patients with an 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 because of its longer life span, lower incidence of stroke, and similar or better performance in terms of improvement in quality of life and functional capacity.¹²⁵ An LVAD is used as a bridge to recovery or transplantation⁷ and increasingly as a destination therapy, making it important how well the LVAD serves the demands of a physically active life.

Clinical Perspective on p 560

The 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.⁸ In contrast, axial-flow LVAD usually works in a continuous mode with a fixed pump speed (=9000 to 10000 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 that 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 after implantation of a fixed-speed LVAD supports a continuous improvement in exercise capacity and general reconditioning of the patient. However, patients with an 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 because 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 2 important organs, that is, 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 patients with end-stage heart failure provided with a HeartMate II LVAD (Thoratec Corp, Pleasanton, CA), who had been clinically stable for more than 4 weeks before 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 patients), β-blockers (8/8 patients), spironolactone (8/8 patients), and warfarin (8/8 patients). 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. Exclusion criteria included INR below 2.0 on the study day to minimize the risk of bleeding. 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.

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Study Design

The patients performed 2 progressive maximal exercise tests on the day of the study. Exertion was rated from 6 (easy) to 20 (strenuous). Before the first exercise test, the patients performed a 30-W stage of 2 minutes on a modified semisupine cycling ergometer at a pedaling rate of 60 rpm. Increasing pump speed did not change the LV diameter, but lowering pump speed provided for an increase in the LV diameter.

Instrumentation and Measurements

After administration of 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 through the right internal jugular vein. Central vascular pressures were referenced to atmospheric pressure through 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 to 15 seconds) at a rate of 120 mL·min⁻¹ to establish a decrease in venous blood temperature of 0.6° to 2.0°C. Resting blood flow measurements were performed at an infusion rate of ~30 mL·min⁻¹ for 30 to 45 seconds. Infusate temperature (0° to 4°C) was measured at the site of entry of the catheter (EdsLab flow-through thermistor). Venous blood temperature and saline temperatures were recorded at a 400-Hz analog-to-digital sampling rate (Powerlab 16 s data acquisition system, Chart v4.13 software, AD Instruments, 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 seconds 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 3-lead ECG, and arterial oxygen saturation (SaO₂) was monitored by pulse oximetry.

To determine cerebral perfusion, middle cerebral artery mean flow velocity (MCAVmean) was followed beat-to-beat by transtemporal Doppler through the temporal ultrasound window with a 2-MHz probe (Multidop X, DWL, Sipplingen, Germany; Figure 1). After obtaining the optimal signal-to-noise ratio and saline injection was secured with a headband and adhesive probe ultrasonic gel (Tensive, Parker Laboratories, Orange, NJ). MCAVmean reflects cerebral blood flow if the arterial diameter remains constant, and changes in MCA pulsation relative to Vmean were assessed by the pulsatility index. For healthy resting human subjects, MCAVmean is ~51 cm·s⁻¹ (range, 36 to 55 cm·s⁻¹). 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. The normal resting value is ~75% (range, 59% to 91%), and a clinically significant decrease in cerebral perfusion is associated with a decrease in ScO₂ of 10% to 15%. Another optode was placed over the left rectus femoris muscle for detection of the exercising skeletal muscle oxygen saturation (SmO₂; normal resting value ~75%; range, 70% to 87%).

Statistical Analysis

One-way ANOVA for repeated measures was used to evaluate changes between and within conditions. Changes from rest to light exercise (60 W, considered to correspond to everyday living) and from rest to maximal exercise were analyzed. Paired data were compared with the Holm-Sidak test if normally distributed and by Dunn test if this was not the case. Data are presented as mean±SD or, if not normally distributed, as medians with ranges. A probability value of <0.05 was considered statistically significant. Prestudy 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 9775 rpm (range, 9400 to 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 rpm (11 300 to 11 700 rpm; 17% [16% to 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 6 patients, whereas 2 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 work load, patients expressed an exertion rate of 19–20. Five patients were exhausted after having completed 4 stages (150 W) and 3 patients after having completed 5 stages (180 W) without differences between exercise conditions. Exercise time was similar between conditions (698 ± 270 seconds for the increased pump speed versus 700 ± 300 seconds for the constant pump speed; P=0.94).

Constant Pump Speed

Light Exercise (60 W)

At rest, the aortic valve was open in only 2 patients. The results documented normal flows and anaerobic metabolism (pH and lactate) during rest but a low cerebral perfusion, with an MCAV_mean of 39 ± 14 cm · s⁻¹ (=80% of normal; Table 2). From rest to the first stage of exercise (60 W), the number of patients with aortic valve opening increased from 2 to 5, but we did not observe any changes in LV dimensions or fractional shortening (Table 2). Systemic hemodynamics, CO, MCAV_mean, ScO₂, central venous pressure, and LV diameters did not change from rest to 60 W (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 7 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 and Table 2), whereas diastolic pulmonary artery pressure was unchanged. SaO₂ remained unchanged, whereas venous pH decreased to 7.21 (7.17 to 7.24) and venous lactate increased to

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<th>Subjects</th>
<th>Age</th>
<th>Sex</th>
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Mean±SD 39±18 . . . 329±190 . . . 9775±311

LVAD indicates left ventricular assist device; DM, diabetes mellitus; and rpm, revolutions per minute.
MCAVmean indicates middle cerebral artery mean velocity. Data are mean±SD for normally distributed data.

*P<0.001 versus rest, †P<0.01 versus rest, ‡P<0.05 versus rest, §P<0.05 versus other exercise condition.

8.1±1.1 L·min⁻¹; P=0.051; Figure 2), and the MCAVmean increased by 5.2±2.8 cm·s⁻¹ (13% increase from rest; P<0.001 versus rest and constant pump speed). Compared with rest, ScO₂ was reduced but by less than what is considered clinically meaningful. Changes in all other variables were similar to those seen during exercise with constant pump speed.

Maximal Exercise
With increasing pump speed, MCAVmean decreased to the resting value, but MCAVmean was still significantly higher than the value attained with the fixed pump speed (Table 2). Compared with 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.

An 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 toward normal values (ie, a left and downward shift). We thus expected the increasing pump speed to shift the LV pressure-volume loop further down and leftward. Flow and pressure across the LVAD covary 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 nonlinearly 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 transpump 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 echocardi-
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 (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 W, respectively) remains far below what is seen in normal subjects (19 L·min⁻¹ at 145 W with a similar protocol), but the changes in CO and lactate are not far from what is seen in patients with heart failure with relatively better LV systolic function.

Figure 2. Changes in cardiac output, middle cerebral artery mean flow velocity (MCAV_{mean}), total central venous oxygen saturation, heart rate, leg blood flow, and skeletal muscle oxygen saturation in 8 patients with heart failure who were provided with an axial-flow continuous left ventricular assist device (HeartMate II) during 2 maximal cycling exercise tests with fixed (mean, 9775 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 MCAV_{mean} (Jorgensen et al, 1992; Reference 20) plots represent delta values seen during exercise in normal subjects. Plots are mean±SEM. *P<0.001 versus rest, †P<0.05 versus rest, ‡P<0.01 versus other condition, §P<0.05 versus other condition.

Oography evaluation did not demonstrate any lowering in LV diameter. Accordingly, we consider that pump speed could be safely increased further.
demonstrated in normal subjects in response to 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.28,29

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 patients with heart failure,10,28,29 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, MCAVmean increases from ≈50 to 65 cm s⁻¹,20,30 and ScO₂ 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,6 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,32 as demonstrated in normal subjects in response to β₁-blockade and in patients with heart failure or atrial fibrillation.33–35 Because 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 suggest that in our patients, an increase in pump speed is associated with an increase in mean arterial pressure of ≈5 mm Hg. 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 transcutaneous 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. Although 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 8600 to 9800 rpm,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.

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

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Disclosures

Dr Gustafsson received consulting fees from Thoratec Inc.

References


**CLINICAL PERSPECTIVE**

The present study shows that patients with end-stage heart failure provided with an axial-flow left ventricular assist device have significant increases in cardiac output and leg blood flow even during strenuous cycling but that cerebral perfusion is compromised. In these patients, cerebral perfusion at rest is only ~80% of what is seen in normal subjects. During exercise, cerebral perfusion decreases, whereas normal subjects show a substantial elevation in cerebral perfusion. In a randomized fashion, with patients being their own controls, we evaluated the effect of increasing left ventricular assist device pump speed in parallel with exercise and found that increased pump speed increased cardiac output during light exercise and improved cerebral perfusion. Although not achieving normalization of cerebral perfusion, the latter nonetheless increased during exercise as seen in normal subjects. In light of these pilot results, we think that it might be advantageous during exercise to increase the pump speed of continuous flow left ventricular assist devices.
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