Left Ventricular Hypertrophy and Impaired Diastolic Filling in Essential Hypertension

Diastolic Mechanisms for Systolic Dysfunction During Exercise

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Left ventricular ejection fraction is normal at rest but may respond abnormally to exercise in many patients with essential hypertension. To assess the determinants of the abnormal ejection fraction response to exercise, we performed radionuclide angiography at rest and during exercise in 41 hypertensive patients without coronary artery disease. In 22 patients (group 1), the ejection fraction increased more than 5% during exercise; in the other 19 patients (group 2), the ejection fraction either increased by less than 5% or decreased with exercise. Left ventricular diastolic filling was impaired at rest in patients in group 2 compared with group 1, with reduced peak filling rate (2.5±0.4 vs. 3.1±0.7 end-diastolic volume/sec; p<0.01) and prolonged time to peak filling rate (175±28 vs. 153±22 msec; p<0.01). Impaired diastolic filling in group 2 was associated with less augmentation in end-diastolic volume during exercise compared with group 1 (p<0.01). These observations were not dependent on the threshold value that was arbitrarily chosen to define an abnormal ejection fraction response, as there were significant correlations for the entire group between the magnitude of change in ejection fraction with exercise and both the resting peak filling rate (r=0.46) and the change in end-diastolic volume with exercise (r=0.62). Echocardiographic left ventricular mass index was greater in group 2 than in group 1 (141±32 vs. 114±25 g/m²; p<0.01), and for the entire group was significantly related to peak filling rate (r=−0.50) and time to peak filling rate (r=0.53). Thus, the abnormal ejection fraction response to exercise in patients with hypertension is related to greater left ventricular mass index and impaired diastolic filling, leading to inadequate augmentation of end-diastolic volume during exercise to maintain systolic function. These findings support the concept that exercise-induced systolic dysfunction in hypertensive patients with left ventricular hypertrophy arises predominantly from diastolic mechanisms. (Circulation 1990;81:978–986)

In many patients with essential hypertension in the absence of coronary artery disease, left ventricular systolic function is normal at rest but may respond abnormally during exercise.1,2 This phenomenon may reflect either altered left ventricular loading or intrinsic myocardial dysfunction,3−5 but the mechanisms responsible for the abnormal ejection fraction response to exercise have not yet been completely clarified. Impaired left ventricular diastolic filling at rest is also a common finding in patients with hypertension, especially in those with ventricular hypertrophy, even in the absence of evidence of decreased systolic performance.6−9 The relation between ventricular diastolic filling and the maintenance of adequate systolic function during exercise has not been addressed. As systolic tension development and ejection performance of the left ventricle depends to a large degree on completeness of relaxation and adequate diastolic filling, we hypothesized that impaired left ventricular filling in patients with hypertension might predispose to the reduced systolic functional reserve observed in many patients during exercise. Therefore, we assessed the determinants of the abnormal left ventricular ejection fraction response to exercise in patients with essential hypertension and the relations, if any, between the ejection fraction response to exercise,
indexes of left ventricular diastolic function, and the presence and severity of left ventricular hypertension.

**Methods**

**Patient Selection**

We studied 41 patients with mild or moderate essential hypertension. There were 21 men and 20 women, ranging in age from 33 to 59 years (mean 48 years). In all patients, blood pressure readings were above 150 mm Hg systolic and 90 mm Hg diastolic on at least three consecutive readings in the outpatient clinic of the National Heart, Lung, and Blood Institute. Antihypertensive therapy was discontinued for at least 2 weeks before the study. Blood pressure was measured with the subjects in the sitting position, after a 10-minute rest in a darkened room, by means of a standard mercury sphygmomanometer with a cuff of appropriate size, according to the recommendations of the American Heart Association. Secondary causes of hypertension were ruled out in all patients by laboratory and x-ray studies. The presence of major cardiac or systemic diseases other than hypertension was excluded in all patients.

Fifteen patients were symptomatic with a history of chest pain and 26 patients were asymptomatic. All patients with chest pain underwent coronary arteriography. Asymptomatic patients with abnormal diastolic function at rest by radionuclide angiography or with a decrease in ejection fraction with exercise underwent exercise thallium 201 scintigraphy to exclude underlying coronary artery disease. No patient in this study had an abnormal coronary arteriogram or evidence of a myocardial perfusion defect by exercise thallium 201 perfusion imaging.

Patients were included in this study under guidelines of protocol 85-H-80 approved by the Clinical Research Subpanel of the National Heart, Lung, and Blood Institute on April 16, 1985. All patients were fully informed about the procedure and the investigational purpose of the study, and written consent was obtained in all cases before the study.

**Gated Blood Pool Cardiac Scintigraphy**

Radionuclide angiography was performed at rest and during maximal supine bicycle exercise using red blood cells labeled in vivo with 15–20 mCi technetium 99m and a conventional Anger camera equipped with a high sensitivity, parallel-hole collimator oriented in a modified left anterior oblique position to isolate the left ventricle. A total of 7.5–10.5 million counts were acquired for each study. High temporal resolution (10–20 msec/frame) cardiac image sequences were constructed by computer-based electrocardiographic gating, with the use of list-mode data acquisition with exclusion of extrasystolic and postextrasystolic cycles and combined forward and reverse gating from the R wave. Left ventricular time-activity curves, representing relative changes in left ventricular volume during the average cardiac cycle, were generated from the cardiac image sequence after background correction with a fixed left ventricular region of interest.

Indexes of left ventricular function were derived by computer analysis of the background-corrected time-activity curve. Ejection fraction was computed on the basis of relative end-diastolic and end-systolic counts. Peak left ventricular ejection and filling rates were determined by fitting third order polynomial functions to the systolic ejection and rapid diastolic filling portions of the time-activity curve by a least-squares technique. The time of occurrence of the peak ejection or peak filling rate was obtained by setting the second derivative of the polynomial function to zero. Time to peak ejection rate was measured from the R wave and time to peak filling rate was measured relative to end systole (minimal volume on the time-activity curve). Peak ejection rate and peak filling rate were computed in left ventricular counts per second, normalized for the number of counts at end diastole and expressed as end-diastolic volume per second (EDV/sec). When normalized for end-diastolic volume, peak ejection rate and peak filling rate are influenced directly by the magnitude of the ejection fraction. To minimize this effect, we also analyzed peak filling rate using two additional normalization methods: peak filling rate was expressed relative to left ventricular stroke volume (SV/sec) and as the ratio of peak filling rate to peak ejection rate. These two latter methods have the additional advantage of being background independent.

Exercise studies were performed using a bicycle ergometer with a restraining harness to minimize patient motion under the camera. Exercise loads were increased by 25 W every 2 minutes until angina, limiting dyspnea or fatigue developed. No patient developed high-grade ventricular arrhythmias necessitating termination of exercise. Heart rate and blood pressure (by cuff sphygmomanometry) were monitored during exercise at each stage. Imaging was begun shortly after the onset of exercise, although only that portion of the data series that occurred during maximal exercise (encompassing approximately the final 2 minutes of exercise) was selected for analysis. In addition to computing the ejection fraction during exercise, we also determined the relative changes in left ventricular end-diastolic and end-systolic volumes occurring during exercise by comparing the end-diastolic and end-systolic counts at rest with those obtained during peak exercise, after correction for physical decay of the isotope.

The hypertensive patients were classified into two groups according to their left ventricular ejection fraction response to exercise (Figure 1). In 22 patients (group 1), the ejection fraction increased more than 5% with exercise. There were 10 men and 12 women with a mean age of 47 years (range, 36–58). In the other 19 patients (group 2), the ejection fraction either increased by less than 5% or decreased with exercise. There were 10 men and nine women with a mean age of 49 years (range, 33–59).
Echocardiography

Echocardiographic studies were performed on the same day or within 1 week of radionuclide ventriculography. The cardiac dimensions were measured by M-mode echocardiography according to the recommendations of the American Society of Echocardiography.\textsuperscript{15} The left ventricular mass was calculated from the end-diastolic wall thickness and cavity dimensions using the formula described by Troy et al.\textsuperscript{16,17} The left ventricular mass index was calculated by dividing mass by body surface area (g/m\textsuperscript{2}). We also estimated the peak systolic left ventricular meridional wall stress from the systolic blood pressure (by cuff sphygmomanometry, measured before radionuclide angiography) and echocardiographic end-diastolic dimension (D) and posterior wall thickness (h) with the formula of Grossman et al.\textsuperscript{18}: peak systolic wall stress=([systolic blood pressure\times D]/[4h(1+h/D)]. We did not attempt to compute end-systolic stress because of the inability to measure end-systolic ventricular pressure.

Statistical Analysis

Data are expressed as mean±SD. Differences in group means were analyzed with the two-tailed unpaired \textit{t} test. A \textit{p} value of 0.05 or less was considered a statistically significant difference. Linear regression analysis was used to relate indexes of left ventricular volume, mass, and function.

Results

Hemodynamic Data

The clinical characteristics of the two groups of patients and the hemodynamic parameters recorded under control conditions and during exercise are presented in Table 1. There were no significant differences in age, gender, or the prevalence of cardiac symptoms between the two groups. In addition, heart rate, systolic and diastolic blood pressure, both at rest and at peak exercise, double product

![Figure 1. Plots of left ventricular ejection fraction at rest and during supine bicycle exercise in the two groups of hypertensive patients. Group 1: 22 patients with an increase in the ejection fraction with exercise >5%; group 2: 19 patients in whom the ejection fraction either increased <5% or decreased with exercise. ⊳, mean values; NS, not significant.](image)

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics and Hemodynamic Data at Rest and During Exercise in the Two Study Groups</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>\textit{n}</td>
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<tr>
<td>Mean age (yr)</td>
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<tr>
<td>Sex (% male)</td>
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<tr>
<td>Asymptomatic (%)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
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<td></td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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<td></td>
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<tr>
<td>Peak workload (W)</td>
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<tr>
<td>Peak double product (×10)</td>
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</table>

(peak systolic blood pressure multiplied by peak heart rate), and peak workload, did not differ between patients in whom the ejection fraction increased during exercise and those in whom the ejection fraction declined during exercise.

Radionuclide Angiographic Data

Indexes of left ventricular systolic function under control conditions were not significantly different between groups 1 and 2. Thus, ejection fraction, peak ejection rate, time to minimal volume, and time to peak ejection rate were similar in the two groups of patients (Table 2). However, all indexes of left ventricular rapid filling at rest differed between the two groups (Table 2), with evidence of impaired diastolic filling in patients with an abnormal ejection fraction response (group 2) compared with those with a normal ejection fraction response (group 1). In particular, the peak rate of left ventricular filling was lower in group 2 than in group 1 patients, whether peak filling rate was normalized to end-diastolic volume (2.5±0.4 vs. 3.1±0.7 EDV/sec; \textit{p}<0.01) or stroke volume (4.2±0.6 vs. 5.5±1.1 SV/sec; \textit{p}<0.001), or expressed as the ratio of peak filling to peak ejection rate (0.8±0.2 vs. 1.2±0.3; \textit{p}<0.001). Moreover, time to peak filling rate was significantly prolonged in patients in group 2 (175±28 vs. 153±22 msec; \textit{p}<0.01) (Table 2). Two examples illustrating this effect are shown in Figure 2.

The division of patients into two subgroups was based on a threshold value of 5% increase in ejection fraction with exercise. However, the observation of impaired diastolic filling at rest in patients with a diminished exercise ejection fraction response was not dependent on this arbitrarily chosen threshold value, as a continuum was observed between the ejection fraction response to exercise and resting measures of diastolic filling. For the entire study
population, the left ventricular ejection fraction response to exercise correlated significantly with the resting peak filling rate, whether peak filling rate was normalized to stroke volume \( (r=0.46, p<0.01) \) (Figure 3) or end-diastolic volume \( (r=0.34, p<0.05) \), or expressed as the ratio of peak filling to peak ejection rate \( (r=0.35, p<0.05) \).

Table 2 and Figure 4 demonstrate the exercise-induced changes in relative end-diastolic and end-systolic volumes in the two groups of patients. The impaired left ventricular filling under resting conditions in patients with abnormal ejection fraction responses to exercise (group 2) was associated with substantially less augmentation in end-diastolic volume during exercise compared with group 1 patients \( (-6\pm20\% \text{ vs. } +17\pm19\%; p<0.001) \). In particular, end-diastolic volume decreased during exercise in four patients of group 1 (18\%) and in 11 patients of group 2 (58\%). In contrast, no significant difference was observed in the exercise-induced change in relative end-systolic volume between groups 1 and 2. Thus, the augmentation in stroke volume during exercise was significantly reduced in group 2 compared with group 1 patients. These observations were not dependent on the threshold value used to define “normal” or “abnormal” exercise ejection fraction responses. For the entire study population, the left ventricular ejection fraction response to exercise correlated significantly with the change in end-diastolic volume with exercise \( (r=0.62, p<0.001) \) (Figure 3). Patient age did not correlate with resting peak filling rate and time to peak filling rate \( (r=-0.03 \text{ for both}) \), the change in end-diastolic volume with exercise \( (r=-0.14) \), or the magnitude of change in ejection fraction during exercise \( (r=-0.26) \).

**Echocardiographic Data**

The morphologic characteristics of the study population, as defined by echocardiography, are shown in Table 2. The two groups of patients differed with respect to the echocardiographic assessment of ventricular septal and posterior free wall thickness and left ventricular mass index, with patients of group 2 showing greater wall thickness and mass. In particular, two patients (9\%) in group 1 and 11 patients (58\%) in group 2 had an increase in the calculated left ventricular mass index above the upper limit of normal (150 g/m² in men and 120 g/m² in women). No significant difference was detected between the two groups regarding the left ventricular internal cavity dimensions. In keeping with the greater wall thickness in group 2 patients, with no differences in blood pressure or end-diastolic diameter, peak systolic left ventricular wall stress was lower in group 2.

### Table 2. Radionuclide Angiographic and Echocardiographic Data

<table>
<thead>
<tr>
<th>Data</th>
<th>Group 1 (n=22)</th>
<th>Group 2 (n=19)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>LV function at rest</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LV systolic function</td>
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<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56±6</td>
<td>58±6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak ejection rate</td>
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<td></td>
</tr>
<tr>
<td>(end-diastolic volume/sec)</td>
<td>2.7±0.4</td>
<td>2.8±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Time to minimal LV volume (msec)</td>
<td>348±41</td>
<td>330±40</td>
<td>NS</td>
</tr>
<tr>
<td>Time to peak ejection rate (msec)</td>
<td>199±19</td>
<td>192±17</td>
<td>NS</td>
</tr>
<tr>
<td>LV diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak LV filling rate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic volume/sec</td>
<td>3.1±0.7</td>
<td>2.5±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke volume/sec</td>
<td>5.5±1.1</td>
<td>4.2±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak filling rate/peak ejection rate</td>
<td>1.2±0.3</td>
<td>0.8±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to peak filling rate (msec)</td>
<td>153±22</td>
<td>175±28</td>
<td>&lt;0.01</td>
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<tr>
<td>LV function during exercise</td>
<td></td>
<td></td>
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<tr>
<td>Ejection fraction (%)</td>
<td>66±6</td>
<td>57±7</td>
<td>...</td>
</tr>
<tr>
<td>Change in end-diastolic volume (%)</td>
<td>+17±19</td>
<td>-6±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in end-systolic volume (%)</td>
<td>-16±15</td>
<td>-5±21</td>
<td>NS</td>
</tr>
<tr>
<td>Change in stroke volume (%)</td>
<td>+24±26</td>
<td>+9±13</td>
<td>&lt;0.05</td>
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<tr>
<td>Change in cardiac output (%)</td>
<td>+116±55</td>
<td>+81±41</td>
<td>&lt;0.05</td>
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<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>1.0±0.1</td>
<td>1.2±0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Interventricular septum thickness (cm)</td>
<td>1.1±0.2</td>
<td>1.3±0.2</td>
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<tr>
<td>LV internal diameter in diastole (cm)</td>
<td>4.8±0.7</td>
<td>5.0±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>LV internal diameter in systole (cm)</td>
<td>3.1±0.5</td>
<td>3.4±0.8</td>
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<tr>
<td>LV mass index (g/m²)</td>
<td>114±25</td>
<td>141±32</td>
<td>&lt;0.01</td>
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<tr>
<td>Peak systolic wall stress (kdynes/cm²)</td>
<td>309±54</td>
<td>285±45</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean±SD. LV, left ventricular.
than in group 1 patients (285±45 vs. 309±54 kdynes/cm; p<0.05).

For the entire group of hypertensive patients, there was a significant linear relation between left ventricular mass index and both resting peak filling rate (r=-0.50 for all three normalization methods, p<0.001) and time to peak filling rate (r=0.53, p<0.001) (Figure 5). The relations between left ventricular mass index and the ejection fraction response to exercise (r=-0.41) and the change in end-diastolic volume with exercise (r=-0.39) were less strong, but statistically significant (p<0.01). Left ventricular mass index did not correlate with ejection fraction at rest (r=0.05) or during exercise (r=-0.26). There was no correlation between peak systolic left ventricular wall stress and peak filling rate (r=-0.03), time to peak filling rate (r=0.09), resting ejection fraction (r=-0.06), or change in the ejection fraction with exercise (r=0.03).

Relation Between End-Diastolic Volume Changes With Exercise and Exercise Tolerance

To determine whether the reduction in end-diastolic volume with exercise in many study patients was associated with important functional consequences, the patient group was subdivided on the basis of the directional change in end-diastolic volume that occurred during exercise. The 23 patients in whom end-diastolic volume increased during exercise were able to achieve greater exercise workloads than the 18 patients in whom end-diastolic volume decreased during exercise (118±42 vs. 92±30 W; p<0.05). Patients with an increase in end-diastolic volume during exercise also manifested a greater augmentation in stroke volume (45±27% vs.

**Figure 2.** Left ventricular time-activity curves at rest from one group 1 patient and from one group 2 patient. Relative left ventricular (LV) volume, expressed as a percent of end-diastolic volume (EDV), is plotted as a function of time during the cardiac cycle. Heart rate (HR) and left ventricular ejection fraction (EF) are not different. However, diastolic filling is impaired in group 2 patients, with reduced peak filling rate (PFR) and prolonged time to peak filling rate (TPFR).

**Figure 3.** Magnitude of change in left ventricular (LV) ejection fraction with exercise plotted as a function of resting peak filling rate (left), and as a function of the change in end-diastolic volume (EDV) with exercise (right). ●, Group 1 patients; ○, group 2 patients; SV/s, stroke volume per second.

**Figure 4.** Plots of individual changes in end-diastolic volume (EDV) and end-systolic volume (ESV) during exercise in the two groups of patients. NS, not significant; †, mean value.
13±13%; p<0.05) compared with those in whom the end-diastolic volume decreased.

Asymptomatic Patients

Because 15 of the 41 patients had a history of chest pain, which could reflect myocardial ischemia at the microvascular level,19,20 a repeat analysis of left ventricular filling, left ventricular hypertrophy, and exercise systolic function was performed in the 26 asymptomatic patients. The results in this subset were comparable with those obtained in the total group. In these 26 patients, the magnitude of change in ejection fraction with exercise correlated significantly with resting filling rate (r=0.65, p<0.001) and with the relative change in end-diastolic volume during exercise (r=0.55, p<0.001). These variables, in turn, were significantly related to the severity of left ventricular hypertrophy. Echocardiographic left ventricular mass index correlated with resting peak filling rate (r=−0.68, p<0.001) and time to peak filling rate (r=0.60, p<0.001) and with the changes in ejection fraction (r=−0.49, p<0.01) that occurred during exercise. End-diastolic volume decreased during exercise in 11 of the 26 asymptomatic patients. In these 11 patients, exercise capacity was reduced compared with the 15 patients in whom end-diastolic volume increased with exercise (94±25 vs. 122±35 W; p<0.05).

Discussion

It has been demonstrated that basal systolic performance of the left ventricle remains normal in many patients with essential hypertension.21 However, the ejection fraction response during exercise is abnormal in a substantial percentage of hypertensive patients who do not have associated coronary artery disease.1,2 Our data support these previous observations. Although it has been correctly surmised that this frequent abnormal functional response makes exercise radionuclide angiography inadequate as a screening test for coronary artery disease in patients with hypertension, the physiologic basis for this abnormality has not been explored.

The abnormal exercise response in chronic hypertension could represent either early evidence of end-organ damage to the heart or altered left ventricular loading conditions, or both. Meercson22 suggested that the left ventricle in chronic hypertension advances through stages of physiologic hyperfunction and compensatory hypertrophy before left ventricular failure occurs. Chronic increases in systemic vascular resistance result in increases in myocardial systolic wall stress and, hence, increases in afterload. The development of left ventricular hypertrophy may serve to reduce (and even normalize) systolic wall stress, thereby permitting maintenance of normal ejection performance under basal conditions. However, this compensatory mechanism may not be sufficient to allow normal systolic function during the acute superimposition of sudden increases in wall stress, such as those developing during exercise. Our data do not support this concept, as the patients with abnormal exercise responses had evidence of reduced wall stress at rest and exercise compared with those with normal responses. That is, patients with abnormal functional responses had greater left ventricular wall thickness, similar blood pressure, and similar internal dimensions at rest, yielding reduced peak systolic wall stress value at rest (Table 2). With exercise, these patients also had smaller increments in end-diastolic volume (Table 2 and Figure 4), despite similar blood pressure responses, indicating that wall stress during exercise was reduced compared with patients with normal systolic function during exercise.

An alternative explanation relates to the effects of hypertension and hypertrophy on left ventricular diastolic performance. Although hypertrophy has the advantageous effect of preserving systolic function, it has important consequences for diastole.23 Increased myocardial mass and the resultant increases in interstitial connective tissue24–26 will increase left ventricular stiffness. In addition, left ventricular relaxation is impaired in left ventricular hypertrophy arising from chronic pressure overload.27–31 These passive and active processes will affect the rate and extent of left ventricular diastolic filling. Indeed, impaired left ventricular diastolic filling is common at rest in patients with hypertension6–9,32 and is often evident when resting systolic function is preserved. Reduced rate and extent of left ventricular filling, in turn, may influence systolic performance during exercise, as left ventricular stroke volume and ejection fraction are augmented during supine exercise in many normal subjects (especially those in middle or old age).
through left ventricular chamber dilatation.\textsuperscript{33–35} Impaired left ventricular filling and restriction of left ventricular dilatation during exercise will limit this physiologic response.

Our results, demonstrating a significant interrelation between indexes of left ventricular rapid filling at rest, the degree of left ventricular dilatation with supine exercise, and the magnitude of change in ejection fraction during exercise, support this concept. Patients with abnormal ejection fraction responses with exercise as a group manifested greater impairment in rapid diastolic filling at rest and less augmentation of end-diastolic volume with exercise than did patients with normal systolic functional responses to exercise. The functional importance of reduced left ventricular filling with exercise is underscored by the findings that patients with a decrease in end-diastolic volume during exercise as a group manifested diminished exercise capacity and less augmentation of stroke volume and cardiac output compared with patients in whom end-diastolic volume increased with exercise.

These physiologic responses were not related to patient age or gender. In normal subjects, there are important physiologic changes in left ventricular function that occur as part of the aging process, such that the rate and extent of left ventricular filling is reduced,\textsuperscript{36–38} and the exercise-induced changes in end-diastolic volume and ejection fraction are altered\textsuperscript{33–35,39} in the course of aging. The absence of such age-related effects in our hypertensive patients indicates that other factors in chronic hypertension contribute to the derangements in left ventricular function and override the effects of aging alone.

Our data indicate that the severity of left ventricular hypertrophy is one such factor contributing importantly to both impaired left ventricular diastolic filling and the systolic functional response to exercise in patients with hypertension. Left ventricular mass index, as estimated by echocardiography, correlated significantly with indexes of diastolic filling at rest, with the extent of left ventricular dilatation during exercise, and with the magnitude of change in ejection fraction during exercise. These observations support the hypothesis that systolic dysfunction during exercise in patients with essential hypertension is related to impaired diastolic filling arising from left ventricular hypertrophy, leading to inadequate augmentation of end-diastolic volume during exercise to maintain ejection fraction.

Many of the associations between left ventricular mass index, indexes of left ventricular filling at rest, and the ejection fraction response to exercise, although statistically significant, did not achieve very high correlation coefficients. This might represent, in part, imprecision in measurement of several of the variables we studied. Alternatively, other factors such as severity of hypertension, chronicity of the disease, and other ultrastructural changes associated with hypertension and left ventricular hypertrophy (such as increased myocardial fibrous tissue content), which were not assessed in this study, could play a role.

Left ventricular hypertrophy in essential hypertension also leads to a reduction in coronary vasodilator reserve.\textsuperscript{19,40} Thus, it is possible that the impairment in resting diastolic filling and the reduction in exercise systolic performance as a function of increased left ventricular mass do not arise from hypertrophy per se, but from associated myocardial ischemia. However, we do not believe that myocardial ischemia explains our observations adequately, as exercise-induced ischemic dysfunction is characterized by an increase in end-diastolic volume with a proportionately greater increase in end-systolic volume,\textsuperscript{41,42} whereas in our patients, systolic dysfunction during exercise was directly related to a decrease in end-diastolic volume.

The abnormal decrease in end-diastolic volume with exercise, and the associated impairment of systolic performance, in patients with more severe degrees of hypertrophy may relate to the effects of exercise tachycardia on the hypertrophied left ventricle. In the normal heart, the stimulatory effects of the sympathetic nervous system and circulating catecholamines during exercise enhance ventricular relaxation on the basis of both inactivation- and load-dependent mechanisms.\textsuperscript{43–47} The increased rate and extent of relaxation, in turn, augments the pressure gradient between left atrium and left ventricle in early diastole, thereby facilitating ventricular filling during exercise and allowing for augmented stroke volume despite the marked reduction in diastolic filling time that occurs at high heart rates. However, this mechanism to increase stroke volume during exercise may be inoperative in the setting of left ventricular hypertrophy because of prolonged or incomplete ventricular relaxation, such that diastolic volume and stroke volume cannot be maintained as the diastolic filling periods diminish during tachycardia.

Several lines of experimental evidence support the concept that systolic dysfunction of the hypertrophied left ventricle may develop during tachycardia-induced alterations in diastolic function. Diastolic lengthening of isolated cardiac myocytes is restricted when subjected to elevated calcium ion concentrations, and the resultant reduced diastolic cell length is associated with diminished systolic shortening.\textsuperscript{48} In mammals with pressure-overload hypertrophy, reduced sarcoplasmic reticulum sequestration of calcium ion and prolongation of the calcium transient\textsuperscript{27–30} is associated with prolonged diastolic tension decay,\textsuperscript{30} which in turn is related to reduction in developed tension during systole. In hypertrophied ventricular trabeculae from humans with end-stage heart failure,\textsuperscript{49} similar prolongation of the calcium transient, prolonged diastolic tension decay, and reduced systolic tension development are exacerbated at higher stimulus cycling rates (mimicking the effects of increased heart rates); higher cycling rates result in elevated intracellular
diastolic calcium levels, increased resting diastolic tone, and further reduction in systolic tension development. Thus, abnormal intracellular calcium handling and altered diastolic performance at elevated heart rates contribute to systolic dysfunction in experimental preparations.

Another explanation for our results relates to differences in venous return and ventricular filling stemming from possible differences in baroreflex responses between the two groups of patients. Although baroreceptors play an important role in the reflex control of the systemic circulation, few data are available on the effects of hypertension-induced left ventricular hypertrophy on arterial and cardiopulmonary baroreceptor function. A resetting of cardiopulmonary as well as arterial baroreceptors has been reported in hypertensive animals. In humans, an enhancement of the tonic influence of cardiopulmonary baroreceptors has been described in patients with borderline hypertension. In contrast, patients with severe hypertension and cardiac hypertrophy do not exhibit this exaggerated reflex response to orthostatic stress.

We did not assess baroreflex responsiveness in our study. Moreover, in the absence of simultaneous left ventricular pressure-volume measurements, we cannot determine whether reduced left ventricular filling, both at rest and during exercise, in patients with more severe hypertrophy resulted from changes in ventricular relaxation and compliance related to hypertrophy, or from reduced preload related to altered baroreceptor function. In either case, our data demonstrate that the hypertrophied left ventricle is dependent on adequate diastolic filling volume to maintain systolic performance. Thus, in patients with essential hypertension and left ventricular hypertrophy, systolic dysfunction during exercise may arise predominantly from impaired diastolic filling.

References


**Key Words** • essential hypertension • left ventricular function • left ventricular hypertrophy
Left ventricular hypertrophy and impaired diastolic filling in essential hypertension.
Diastolic mechanisms for systolic dysfunction during exercise.
A Cuocolo, F L Sax, J E Brush, B J Maron, S L Bacharach and R O Bonow

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