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Exercise Intolerance in Patients With Heart Failure and Preserved Left Ventricular Systolic Function: Failure of the Frank-Starling Mechanism

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Invasive cardiopulmonary exercise testing was performed in 7 patients who presented with congestive heart failure, normal left ventricular ejection fraction and no significant coronary or valvular heart disease and in 10 age-matched normal subjects. Compared with the normal subjects, patients demonstrated severe exercise intolerance with a 48% reduction in peak oxygen consumption (11.6 ± 4.0 versus 22.7 ± 6.1 ml/kg per min; $p < 0.001$), primarily due to a 41% reduction in peak cardiac index (4.2 ± 1.4 versus 7.1 ± 1.1 liters/min per m^2; $p < 0.001$).

In patients compared with normal subjects, peak left ventricular stroke volume index (34 ± 9 versus 46 ± 7 ml/min per m^2; $p < 0.01$) and end-diastolic volume index (56 ± 14 versus 68 ± 12 ml/min per m^2; $p < 0.08$) were reduced, whereas peak ejection fraction and end-systolic volume index were not different. In patients, the change in end-diastolic volume index during exercise correlated strongly with the change in stroke volume index ($r = 0.97$; $p < 0.0001$) and cardiac index ($r = 0.80$; $p < 0.03$).

Pulmonary wedge pressure was markedly increased at peak exercise in patients compared with normal subjects (25.7 ± 9.1 versus 7.1 ± 4.4 mm Hg; $p < 0.0001$). Patients demonstrated a shift of the left ventricular end-diastolic pressure-volume relation upward and to the left at rest. Increases in left ventricular filling pressure during exercise were not accompanied by increases in end-diastolic volume, indicating a limitation to left ventricular filling.

These data suggest that abnormalities in left ventricular diastolic function limited the patients' ability to augment stroke volume by means of the Frank-Starling mechanism, resulting in severe exercise intolerance. These findings provide a pathophysiologic rationale for symptoms of chronic fatigue and dyspnea on exertion, which are often present in patients with a history of congestive heart failure and preserved systolic function.

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Recent studies (1–7) have demonstrated that congestive heart failure can occur in patients with preserved indexes of left ventricular systolic function, even in the absence of coronary and valvular heart disease. This syndrome may account for >30% of cases of congestive heart failure (4,5,8–10), is often unrecognized (5,9–11) and may have diagnostic, prognostic and therapeutic implications distinct from those of heart failure associated with systolic dysfunction (3,5,7,10,12–14).

Patients with this syndrome often have chronic symptoms of easy fatigability and dyspnea on exertion (1,5,10,15,16), similar to those of patients with heart failure associated with systolic dysfunction. Although previous studies demonstrating abnormal noninvasive variables of left ventricular diastolic filling (1,4,11) and normal left ventricular ejection fraction (5,9) measured at rest support the hypothesis that heart failure in patients with this syndrome is due to left ventricular diastolic dysfunction, the pathophysiology of exertional symptoms in these patients is unknown. Invasive hemodynamic studies (17–20) during exercise have been useful in defining the mechanisms of exercise limitation and monitoring the results of interventions in patients with heart failure due to systolic dysfunction; however, similar techniques have not been applied to patients with heart failure and preserved systolic function.

The present study characterizes the left ventricular pressure/volume response and mechanisms of exercise intolerance in seven patients with congestive heart failure, normal ejection fraction and no significant coronary or valvular heart disease using invasive cardiopulmonary exercise test-

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Table 1. Clinical Characteristics of Seven Patients

Pt No.	Age (yr)/ Gender	Disease	P Edema	CA	EF (%)	MR	PWT (cm)	VST (cm)	LVM (g/m^2)
1	74/M	HTN	+	RCA, 25%	52	1+	1.0	1.1	126
2	81/F	HTN	+	RCA, 25%, LAD, 25%	56	1+	1.9	1.7	137
3	72/F	HTN	−	RCA, 25%, LAD, 50%	58	1+	1.1	1.0	71
4	58/M	HTN	+	NL	60	0	1.4	0.6	133
5	46/M	HCM	+	NL	52	0	1.4	1.9	72
6	67/F	HCM	+	NL	62	0	1.1	1.4	100
7	55/F	Amyloid	+	NL	64	0	1.6	1.6	111

CA = coronary artery anatomy, % stenosis; EF = left ventricular ejection fraction; F = female; LAD = left anterior descending coronary artery; LVM = left ventricular mass index on echocardiography; M = male; MR = degree of mitral regurgitation on contrast ventriculography; NL = normal; P Edema = pulmonary edema; Pt = patient; PWT, VST = left ventricular posterior wall and ventricular septal thickness on echocardiography; RCA = right coronary artery; + = present; − = absent.

ing combined with radionuclide ventriculography. The patients had a variety of disorders thought to predispose to diastolic dysfunction but shared a common pathophysiology. Ten age- and gender-matched healthy volunteers underwent an identical study protocol to serve as a normal control group.

Methods

Patient selection. From April 1986 to April 1988, seven patients who had had at least one episode of clinically and radiographically documented pulmonary edema or severe chronic heart failure (New York Heart Association functional class III or IV) were referred for clinical evaluation to the cardiopulmonary exercise laboratory at Duke University Medical Center. All patients underwent cardiac catheterization after the onset of symptoms showing a normal left ventricular ejection fraction (≥50%) on biplane radiocontrast ventriculography and no significant coronary artery disease on arteriography. No patient had clinical or echocardiographic evidence of myocardial infarction, valvular dysfunction or pericardial disease or spirometric evidence of pulmonary disease.

Ten healthy community-dwelling volunteers were recruited to serve as normal control subjects. All subjects had a normal history, physical examination, spirometry and rest and maximal exercise electrocardiogram (ECG). The subjects were closely matched to the patients for age (61 ± 8 versus 65 ± 12 years; $p = 0.44$), gender (four women in each group), weight (74.3 ± 10.1 versus 71.3 ± 13.8 kg; $p = 0.62$) and body surface area (1.85 ± 0.14 versus 1.77 ± 0.20 m^2; $p = 0.28$).

Patient characteristics (Table 1). Patients 1 to 4 had moderate to severe chronic (>5 years) systemic hypertension. Patients 5 and 6 had hypertrophic cardiomyopathy with disproportionate septal thickening and systolic anterior motion of the mitral valve on two-dimensional echocardiography. Patient 5 had no demonstrable left ventricular outflow tract gradient at rest or with provocation at cardiac catheterization and no gradient during vigorous bicycle exercise by pulsed wave Doppler echocardiography. Patient 6 had no gradient at rest, but had a maximal gradient of 85 mm Hg after amyl nitrite inhalation and did not have a Doppler examination during exercise. Patient 7 had endomyocardial biopsy-proved cardiac amyloidosis. Patients 3 and 5 also had type 2 diabetes mellitus controlled with an oral hypoglycemic agent.

Six of seven patients presented with acute pulmonary edema and all patients had chronic, severe exertional fatigue and dyspnea. At coronary angiography, four patients had normal coronary arteries. Three patients had insignificant coronary artery lesions and after intravenous ergonovine (0.3 mg) showed no evidence of focal coronary artery spasm. Furthermore, none of these three patients had ECG ST segment shifts or radionuclide ventriculographic wall motion abnormalities during exercise. Three patients had mild mitral regurgitation on radiocontrast ventriculography. All patients were in normal sinus rhythm.

Five of the patients had increased left ventricular wall thickness (>1.1 cm) on echocardiography and four had ECG criteria for left ventricular hypertrophy (21). Echocardiographic left ventricular mass index, measured by methods previously described (22), was increased in the patients compared with 23 age- and gender-matched normal subjects in our laboratory (107 ± 27 versus 79 ± 14 g/m^2; $p < 0.01$).

Study protocol. Normal subjects were studied under research protocols approved by the institutional review boards of the Duke University and the Durham Veterans Administration Medical Centers on March 7, 1986 and November 11, 1987, respectively, and written informed consent was obtained from all participants. Patients were studied after resolution of pulmonary edema in a baseline compensated nonedematous state. No patient was taking digoxin and all

cardioactive medications and diuretic drugs were discontinued the day before testing.

Patients and normal subjects were studied under identical laboratory conditions in the postabsorptive state. After administration of a local anesthetic, a 7F Swan-Ganz catheter was introduced under fluoroscopic control into the right pulmonary artery through the right antecubital vein and a plastic cannula was introduced percutaneously into the left brachial artery. Exercise testing was performed in the upright position on a Fitron isokinetic bicycle (Lumex). The work load was begun at 150 kpm/min and was advanced by 150 kpm/min increments in 3 min stages until exhaustion.

Gas exchange, hemodynamic and radionuclide measurements were simultaneously obtained at rest in the sitting position and then at each work load, as previously described by our laboratory (17,18,23). Continuous expired gas analysis was performed with a commercially available Sensormedics 4400 unit that was calibrated before each study, as previously described (17). Pulmonary capillary wedge and systemic arterial pressures were obtained with Hewlett-Packard pressure transducers and amplifiers and recorded as previously described (17,23). Blood samples were obtained at rest and in the last minute of each exercise stage and were immediately placed in an ice bath. Oxygen content and saturation of arterial and mixed venous blood samples were measured on a calibrated Instruments Laboratories 282 CO-Oximeter. Arterial lactate concentration was determined with a Calbiochem-Behring rapid lactate kit.

Gated equilibrium radionuclide ventriculograms were acquired at rest and at each work load with a Searle LEM mobile gamma camera with a high sensitivity 30° slant-hole collimator interfaced with an A^2 computer (Medical Data Systems) after injection of technetium 99-m pertechnetate (30 mCi), as previously described (23).

Derived variables. Cardiac output was determined by the Fick principle for oxygen and was indexed to body surface area. Left ventricular end-diastolic volume index (EDVI) and end-diastolic volume index (ESVI) were calculated from the Fick stroke volume index (SVI) and the radionuclide ejection fraction (LVEF), as previously described (20,23), according to the formulas: EDVI = SVI/LVEF and ESVI = EDVI − SVI.

Statistics. Intergroup comparisons were performed using the unpaired *t* test. Linear regression analyses were performed using the least-squares method to determine the relation of the increase in oxygen consumption, cardiac index and stroke volume index from rest to peak exercise to other measured variables. Significance was established at the level of $p < 0.05$ (two-tailed analysis). Data are presented as mean values ± 1 SD.

Results

Exercise end points. Patients exhibited marked exercise intolerance, as indicated by a reduction in peak work load compared with normal subjects (407 ± 143 versus 705 ± 174 kpm/min; $p < 0.01$) and this corresponded to a 48% reduction in peak oxygen consumption (11.6 ± 4.0 versus 22.7 ± 6.1 ml/kg per min; $p < 0.001$). Oxygen consumption (VO_2) was similar at the submaximal work loads (150 and 300 kpm/min) (Fig. 1). In all patients and normal subjects, exercise was limited primarily by leg fatigue, although dyspnea was also frequently reported at peak exercise. The peak respiratory exchange ratio during bicycle exercise was not different in patients compared with normal subjects (1.24 ± 0.15 versus 1.33 ± 0.16; $p = 0.24$), suggesting a near maximal exercise effort in both groups. Arterial lactate concentration increased from 0.5 ± 0.3 mmol/liter at rest to 3.7 ± 2.8 mmol/liter at peak exercise in patients and from 0.5 ± 0.4 to 7.2 ± 2.0 mmol/liter in normal subjects. During submaximal exercise at 300 kpm/min, lactate concentration tended to be increased in patients compared with normal subjects (2.2 ± 1.1 versus 1.4 ± 0.7 mmol/liter; $p < 0.07$).

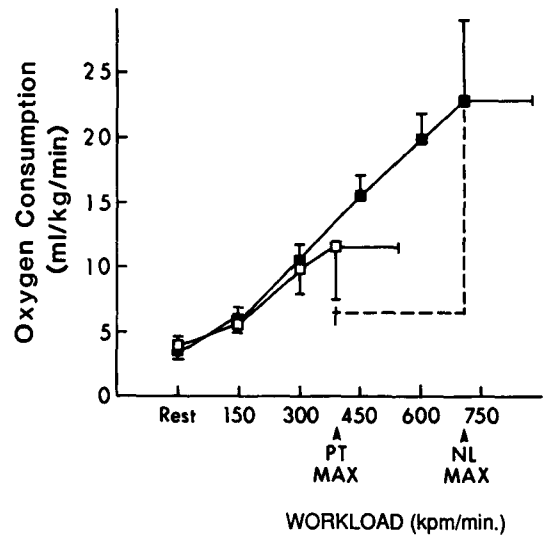


Figure 1. Plot of rest and exercise oxygen consumption in 7 patients (PT) (□) and 10 normal (NL) subjects (■); †$p < 0.01$ by Student's unpaired *t* test. MAX = maximal work load.

Determinants of oxygen consumption (Fig. 2). The components of the Fick equation were examined to determine the mechanism of the reduction in peak exercise oxygen consumption (VO_2) in patients compared with normal subjects. At rest, there was no difference in cardiac index, central arteriovenous oxygen difference, stroke volume index or heart rate between the two groups. However, during exercise, several abnormalities became apparent in patients. Compared with normal subjects, cardiac index was significantly reduced at comparable submaximal work loads and was markedly reduced by 41% at peak exercise (4.2 ± 1.4 versus 7.1 ± 1.1 liters/min per m^2; $p < 0.001$), proportionate to the reduction in peak VO_2 (Fig. 2A). Central arteriovenous oxygen difference was increased by approximately 10% in patients during the submaximal exercise workloads, partially compensating for the reduced cardiac index (Fig. 2B). At peak exercise, arteriovenous oxygen difference was reduced by 13% compared with normal subjects (11.1 ± 1.6

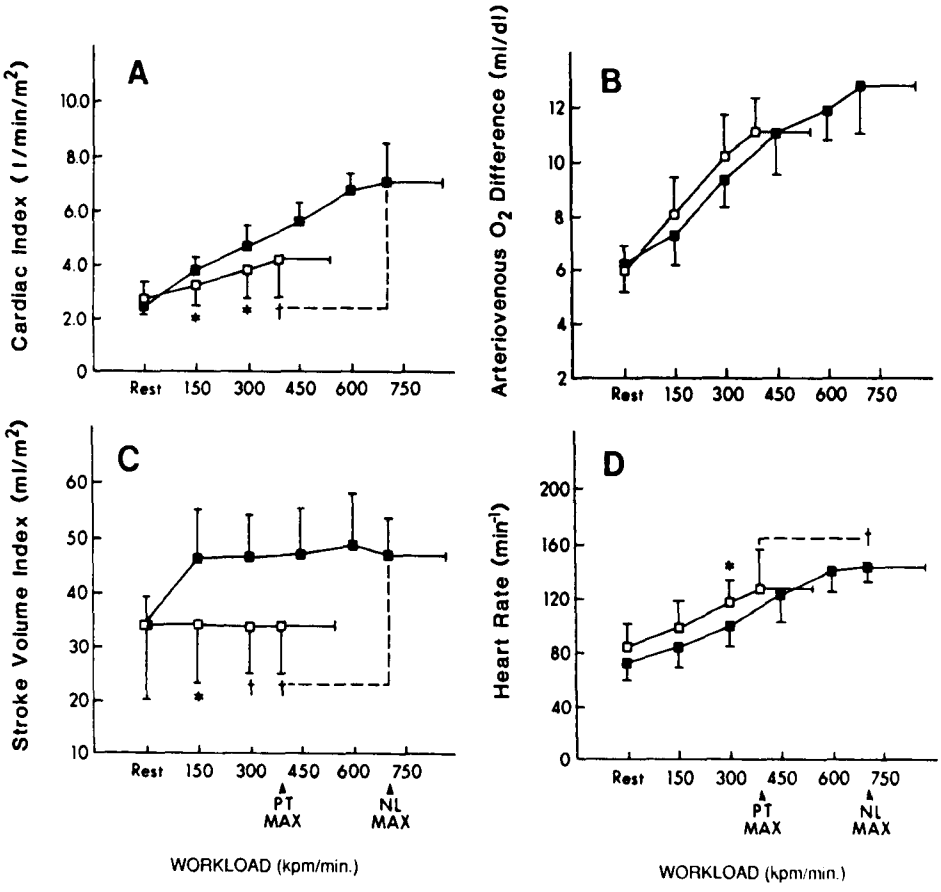


Figure 2. Plot of rest and exercise cardiac index (**A**), arteriovenous oxygen (O_2) difference (**B**), stroke volume index (**C**) and heart rate (**D**) in patients (□) and normal subjects (■); *p < 0.05, †p < 0.01 by Student's unpaired *t* test. Abbreviations as in Figure 1.

versus 12.7 ± 1.8 ml/dl; p = 0.08). In patients, the change in cardiac index from rest to peak exercise correlated closely with the increase in VO_2 during exercise (r = 0.81; p < 0.03), but the change in arteriovenous oxygen difference did not (r = 0.34; p = 0.43).

Stroke volume index was reduced in patients compared with normal subjects during submaximal exercise and was markedly reduced by 26% at peak exercise (34 ± 9 versus 46 ± 7 ml/min per m^2; p < 0.01) (Fig. 2C). In contrast to the increase in stroke volume index during low levels of exercise followed by a plateau observed in normal subjects, a flat stroke volume response was observed in patients. In patients versus normal subjects, heart rate was slightly increased during submaximal exercise, but was reduced by 18% at peak exercise (126 ± 27 versus 154 ± 11 min^{-1}; p < 0.01) (Fig. 2D). In patients, the change in stroke volume index from rest to peak exercise correlated closely (r = 0.86; p < 0.01) and the change in heart rate correlated modestly (r = 0.60; p = 0.14) with the increase in cardiac index during exercise. Thus, in patients at peak exercise, reduced stroke volume index was the primary factor responsible for reduced cardiac index, and reduced peak cardiac index was the primary factor responsible for the 48% reduction in peak VO_2.

Determinants of abnormal stroke volume response (Fig. 3). The rest and exercise ejection fraction in patients were not different from those of the normal subjects (Fig. 3A). In all patients and normal subjects at rest and peak exercise, left ventricular ejection fraction was >50% and there were no wall motion abnormalities. In patients, the change in ejection fraction from rest to peak exercise was not significantly different from that of normal subjects (1.1 ± 9.9% versus 6.0 ± 8.9% units; p = 0.32) and correlated only modestly with the increase in stroke volume index during exercise (r = 0.60; p = 0.12). End-systolic volume index at rest and during exercise was not different from that of normal subjects (peak 22 ± 8 versus 23 ± 9 ml/min per m^2; p = 0.81), confirming that left ventricular systolic emptying in patients was within normal limits (Fig. 3B). In contrast, end-diastolic volume index was reduced during submaximal exercise in patients compared with normal subjects and at peak exercise (peak 56 ± 14 versus 68 ± 12 ml/min per m^2; p < 0.08); this resulted in an abnormal flattened curve that was similar to the abnormal stroke volume response (Fig. 3C). In patients, the change in end-diastolic volume index from rest to peak exercise correlated strongly with the change in stroke volume index (r = 0.97; p < 0.0001) and cardiac index (r = 0.80; p < 0.03) during exercise.

Pulmonary wedge pressure was mildly increased in patients compared with normal subjects at rest (10 ± 6 versus 3 ± 3 mm Hg; p < 0.02) and became markedly elevated during exercise (peak 25.7 ± 9.1 versus 7.1 ± 4.4 mm Hg; p < 0.0001) (Fig. 3D). In patients, the change in pulmonary wedge pressure from rest to peak exercise did not correlate significantly with the change in stroke volume index (r = 0.45; p = 0.16) or the increase in oxygen consumption (r =

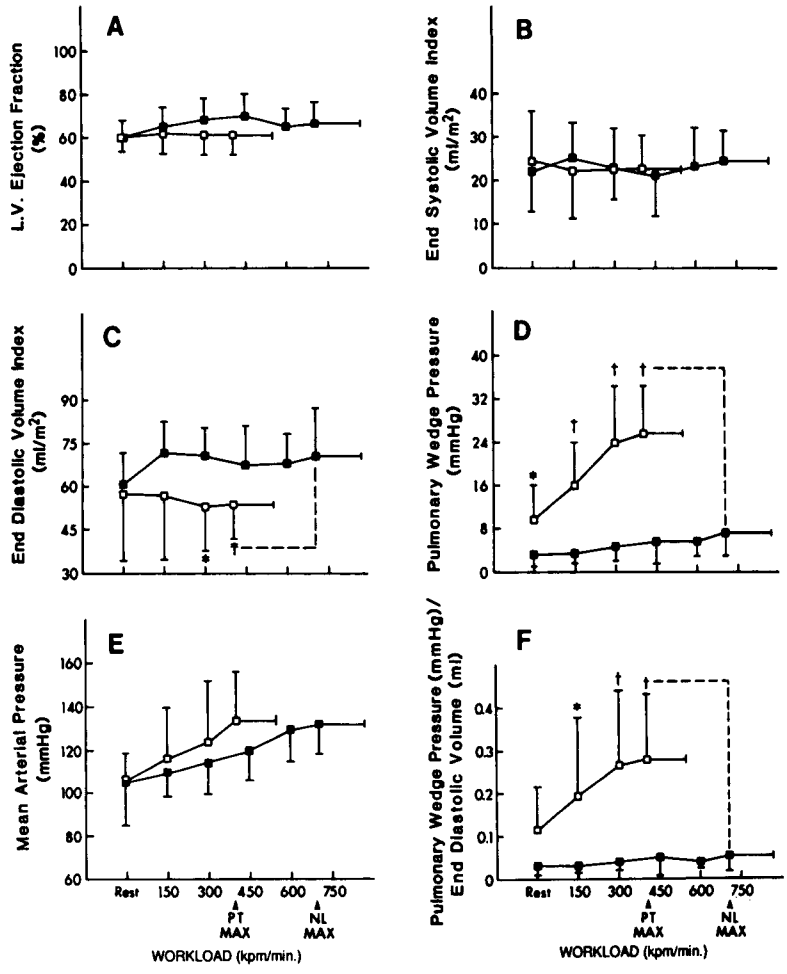
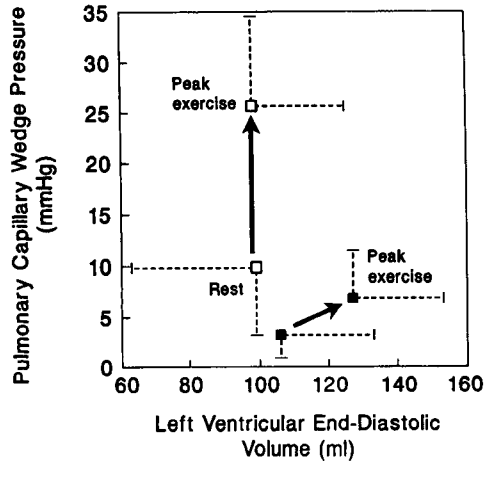


Figure 3. Plot of rest and exercise left ventricular (L.V.) ejection fraction (**A**), end-systolic volume index (**B**), end-diastolic volume index (**C**), pulmonary wedge pressure (**D**), mean arterial pressure (**E**) and left ventricular diastolic pressure-volume relation (**F**) in patients (□) and normal subjects (■); *p < 0.05, †p < 0.01, ‡p = 0.08 by Student's unpaired *t* test. Abbreviations as in Figure 1.

0.03; p = 0.94) during exercise. Mean arterial pressure in patients was not different from that of normal subjects at rest or during exercise (Fig. 3E) and did not correlate with stroke volume index.

Abnormal diastolic pressure-volume relations (Fig. 4). Although at rest the left ventricular end-diastolic pressure-volume ratio tended to be elevated in patients compared with normal subjects (0.12 ± 0.11 versus 0.03 ± 0.03 mm Hg/ml; p = 0.07), this difference did not reach statistical significance (Fig. 3F). However, during exercise, this ratio became markedly elevated in patients compared with normal subjects (peak 0.28 ± 0.15 versus 0.06 ± 0.05 mm Hg/ml; p < 0.0001). The abnormal left ventricular end-diastolic pressure-volume relation demonstrated by patients is further illustrated in Figure 4. At rest, there was a shift upward and to the left in patients compared with normal subjects. During exercise, the disparity between the two groups increased further. In contrast to the approximately linear increase in end-diastolic volume and pulmonary wedge pressure in normal subjects, progressive increases in pulmonary wedge pressure in patients were not accompanied by increases in end-diastolic volume, suggesting a limitation to left ventricular filling. In patients, left ventricular mass index did not correlate with this relation at rest or with the change from rest to peak exercise.

Figure 4. Plot of pulmonary capillary wedge pressure versus left ventricular end-diastolic volume indicating the directional change from rest to peak exercise in patients (□) and normal subjects (■).



Discussion

Principal findings. This study provides new insights concerning the pathophysiologic basis of symptoms of exertion intolerance in patients with chronic heart failure, preserved left ventricular systolic function and no significant coronary

or valvular heart disease. After achievement of clinical compensation, the only hemodynamic abnormality noted in these patients at rest was a mild increase in pulmonary wedge pressure. However, exercise testing revealed marked hemodynamic abnormalities and severe exercise intolerance. Markedly reduced peak oxygen consumption (VO_2) in patients resulted from a proportionate reduction in cardiac output, primarily due to failure of left ventricular stroke volume to increase. The reduced stroke volume response in turn resulted from a fixed end-diastolic volume despite markedly elevated left ventricular filling pressure and reduced heart rate; ejection fraction and end-systolic volume, indexes of systolic function, were maintained. The inability to augment stroke volume by means of the Frank-Starling mechanism was accompanied by a shift of the left ventricular end-diastolic pressure-volume relation upward and to the left during exercise. These data suggest that exercise tolerance was reduced primarily because of abnormalities of diastolic function that limited left ventricular filling and consequently reduced the stroke volume response to exercise.

Relation of exercise hemodynamics to symptoms. It is widely accepted that peak oxygen consumption (VO_2), an objective measure of exercise capacity, is related to symptoms in patients with heart failure. The Fick equation defines the relation of cardiac output (CO) and arteriovenous oxygen difference (AVO_2) to VO_2 during exercise:

$$VO_2 = CO \times AVO_2.$$

This can also be expressed using left ventricular stroke volume (SV), heart rate (HR), ejection fraction (EF) and end-diastolic volume (EDV) as follows:

$$VO_2 = SV \times HR \times AVO_2$$

$$VO_2 = EDV \times EF \times HR \times AVO_2.$$

During bicycle exercise in the upright position in normal subjects, cardiac output increases linearly with VO_2 as a result of increases in both stroke volume and heart rate (19,23). Stroke volume increases as a result of an increase in end-diastolic volume by means of the Frank-Starling mechanism and as a result of increased contractility reflected by an increase in ejection fraction (23–25). During upright bicycle exercise in normal subjects, increases in end-diastolic volume occur with small increases in pulmonary wedge pressure (23). In the present study, peak stroke volume was reduced in patients despite normal left ventricular ejection fraction, an exaggerated increase in pulmonary wedge pressure and reduced peak heart rate due to a relative inability to use the Frank-Starling mechanism.

The stroke volume response curve of normal subjects in this study conformed to that described during upright bicycle exercise in previous studies of normal subjects in this laboratory (23,26), with an increase in stroke volume early during exercise and maintenance thereafter. In contrast, patients had a flat stroke volume response and this was reflected in a similarly flat end-diastolic volume response. Accordingly, stroke volume index, end-diastolic volume index and cardiac index were reduced during submaximal as well as at peak exercise. These data emphasize the importance of increases in end-diastolic volume in the normal stroke volume response to exercise.

Heart rate at peak exercise was reduced in patients compared with normal subjects. This phenomenon has also been observed in patients with heart failure due to left ventricular systolic dysfunction (27). Although a contribution of reduced heart rate to patients' reduced cardiac index at peak exercise cannot be excluded, the primary role of reduced stroke volume is further supported by two additional considerations. First, left ventricular stroke volume and end-diastolic volume tend to be inversely related to heart rate (28), such that it cannot be certain that a higher peak heart rate would have resulted in a higher peak cardiac index. Second, reduced cardiac index during submaximal work loads in patients was solely due to reduced stroke volume because heart rate was increased, rather than reduced, during these work loads.

Causes of symptoms in diastolic heart failure. As previously noted (1,5,10,15,16), all patients in the present study had chronic symptoms of exertional fatigue and dyspnea, similar to those found in patients with heart failure due to systolic dysfunction (17). Although there is controversy regarding the cause of symptoms that limit exercise tolerance in patients with heart failure, recent studies in patients with heart failure due to systolic dysfunction from this laboratory (19,20) and others (29) suggest that early anaerobic metabolism due to decreased skeletal muscle perfusion rather than increased pulmonary wedge pressure plays the predominant role in causing symptoms that limit exercise tolerance. Although the basis for exercise intolerance in patients in the present study is not defined with certainty by the available data, several findings suggest that early anaerobic metabolism due to decreased skeletal muscle blood flow may have been responsible: exercise in all patients was limited primarily by leg fatigue, submaximal lactate concentration tended to be increased and the increase in pulmonary wedge pressure did not correlate with the increase in oxygen consumption (VO_2) during exercise. A recent study (30) in patients with hypertrophic cardiomyopathy also found no correlation of pulmonary wedge pressure with peak VO_2.

Most previous studies of diastolic heart failure have inferred that symptoms of congestive heart failure in patients were due to diastolic dysfunction on the basis of abnormal noninvasive variables of diastolic filling (1,4,11) or a normal left ventricular ejection fraction (5,9) measured at rest. In the present study, invasive hemodynamic measurements that directly translate into exercise performance were acquired simultaneously with continuous measurement of VO_2 during progressive exercise, thereby allowing a meaningful interpretation of the functional significance of the observed abnormalities in cardiac performance. The only hemodynamic abnormality noted in patients at upright rest was a mild increase in pulmonary wedge pressure. However, these

data do not prove that the hemodynamic abnormalities seen during exercise were responsible for the patients' episodes of acute pulmonary edema.

Disorders associated with diastolic dysfunction. All the patients in this study had a disorder thought to predispose to diastolic dysfunction, including systemic hypertension, hypertrophic cardiomyopathy and cardiac amyloidosis. These results may not apply to patients with other disorders associated with heart failure and preserved systolic function, including constrictive pericarditis and valvular regurgitation, because patients with these disorders were excluded from the study.

Hypertrophy, most commonly due to systemic hypertension, can alter left ventricular diastolic as well as systolic performance (31,32); however, patients without appreciable hypertrophy may have measurable and clinically significant alterations in indexes of diastolic function (5,33,34). Other factors, such as alterations in the collagen network and infiltration of the myocardium, can also adversely affect the left ventricular diastolic pressure-volume relation (33–35). Although the patient group was relatively small and heterogeneous, the hemodynamic changes seen were dramatic and relatively uniform. It was not the purpose of this study to describe a discrete diagnostic entity, but rather to examine the mechanisms of exercise intolerance in patients with heart failure and preserved left ventricular systolic function. Although each of the patients may have had variable impairment of diastolic relaxation versus compliance, the net effect during exercise was limited left ventricular diastolic filling with resultant inability to augment stroke volume by means of the Frank-Starling mechanism.

Effect of normal aging on diastolic function. Patients in this study tended to be elderly, as noted in previous studies (4,7,9,11), and were carefully matched for age to normal subjects. Noninvasive measurements of left ventricular diastolic function and mass are significantly altered with advancing age in normal subjects (10,14,33,36). Downes et al. (37) recently suggested that there is an age-related shift of the left ventricular end-diastolic pressure-volume relation at rest in subjects without cardiac disease. Recent studies from this laboratory (26,38) showed that oxygen consumption, cardiac output, stroke volume, ejection fraction, heart rate and Frank-Starling response at maximal exercise are significantly reduced in normal elderly compared with younger subjects. It may be that normal age-related changes in left ventricular mass, geometry and myocardial composition lower the threshold for expression of heart failure (39).

Therapeutic implications. Currently, the effect of therapeutic maneuvers on left ventricular diastolic function is controversial (40). Most studies to date have monitored noninvasive variables of diastolic function. Bonow et al. (13) showed that in hypertrophic cardiomyopathy, indexes of diastolic filling derived from radionuclide ventriculography correlated with reduced exercise tolerance and that both variables improved during therapy with verapamil. However, it remains to be shown whether agents such as calcium channel blockers have a direct effect on left ventricular diastolic properties or simply alter loading conditions (40–42). The results of the present study suggest that successful therapy will need to improve the left ventricular end-diastolic volume response during exercise and they provide a rationale for devising future therapeutic trials for patients with heart failure due to diastolic dysfunction.

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