Reduced Peak Aerobic Capacity in Asymptomatic Left Ventricular Systolic Dysfunction

A Substudy of the Studies of Left Ventricular Dysfunction (SOLVD)

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Background  Peak oxygen consumption is reduced in patients with symptomatic congestive heart failure, but functional capacity of patients with asymptomatic left ventricular systolic dysfunction has not been assessed by measurement of peak oxygen consumption attained during graded exercise testing.

Methods and Results  Peak oxygen consumption, that is, aerobic capacity (VO₂, mL/kg per minute), was determined during graded treadmill exercise using the modified Naughton protocol in 40 patients with left ventricular systolic dysfunction (mean ejection fraction ranging from 14% to 35%; mean, 29%) who, while not receiving any cardiac medications, were totally asymptomatic, and in 41 age-matched normal subjects. Peak exercise duration and VO₂ were significantly lower in patients with asymptomatic left ventricular systolic dysfunction than in normal subjects (948±273 versus 1239±372 seconds, P<.001, and 22.1±5.9 versus 29.8±7.7 mL/kg per minute, respectively, P<.001), while asymptomatic patients and normal subjects reached similar respiratory equivalents (1.14±0.11 versus 1.11±0.11 [NS]) and level of perceived exertion, using the modified Borg scale (7.4±2.6 versus 8.1±1.5 [NS]). Heart rate, systemic blood pressure, and oxygen pulse responses to peak exercise were significantly lower in asymptomatic patients than in normal subjects.

Conclusions  Although patients with left ventricular systolic dysfunction can be totally asymptomatic in their daily activities, they have experienced a substantial reduction in peak aerobic capacity when compared with normal subjects of similar age. (Circulation. 1994;90:2757-2760.)

Key Words:  oxygen • ventricles • systole • heart rate • respiration • exercise

The severity of left ventricular systolic dysfunction is known to be a strong predictor of mortality in patients with various cardiovascular disorders.1-3 While therapeutic trials have previously focused on the symptomatic phase of left ventricular systolic dysfunction, the asymptomatic phase is now receiving increasing attention.4-8 Neuroendocrine activation has been found to be present at the asymptomatic stage of left ventricular systolic dysfunction, but little is known concerning the peak functional capacity of these asymptomatic patients.9,10 Early studies in patients with congestive heart failure have demonstrated that resting indices of left ventricular performance do not correlate with peak aerobic capacity.11,12 The lack of correlation may be, in part, explained by abnormalities of the skeletal muscle metabolism and vasculature as well as skeletal muscle atrophy, which have been subsequently reported to limit peak aerobic capacity in patients with congestive heart failure.13,14 Patients with asymptomatic left ventricular systolic dysfunction are less likely to develop abnormalities of the skeletal muscle metabolism and vasculature than patients with congestive heart failure.15,16 To the contrary, peak aerobic capacity of patients with asymptomatic left ventricular systolic dysfunction is likely to be contingent on their level of physical conditioning.20 Nevertheless, depressed cardiac reserve could, overall, prevent patients with asymptomatic left ventricular systolic dysfunction from reaching a normal peak aerobic capacity for their age.

The Prevention Trial of the Studies of Left Ventricular Dysfunction (SOLVD),6 which recruited patients with left ventricular ejection fractions ≤35% and without a history of overt congestive heart failure, provided an opportunity to determine peak aerobic capacity in a large cohort of these patients. The majority of patients enrolled in the Prevention Trial of SOLVD were either receiving cardiovascular medications for reasons other than congestive heart failure and/or were unable to perform a graded maximal exercise test caused by angina pectoris or other incapacitating disease. Since both conditions can alter peak aerobic capacity, only patients totally free of symptoms and not receiving any cardiovascular medications were considered for the present study. Five SOLVD clinical centers measured peak aerobic capacity in these patients before random-
ization with the study medication enalapril and in normal age-matched subjects.

Methods

Patient Population

The patient population represents a subset of patients enrolled into the Prevention Trial of SOLVD in five participating centers. The overall inclusion and exclusion criteria for eligibility into the prevention arm of SOLVD have been described previously.6 Of the 160 patients enrolled into the exercise substudy of the Prevention Trial, 40 patients, who were totally free of symptoms while not taking any cardiovascular medications for any indications, were considered for the present study. All patients were identified during the routine follow-up of a myocardial infarction or by screening of the logs of the Echocardiography, Cardiac Catheterization, or Nuclear Medicine laboratories. None had symptoms of exertional fatigue, dyspnea, or angina during ordinary activities, nor did they limit their physical activity. All patients were deemed to be in functional class I according to the criteria of the New York Heart Association21 by both the referring physician and the SOLVD investigator at their clinical center. In addition, patients with clinical evidence or history of chronic obstructive lung disease, musculoskeletal abnormalities, and joint or symptomatic peripheral vascular disease were excluded from the study. None of the patients were smoking or consuming alcohol at the time of the study. Their hemoglobin concentration was within normal range. Left ventricular ejection fraction was assessed by either radionuclide or contrast ventriculography or by two-dimensional echocardiography using Simpson’s rule. Thirty-eight men and 2 women were studied. Their age averaged 56±10 years. Mean body weight was 80±10 kg. Left ventricular ejection fraction averaged 29±5%. Left ventricular systolic dysfunction was thought to be secondary to coronary artery disease in 32 patients and secondary to idiopathic dilated cardiomyopathy in the remaining 8 patients. None of the patients with coronary artery disease had angina at the time of the study, and none complained of chest pain or discomfort during exercise testing. All patients were in sinus rhythm.

The normal subjects were selected from volunteers at each of the five participating centers on the basis of age and sex. Thirty-five normal men and 6 normal women were studied. Their ages averaged 59±7 years. All normal subjects were free of history of hypertension (arterial blood pressure ≥140/90 mm Hg), exertional dyspnea or chest discomfort, claudication, syncope, palpitation, or peripheral edema. They did not smoke or drink alcohol socially. All patients underwent a physical examination that was normal, had a normal 12-lead ECG, and were not receiving cardiovascular medications at the time of the study. Left ventricular ejection fraction obtained by two-dimensional echocardiography averaged 59±5%. Routine hematology and biochemistry tests were normal. The larger number of women in the normal group (15%) compared with the group of asymptomatic patients with depressed left ventricular ejection fraction (5%) was not statistically significant. The study was approved by the Human Review Board at each participating center.

Exercise Testing

Maximal graded exercise testing was performed on a treadmill using a modified Naughton protocol. After a rest period of 2 minutes, exercise was started at 1 mph at 0° grade. Two minutes later, the speed was increased to 1.5 mph, still at 0° grade. Subsequently, treadmill speed and/or grade were increased every 2 minutes. Exercise was discontinued when the imposed workload could not be maintained by the normal subjects or the patients. Subjective assessment of perceived exertion was obtained every minute and at maximal exercise using the modified Borg scale (0 to 10 scale). ECG, which was continuously monitored, did not show any electrical evidence of ischemia during and after graded treadmill exercise in normal subjects or in patients. Systemic arterial blood pressure was measured by cuff plethysmography at rest, every 2 minutes during exercise, and at maximal exercise. Maximal graded exercise testing was performed once normal subjects and patients had been fully familiarized on a separate day with the apparatus. In patients with ischemic heart disease, maximal exercise testing was not carried out until 12 weeks after an acute coronary event.

Measurement of Expired Gas

In all five centers, expired gas was continuously determined during maximal exercise testing using either a Medical Graphics System 2001 or a Sensor Medics 4400. These metabolic carts were calibrated immediately before each exercise test.

Raw ventilatory and gas exchange parameters were stored on floppy discs and analyzed for the measured and derived variables, which included time, VO₂, production of carbon dioxide (VCO₂), minute ventilation (VE), end-tidal Po₂ (PETO₂), ventilatory equivalents of O₂ and CO₂ (Ve/VO₂, Ve/VCO₂), exercise duration, workload, and respiratory equivalent (VCO₂/VO₂). Data were sent to the exercise Substudy Core Laboratory at the University of Rochester Medical Center for determination of peak VO₂ and V̇E at anaerobic threshold and for ensuring appropriate uniformity of maximal exercise testing. Peak VO₂ was determined as the highest VO₂ achieved during exercise. Patients were considered to have reached maximum VO₂ when VO₂ increased ≤1 mL/kg per minute over that attained at the previous workload.22 Ventilatory anaerobic threshold was determined as the point where the ventilatory equivalent of O₂, that is, Ve/V̇O₂, increases, which is associated with an increase in PETO₂ and change in slope of the V̇CO₂/V̇O₂ curve.23

Statistical Analysis

The data were kept and analyzed by the SOLVD Coordinating Center at the University of North Carolina at Chapel Hill. Results are given as mean±SD. The sample size computation for the normal control subjects was based on a power calculation using a two-sided t test at α=.05 and β=.10 (power=.90). A group of at least 40 normal subjects was required to detect an expected difference in exercise time of at least 250 seconds between normal subjects and asymptomatic patients with left ventricular systolic dysfunction, assuming a coefficient of variation of 30%. The statistical significance of difference between normal subjects and patients was determined using a two-way ANOVA.

Results

Normal Subjects

Eighteen of the 41 normal subjects reached maximum VO₂ and 23 did not because exhaustion prevented them from reaching maximum VO₂. All these 23 normal subjects reached a peak respiratory exchange ratio (RER) >1.0. Mean exercise duration and peak VO₂ were 1239±372 seconds and 29.8±7.7 mL/kg per minute, respectively, while peak perceived level of exertion and RER were 8.1±5.5 and 1.11±0.11, respectively. Mean VO₂ at anaerobic threshold was 23.2±6.0 mL/kg per minute. Heart rate increased from 78±11 beats per minute (bpm) at rest to 164±16 bpm at peak exercise (P<.001), as did systolic blood pressure from 126±22 to 183±22 mm Hg (P<.001). Oxygen pulse increased from 3.8±1.6 to 14.6±4.2 mL/beat (P<.001).

Asymptomatic Patients With Left Ventricular Systolic Dysfunction

Twenty-three of the 40 asymptomatic patients reached maximum VO₂ and 18 did not because fatigue
and/or dyspnea led them to stop exercising before reaching maximum \( \dot{V}O_2 \). All these 18 patients reached a peak RER >1.0. Mean exercise duration and peak \( \dot{V}O_2 \) were 948±273 seconds and 22.1±5.9 mL/kg per minute, respectively, while peak measured level of exertion and mean RER were 7.4±2.6 and 1.14±0.11, respectively. Mean \( \dot{V}O_2 \) at anaerobic threshold was 17.5±4.4 mL/kg per minute. Heart rate increased from 86±15 bpm at rest to 128±14 bpm at peak exercise (\( P<.001 \)); systolic blood pressure also increased, from 122±15 to 171±22 mm Hg (\( P<.001 \)). Oxygen pulse increased from 3.4±0.9 to 11.1±2.9 mL/beat (\( P<.001 \)). Left ventricular ejection fraction at rest did not correlate with peak \( \dot{V}O_2 \) or oxygen pulse (\( r=0.045 \) and .124, respectively).

These asymptomatic patients enrolled in the present study were followed up during the entire duration of the prevention trial of SOLVD, which averaged 808±181 days. During the entire period of follow-up, medical therapy for heart failure was initiated in only 3 of the 40 patients. The peak \( \dot{V}O_2 \) of the 37 patients who remained asymptomatic and received no cardiovascular agents for treatment of congestive heart failure was identical to those of the entire 40 patients (22.2±6.0 versus 22.1±5.9 mL/kg per minute).

**Asymptomatic Patients Versus Normal Subjects**

Peak \( \dot{V}O_2 \) attained by asymptomatic patients was significantly lower than that attained by normal subjects (Figure). Similarly, exercise duration was significantly lower (948±273 versus 1239±372 seconds, \( P<.001 \)). When only patients and normal subjects who reached a maximum \( \dot{V}O_2 \) were analyzed, maximum functional capacity was also substantially lower in patients than in normal subjects (21.8±5.8 versus 28.6±5.6 mL/kg per minute, respectively, \( P<.001 \)). Heart rate, systolic blood pressure, and oxygen pulse responses to exercise were significantly attenuated in asymptomatic patients when compared with normal subjects (\( P<.05 \)), while perceived levels of exertion and respiratory equivalent ratio attained by asymptomatic patients and normal subjects during exercise were similar.

**Discussion**

The present findings indicate that patients with moderate to severe left ventricular systolic dysfunction at rest, who nevertheless were completely asymptomatic, have already experienced a substantial reduction in peak aerobic capacity when compared with normal subjects of similar age. Although a greater number of women among normal subjects than among asymptomatic patients could have led to underestimating peak aerobic capacity in the former group, the findings were similar when only men were considered in asymptomatic patients and normal subjects (22.3±5.9 versus 30.9±7.7 mL/kg per minute). The peak \( \dot{V}O_2 \) of asymptomatic patients with left ventricular systolic dysfunction is halfway between that of age-matched normal subjects (30.9 mL/kg per minute) and severely symptomatic patients with congestive heart failure (<12 mL/kg per minute). The substantial reduction in peak aerobic capacity observed in asymptomatic patients resulting from both decreased heart rate and oxygen pulse responses to maximal exercise. During exercise, heart rate increased by 93% in asymptomatic patients with depressed ejection fraction and 119% in normal subjects, and oxygen pulses increased by 220% and 270%, respectively. The reduced increase in heart rate experienced by patients with congestive heart failure during exercise is secondary to abnormalities of the parasympathetic and sympathetic nervous system. The abnormalities of the sympathetic system appear to be due in part to postsynaptic desensitization of the \( \beta \)-adrenergic receptor pathway. The inability of the oxygen pulse to adequately increase during exercise in asymptomatic patients most probably reflects the lack of or minimal increase in stroke volume in patients. The importance of normal regulation of the stroke volume to reach maximal functional capacity has been pointed out by Higginbotham et al in normal humans. The lack of correlation between resting indices of left ventricular performance and peak aerobic capacity, which was previously reported in patients with congestive heart failure, may result in part from a dual limitation to exercise capacity. Patients with severe congestive heart failure appear to be predominantly limited by peripheral factors such as fixed vasodilatory response to exercise and/or abnormal skeletal muscle metabolism and not by central factors such as cardiac output response. Thus, at a late stage of congestive heart failure, resting indices of left ventricular performance are not expected to correlate with peak aerobic capacity. At the earlier stage of asymptomatic left ventricular systolic dysfunction, limited myocardial contractile reserve may substantially lower peak aerobic capacity. It cannot be determined from the present data to what extent physical conditioning may have offset the detrimental effect of reduced cardiac reserve on peak aerobic capacity in some patients. Similarly, whether abnormalities of the skeletal muscle vasculature and/or metabolism were present in other patients and, if present, whether they contributed to lower peak aerobic capacity, cannot be ascertained.

**Summary**

Although patients with left ventricular systolic dysfunction may be totally asymptomatic during the course of their daily activities, objective measurement of functional capacity reveals that their peak aerobic capacity is substantially lower than that of normal subjects of similar age.
References
Reduced peak aerobic capacity in asymptomatic left ventricular systolic dysfunction. A substudy of the studies of left ventricular dysfunction (SOLVD). SOLVD Investigator. Studies of Left Ventricular Dysfunction.

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