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iCONCEPTS

TECHNOLOGY ON THE VERGE OF TRANSLATION

Hemodynamic Stress Echocardiography in Patients Supported With a Continuous-Flow Left Ventricular Assist Device

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Functional assessment of continuous-flow left ventricular assist devices (LVADs) is usually performed with the patient at rest. This study compared echocardiographic indices of contraction and filling pressure with invasive measures in 12 ambulatory LVAD patients undergoing symptom-limited bicycle exercise. Exercise induced an increase in cardiac output, systolic pulmonary artery pressure, and diastolic pulmonary artery pressure. Although no changes in left ventricular dimensions or fractional shortening were seen on echocardiography, systolic mitral annular motion (S′) increased significantly (in parallel with cardiac output) and diastolic E/e′ ratio decreased (correlating inversely with diastolic pulmonary artery pressure). These findings emphasize the potential role of exercise echocardiography in studying exercise hemodynamics in LVAD patients. (J Am Coll Cardiol Img 2010;3:854–9) © 2010 by the American College of Cardiology Foundation

Mechanical circulatory support has evolved to be an important therapy in the treatment of severe heart failure, either as bridge to heart transplantation in those with severe symptoms despite maximal therapy, as definitive therapy in selected patients not eligible for transplantation, or as a bridge to recovery in very selected patients in whom pharmacological therapy and left ventricular (LV) unloading restores myocardial function (1). The new generation of left ventricular assist devices (LVADs) provides a continuous flow, resulting in little or no pulsatile flow in the systemic circulation. This has created new challenges for the optimal observation and management of these patients. Echocardiography is often used to detect complications, adjust pump speed, and monitor these patients. However, little is known about the physiological response to exercise and the association between conventional echocardiographic measures of LV function and invasive hemodynamics in patients on mechanical circulatory support. The purpose of this study was to describe the physiological

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response to exercise in patients with continuous-flow LVADs assessed simultaneously with right heart catheterization and exercise echocardiography.

Methods

Patients. We studied 12 patients older than 18 years of age with a history of severe heart failure in whom a HeartMate II (Thoratec, Pleasanton, California) continuous-flow LVAD had been implanted at least 2 months before enrollment in this study. All patients were in stable condition, and all were ambulatory patients. Patients with active infection or bleeding and those who had required inotropic support within 30 days were not eligible. All subjects signed informed consent. The study was approved by the Ethics Committee for Region Hovedstaden.

Resting protocol. Before exercise, a resting study was performed at the pump speed that was judged optimal for the individual patient. Subsequently, a decrease and an increase in pump speed by 1,000 revolutions per minute (RPM) from baseline were performed. At each pump speed, echocardiographic images and invasive measurements were repeated (Fig. 1).

Exercise protocol. All 12 patients performed a multistage symptom-limited supine bicycle exercise test using a modified Krogh bicycle. Load was increased every 2 min by 0.5 kg corresponding to 30 W, and the initial load was 60 W. A 3-lead electrocardiogram continuously monitored each patient. Patients were encouraged to exercise maximally, and perceived exertion was monitored using the Borg scale. The test was interrupted if the subject experienced severe symptoms of angina, significant ventricular arrhythmia, or dizziness. Patients' medications, including β-blockers, were not withheld during the study. Echocardiographic and invasive measurements were recorded for this study at rest, at submaximal exercise (90 W), and immediately before the test was stopped (maximal exercise) (Fig. 1).

Invasive measurements. Right heart catheterization was performed using a 7.5-F triple-lumen Swan-Ganz thermistor and balloon-tipped catheter (Edwards Lifesciences, Irvine, California) introduced under local anesthesia via the right internal jugular vein and advanced to the proximal pulmonary artery. At rest, submaximal and maximal exercise systolic, diastolic, and mean pulmonary artery pressures (PAP) were recorded. Cardiac output (CO) was measured at the previously described exercise stages using the thermodilution method. A central venous blood sample was drawn at rest and at submaximal and maximal exercise and analyzed for lactate concentration, oxygen saturation, and pH.

Echocardiography. All patients underwent 2-dimensional and Doppler echocardiographic examinations by an experienced echocardiographer using a Philips iE33 (Philips Healthcare, Best, the Netherlands) cardiac ultrasound system. Images were stored digitally for offline analysis using Phillips Xcelera analysis software version 1.2 (Philips Healthcare). The analyses were performed blinded to all invasive measurements.

From the parasternal long-axis window, LV dimensions and fractional shortening were measured; and systolic opening of the aortic valve and severity of aortic regurgitation were noted. From the best achievable apical 4-chamber view avoiding the inlet of the LVAD, mitral inflow was recorded using pulsed-wave Doppler. The Doppler sample volume was placed between the tips of the mitral leaflets during diastole. From the inflow profile, peak E and peak A wave velocity and mitral deceleration time were measured. In case of fusion of the E and A waves, the peak velocity of the fused wave was recorded as peak E wave velocity. Tissue Doppler images were performed in the apical 4-chamber view. With a Doppler sample volume placed in the septal and lateral mitral annulus, pulsed-wave tissue Doppler images were acquired. From the images, tissue Doppler peak systolic velocity S′, peak early diastolic e′, and late a′ velocity were measured. In case of fusion of the e′ and a′ waves, the maximal diastolic velocity was considered e′ (2). All Doppler recordings were performed with a horizontal sweep of 75 cm/s and a mean of 3 consecutive beats was measured and averaged.

Measurement of skeletal muscle blood flow. In 3 patients, right leg blood flow, primarily reflecting exercising skeletal muscle blood flow, was evaluated. A catheter (20-gauge; Baxter Healthcare Corp., Deerfield, Illinois) 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. The catheter was used both for blood flow measurements, which was determined by measuring the decrease in venous blood temperature during a constant infusion of ice-cooled 0.9% saline solution by the use of a thermistor inserted in the catheter and advanced to a position 8 to 10 cm proximal to the tip of the catheter.

ABBREVIATIONS AND ACRONYMS

CO = cardiac output
LV = left ventricular
LVAD = left ventricular assist device
PAP = pulmonary artery pressure
PVR = pulmonary vascular resistance

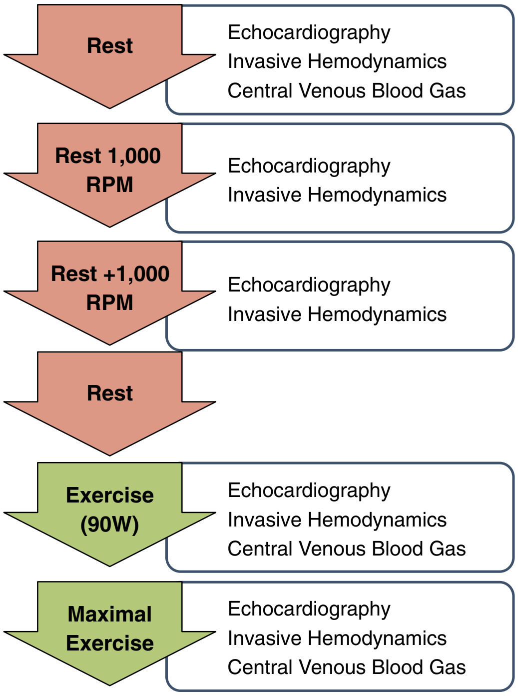

Figure 1. Schematic Presentation of the Study Protocol

All patients underwent a symptom-limited bicycle exercise test with simultaneous assessment of central hemodynamics using a Swan-Ganz catheter and Doppler echocardiography. At rest, echocardiography and invasive measurements were repeated with an increase and decrease of 1,000 revolutions per minute (RPM) on the continuous-flow left ventricular assist device.

Statistical analyses. Data are presented as mean ± SD or range. Exercise-induced changes in hemodynamic and echocardiographic variables were tested with a paired-sample *t* test with a Bonferroni correction to adjust for multiple comparisons and repeated-measure analysis of variance. Bivariate correlations between variables were assessed with Pearson correlation coefficient. A p value <0.05 was considered significant. Analyses were performed using SPSS version 17.0 software (SPSS, Inc., Chicago, Illinois).

Table 1. Patient Characteristics

Variable	
Age, yrs (range)	38 (20–65)
Male sex, no. (%)	10 (83)
Nonischemic cardiomyopathy, no. (%)	9 (75)
Ischemic cardiomyopathy, no. (%)	3 (25)
Diabetes, no. (%)	0 (0)
Glomerular filtration rate, ml/min/1.73 m^2, ± SD	68 ± 17
Pre-operative CO, l/min, ± SD	3.6 ± 1.0
Pre-operative CI, l/min/m^2, ± SD	1.7 ± 0.9
Pre-operative PCWP, mm Hg, ± SD	30 ± 6
Pre-operative PVR, Wood units, ± SD	2.4 ± 1.2
Duration of LV assist, days (range)	299 (62–634)
Pump speed, RPM (range)	9,711 (9,200–10,200)

CI = cardiac input; CO = cardiac output; LV = left ventricular; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RPM = revolutions per minute.

Results

The characteristics of the study population are presented in Table 1. Continuous-flow LVAD was intended as bridge to transplantation in 11 and as destination therapy in 1 patient. In 3 patients (25%), the heart failure etiology was ischemic; in 7 (58%), it was nonischemic dilated cardiomyopathy; and in 2 (17%), it was antracycline-induced cardiomyopathy.

Resting hemodynamics and LV function. Mean resting pump speed was 9,711 RPM (range 9,200 to 10,200 RPM). At this speed, aortic valve closure was present during the entire cardiac cycle in 10 patients (83%), whereas 2 had intermittent opening with no detectable flow across the valve with pulsed-wave Doppler. With an increase in pump speed of 1,000 RPM, no significant increase in CO or change in diastolic PAP was seen (Fig. 2). In addition, echocardiographic determined S′ and diastolic E/e′ ratio (Fig. 2), LV end-diastolic diameter (60 ± 10 mm vs. 58 ± 12 mm, p = 0.39) and fractional shortening remained unchanged. No cases of ventricular suction were seen during the increase in pump speed. With a decrease in pump speed of 1,000 RPM, CO, diastolic PAP, S′, and E/e′ remained unchanged (Fig. 2). However, the LV end-diastolic diameter increased (60 ± 10 mm vs. 62 ± 10 mm, p = 0.01), and the proportion of patients with aortic valve opening increased from 16% to 66% (p = 0.05).

Exercise hemodynamics and LV function. In all cases, the test was terminated by the patient due to dyspnea and fatigue (Borg scale score >18). The mean maximal workload was 6.5 METs (range 5.1 to 8.7 METs). During exercise, significant decreases in central venous oxygen saturation and pH and an increase in lactate were seen (Table 2). With submaximal (90 W) and maximal exercise, the proportion of patients with aortic valve opening increased (rest, 2 patients [16%]; submaximal, 8 patients [66%], p = 0.05; maximal, 10 patients [83%], p = 0.01). With exercise, a significant increase in CO was seen at submaximal and maximal exercise (Fig. 2 and Table 2). In addition, the systolic, diastolic, and mean PAPs increased (Fig. 2 and Table 2). Despite significant changes in CO,

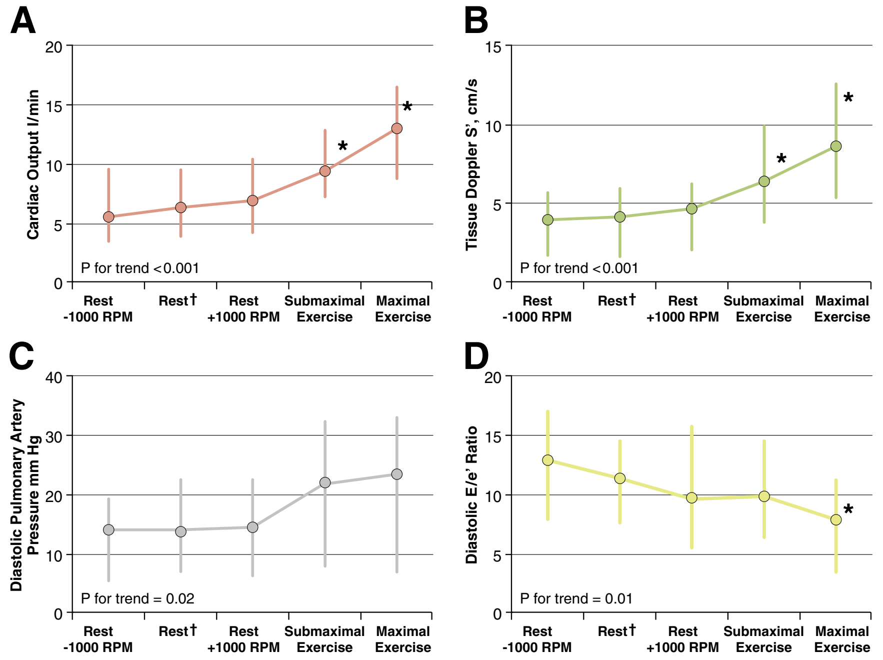

Figure 2. **Invasively Assessed and Doppler Estimates of Contraction and Filling Pressure at Rest and Exercise**

Cardiac output **(A)**, tissue Doppler–assessed systolic annular motion **(B)**, diastolic pulmonary artery pressure **(C)**, and diastolic E/e′ ratio **(D)**. Data are mean and range. *$p < 0.05$ by a paired *t* test with a Bonferroni correction compared with values at rest (†).

no changes in LV dimensions or fractional shortening were seen (Table 2). In contrast, S′ increased significantly with exercise (Figs. 2 and 3). The diastolic E/e′ ratio was decreased during exercise, in particular due to a significant increase in mitral E-wave velocity (Table 2). With exercise, a marked increase in skeletal muscle blood flow was seen at rest (0.7 [0.5 to 0.8] l/min) to peak exercise (4.4 [3.9 to 4.8] l/min).

Association between invasive and noninvasive parameters. At rest ($r = 0.41$) and at peak exercise ($r = 0.61$), CO demonstrated a positive correlation with S′. The E/e′ ratio demonstrated a positive correlation with diastolic PAP at rest ($r = 0.39$), whereas

Table 2. **Changes With Exercise in Invasive Hemodynamic and Echocardiographic Variables**

Variable	Rest	Submaximal Exercise	Maximal Exercise	p Value for Trend
Cardiac output, l/min	6.3 ± 2.2	9.4 ± 2.2*	13.0 ± 3.0*	<0.001
Systolic PAP, mm Hg	25 ± 7	39 ± 12*	43 ± 10*	<0.001
Diastolic PAP, mm Hg	14 ± 5	21 ± 9	23 ± 9	0.02
Mean PAP, mm Hg	19 ± 6	29 ± 10	33 ± 9*	0.009
Heart rate, beats/min	73 ± 8	109 ± 19*	131 ± 23*	<0.001
SvO_2, %	64 ± 5	38 ± 6*	31 ± 9*	<0.001
pH	7.36 ± 0.03	7.27 ± 0.03*	7.20 ± 0.08*	<0.001
Lactate, mmol/l	0.9 ± 0.4	4.3 ± 0.7*	8.5 ± 2.7*	<0.001
LVEDD, mm	60 ± 10	61 ± 10	60 ± 10	0.70
LVESD, mm	55 ± 11	53 ± 10	54 ± 10	0.49
Fractional shortening	0.09 ± 0.06	0.12 ± 0.08	0.10 ± 0.09	0.19
S′, cm/s	4.1 ± 1.3	6.4 ± 2.7	8.7 ± 3.7*	0.007
E′, cm/s	7.4 ± 2.4	10 ± 4	13.4 ± 4.5*	0.005
Mitral E, cm/s	81 ± 22	94 ± 21	99 ± 24	0.06
E/e′ ratio	11.2 ± 2.5	9.8 ± 3.0	7.8 ± 1.7*	0.01

*$p < 0.05$ compared with resting by paired *t* test with a Bonferroni correction. Values shown are ± SD.
LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; PAP = pulmonary artery pressure; SvO_2 = venous oxygen saturation.

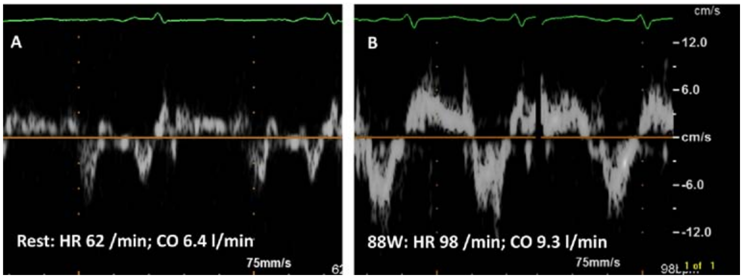

Figure 3. **Pulsed Wave Tissue Doppler Recordings From Septal Mitral Annulus**

Representative tissue Doppler example of change in systolic and diastolic annular motion at rest **(A)** and during submaximal exercise **(B)**. CO = cardiac output; HR = heart rate.

the correlation at peak exercise was negative (r = −0.69).

Discussion

The HeartMate II system consists of a small, fully implantable rotary pump that connects to the circulatory system through an apical cannula through which blood is pumped by an impeller from the apex of the left ventricle to an outflow cannula anastomosed to the ascending aorta. Continuous-flow LVADs work in a continuous mode with a fixed pump speed, with delivery of blood from the left ventricle to the circulation with little pulsatility. Although the device is equipped with a negative feedback mechanism lowering the pump speed in case of excessive emptying of the LV (suction), the device does not adjust the speed in response to increased LV filling induced by increased delivery of blood from the right ventricle. In vivo, the pressure across the pump will depend on the pressure developed with cardiac contraction, preload, and afterload (3). In most circumstances, the aortic valve remains closed during the entire cardiac cycle at rest, but an increase in pressure is seen at the pump inlet during systole, followed during diastole by the inlet pressure decreasing to its lowest level. This will cause a change in the pressure across the pump, which in turn will cause corresponding fluctuations of flow delivered to the aorta (3). The response in healthy subjects and patients with heart failure to exercise is a decrease in systemic vascular resistance (4). This exercise-induced vasodilation is closely linked with decreased muscle tissue oxygen tension and accumulation of lactate and is mediated by a decreased response to adrenergic vasoconstrictor mechanisms. Although blood pressure was not directly measured, we consider that the increase in CO, increased skeletal muscle blood flow with exercise, and increase in (S)-lactate indirectly suggest peripheral vasodilation and decreased vascular resistance. Therefore, with a lowered systemic vascular resistance and increased preload (increased diastolic PAP), the pressure difference across the pump will favor an increased flow across the pump with exercise. However, there was likely also a contribution to CO during exercise by the native heart, as evidenced by the increase in aortic valve opening. In addition, systolic annular motion assessed with tissue Doppler increased significantly with exercise. Using this method, the Doppler signal will reflect the movement of myocardium parallel with the Doppler cursor. Because the apex of the LV is relatively fixed throughout the cardiac cycle and the motion of the LV base is nearly parallel with the long axis, assessment of the movement of the basal LV segments reflects the longitudinal vector of contraction and relaxation. Therefore, the increase in S′ could imply increased contractility of predominantly longitudinally oriented myocardial fibers. Although this was not accompanied by a concomitant increase in fractional shortening (a function of radially oriented myocardial fibers), the observed increase in S′ paralleled the increase in CO. Consequently, the combination of maintained preload, assumed lower afterload, increased heart rate, and increased myocardial contractility all facilitate increased CO, both through the system and across the aortic valve.

Early diastolic mitral annulus velocity (e′) is a useful indicator of LV relaxation. Invasive studies have demonstrated that e′ correlates inversely with invasive indices of relaxation. In the presence of low (<0.1 m/s) velocities, e′ is less affected by changes in preload than many other Doppler indices of LV filling. Using the ratio of peak mitral E-wave velocity to early mitral annulus velocity (E/e′), numerous studies have demonstrated a good approximation of LV filling pressures also in the presence of sinus tachycardia, in which an increase in E/e′ suggests an increase in left atrial pressure (2). This relationship has been validated during exercise in patients with dyspnea and patients with suspected ischemic heart disease undergoing cardiac catheterization (5). These studies have suggested in patients with normal filling pressure that E and e′ will increase proportionally, leaving E/e′ ratio unchanged, whereas in patients with an increase in filling pressure during exercise, a disproportional increase in E relative to e′ will occur, causing an increase in E/e′ ratio. In the present study, we did not see an increase in E/e′ despite a significant increase in diastolic PAP; rather, an inverse association was seen. Overall we found that both E and e′ increased with exercise, although e′ increased relatively more. The reason for this is not apparent from the present study but may be related to the increased systolic mitral annular motion. In addition, it is often difficult to align the Doppler cursor with the long axis of the left ventricle in patients with an LVAD because the apical cannula often interferes with image acquisition. Accordingly, the tissue Doppler velocities may not reflect true longitudinal dynamics. Although the within-subject changes in Doppler parameters are less affected by these issues, and this may help explain the differences in tissue Doppler indices in the native heart and the unloaded heart with a continuous-flow LVAD. Thus, in patients with mechanical circulatory support, current guidelines for assessment of filling pressure based on diastolic E/e′ ratio do not seem to apply.

Study limitations. The present data must be interpreted with caution given the small sample size, which increases the risk of a type II error, and the conclusions of the study must be regarded as hypothesis generating. We estimated LV filling pressure by measuring diastolic PAP rather than direct measurement of left atrial pressure. However, diastolic PAP correlates well at rest and during exercise with pulmonary capillary wedge pressure and left atrial pressure in patients with normal pulmonary arterial resistance, which was confirmed before implantation of an LVAD in all studied patients. Therefore, we consider alterations in diastolic PAP to be an acceptable surrogate for estimating changes in LV filling pressure. Measurement of brachial blood pressure is challenging, even at rest in patients with axial-flow LVAD and not feasible during exercise, and we chose not to have the patients with an arterial line in place perform exercise. Thus, the assumed decrease in systemic vascular resistance is based on observed increased leg blood flow in 3 patients and significantly increased prevalence of aortic valve opening with exercise.

Conclusions

The present study demonstrates a hemodynamic response to exercise in patients with continuous-flow LVADs characterized by a considerable increase in CO with little concomitant increase in filling pressure. When comparing invasive and noninvasive indexes, mitral annular systolic motion was associated with CO. We also found that diastolic E/e′ was associated with diastolic PAP. However, in contrast to patients without mechanical circulatory support, there was no correlation. Thus, current guidelines for noninvasive assessment of filling pressure using the diastolic E/e′ ratio does not apply in patients with continuous-flow LVADs.

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Key Words: echocardiography ■ exercise test ■ heart failure ■ left ventricular assist device.