Size, Shape, and Stamina

The Impact of Left Ventricular Geometry on Exercise Capacity

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Abstract—Although several studies have examined the cardiac functional determinants of exercise capacity, few have investigated the effects of structural remodeling. The current study evaluated the association between cardiac geometry and exercise capacity. Subjects with ejection fraction ≥50% and no valvular disease, myocardial ischemia, or arrhythmias were identified from a large prospective exercise echocardiography database. Left ventricular mass index and relative wall thickness were measured to classify geometry into normal, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy. All of the subjects underwent symptom-limited treadmill exercise according to standard Bruce protocol. Maximal exercise tolerance was measured in metabolic equivalents. Of 366 (60±14 years; 57% male) subjects, 166 (45%) had normal geometry, 106 (29%) had concentric remodeling, 40 (11%) had eccentric hypertrophy, and 54 (15%) had concentric hypertrophy. Geometry was related to exercise capacity: in descending order, the maximum achieved metabolic equivalents were 9.9±2.8 in normal, 8.9±2.6 in concentric remodeling, 8.6±3.1 in eccentric hypertrophy, and 8.0±2.7 in concentric hypertrophy (all P<0.02 versus normal). Left ventricular mass index and relative wall thickness were negatively correlated with exercise tolerance in metabolic equivalents (r=-0.14; P=0.009 and r=-0.21; P<0.001, respectively). Augmentation of heart rate and ejection fraction with exercise were blunted in concentric hypertrophy compared with normal, even after adjusting for medications. In conclusion, the pattern of ventricular remodeling is related to exercise capacity among low-risk adults. Subjects with concentric hypertrophy display the greatest limitation, and this is related to reduced systolic and chronotropic reserve. Reverse remodeling strategies may prevent or treat functional decline in patients with structural heart disease. (Hypertension. 2010;55:1143-1149.)

Key Words: left ventricle ■ remodeling ■ exercise capacity ■ hypertrophy ■ hypertension

A decline in exercise capacity is one of the most notable effects of aging and an almost ubiquitous symptom of cardiovascular diseases. To better understand how age- and disease-related changes can affect exercise capacity, several recent studies have examined cardiac functional correlates of reduced exercise capacity with aging2,3 or hypertension.3,5 In contrast, few have studied the effects of left ventricular structural remodeling and geometry on exercise performance.6,7

Echocardiography is a well-established tool to characterize cardiac remodeling in hypertension8 and systolic heart failure.9 On the basis of the noninvasive measurements of left ventricular (LV) mass and relative wall thickness (RWT) by echocardiography, the spectrum of LV geometric patterns can be classified into 4 patterns: normal (NL), concentric remodeling (CR), concentric hypertrophy (CH), and eccentric hypertrophy (EH). Although the prognostic implications of LV remodeling are widely recognized in terms of cardiovascular events,11 the influence of LV geometry on exercise capacity remains unclear. A greater appreciation of how adverse LV remodeling may contribute to exercise limitation is needed, because any such abnormalities may represent novel therapeutic targets in the prevention or treatment of exertional symptoms in patients with structural heart disease.12,13

Accordingly, the aims of this study were to investigate how LV geometry and its components (LV mass and RWT) are related to exercise capacity and to determine the functional correlates of LV remodeling in low-risk adults undergoing exercise echocardiography. We hypothesized that abnormal LV geometry would be related to reduced exercise capacity. Specifically, we hypothesized that the pattern of geometry with both abnormal components of relative wall thickness and LV mass (ie, CH) would be associated with the greatest reduction in exercise capacity compared with normal geometry, whereas geometry patterns with only one abnormal component of relative wall thickness or LV mass (ie, CR or EH, respectively) would be associated with intermediate exercise capacity. We further hypothesized that there would be differences in blood pressure, heart rate, or LV diastolic or systolic responses to exercise among LV geometry groups, even in the absence of myocardial ischemia or overt systolic failure.

Methods

Study Population

Subjects were identified from a prospective database of consecutive patients referred for exercise echocardiography at the Mayo Clinic during the year 2006. Patients were included if they had a comprehensive resting transthoracic echocardiogram (to allow characteriza-
tion of cardiac geometry) within 90 days (median: 1 day) of exercise echocardiography. Patients were excluded if they had reduced ejection fraction (<50%), moderate or severe valvular heart disease, evidence of exercise-induced myocardial ischemia, or atrial fibrillation/flutter at the time of exercise. This study was approved by the institutional review board.

Clinical and anthropometric variables were recorded at the time of the baseline echocardiogram. Medication use and medical history were abstracted from the record and entered into a prospectively maintained database by specially trained nurses. Coronary artery disease was defined as previous coronary revascularization or history of myocardial infarction.

**Characterization of Cardiac Geometry**

LV mass index (LVMI) was determined using the American Society of Echocardiography–recommended formula on the basis of modeling the ventricle as a prolate ellipse of revolution. RWT was calculated by the formula 2(PWTd)/LVIDd, where PWTd is the posterior wall thickness and LVIDd is the LV internal diameter at end diastole. Cardiac geometry was classified as follows: (1) for NL, LVMI was <95 g/m² in women or <115 g/m² in men and RWT was <0.42; (2) for CR, LVMI was <95 g/m² in women or <115 g/m² in men and RWT was >0.42; (3) for EH, LVMI was >95 g/m² in women or >115 g/m² in men and RWT was <0.42; or (4) for CH, LVMI was >95 g/m² in women or >115 g/m² in men and RWT was >0.42. Left atrial volume was measured offline using the biplane area-length method. All of the volume measurements were indexed to body surface area.

**Exercise Echocardiography**

Doppler echocardiography was performed before starting exercise and immediately after symptom-limited treadmill exercise according to standard Bruce protocol, with maximal exercise tolerance measured in metabolic equivalents (METs). One MET of task is the energy expended by an average individual at rest, defined by convention as a whole-body oxygen consumption of 3.5 mL of oxygen per kilogram of body weight per minute. Because oxygen consumption was not directly measured, exercise capacity (in METs) was estimated on the basis of standardized increments in the speed and grade of the treadmill. Patients were not allowed to grip the handle bars during exercise. Blood pressure was measured at the end of each stage of exercise using an aneroid gauge sphygmomanometer with the cuff placed over the upper arm and auscultation of the brachial artery. Echocardiographic images were uniformly acquired and analyzed according to standard recommendations. Ejection fraction was measured using the modified method of Quinones et al or by visual estimation. The reliability of these methods and close agreement between subjective and volumetric assessments of ejection fraction in our institution have been published previously. In the apical 4-chamber view, transmitial early inflow velocity (E) was recorded in the pulsed-wave Doppler mode, and the early diastolic velocity within the septal mitral annulus (e’) was measured by Doppler tissue imaging using the pulsed-wave Doppler mode, placing a 5-mm sample volume at the septal region of the mitral annulus. E and e’ were defined as the first occurring peak velocities in diastole after the isovolumic relaxation signals.

**Statistical Analysis**

Baseline characteristics were compared across the 4 geometry groups using the Pearson χ² test (categorical variables) or 1-way ANOVA (continuous variables) with comparison of each abnormal geometry group to the normal geometry group using the Dunnett test. During exercise echocardiography, rest versus stress parameters were analyzed using the paired t test for within-group comparisons and using 1-way ANOVA with Dunnett test for comparisons among groups. The univariate associations of LVMI and RWT with achieved METs were assessed by Pearson (parametric) or Spearman (nonparametric) correlation coefficient. For multivariate analyses, multiple linear regression was used to adjust for age and sex in group comparisons, where the dependent variable was achieved METs (log transformed to satisfy normality assumptions) and factors entered into the model included age, sex, and geometry group. All of the analyses were 2-sided, and significance was judged at P<0.05.

**Results**

Of a total of 366 patients (age: 60±14 years; 57% men), 166 (45%) had NL geometry, 106 (29%) had CR, 40 (11%) had EH, and 54 (15%) had CH (Table 1). Test indications (P=0.13) and reasons for stopping exercise (P=0.08) were similar among geometry groups. Across geometry groups, patients varied in age, systolic blood pressure, and history of hypertension, with the CH group being the oldest, having the greatest proportion with a history of hypertension, and having the highest systolic blood pressure at the time of baseline echocardiography. Patients with any abnormal geometry were more likely to be treated with angiotensin system blockers than those with normal geometry, with a similar trend for β-blockers. LV volumes differed across groups, with CR having the smallest volume. Resting heart rate was highest in CR; cardiac index was similar across groups. Left atrial volume and E/e’ ratio increased across the groups from NL to CH.

**Association Between Overall LV Geometry and Exercise Capacity**

In the entire sample, LV geometry was related to exercise capacity (ANOVA P<0.0001; Figure 1A). In descending order, the maximum achieved METs was 9.9±2.8 in NL, 8.9±2.6 in CR (P=0.008 versus NL), 8.6±3.1 in EH (P=0.016 versus NL), and 8.0±2.7 in CH (P<0.001 versus NL). Results were similar after excluding the 13 subjects who stopped exercising because of electrocardiographic changes: 9.9±2.8 METs in NL, 8.9±2.7 in CR, 8.7±3.2 in EH, and 8.0±2.7 in CH (P<0.001). In multivariable analyses adjusting for age and sex, the geometry group remained independently associated with METs (P=0.04). After adjusting for relevant baseline clinical differences (as listed in Table 1, ie, age, systolic blood pressure, heart rate, hypertension, smoking status, and usage of β-blockers, angiotensin-converting-enzyme inhibitors, and angiotensin receptor blockers), the association between geometry and METs remained statistically significant (P=0.037).

**Association Between Individual Components of LV Geometry and Exercise Capacity**

The individual components of geometry, LVMI, and RWT were negatively correlated with METs (r=-0.14; P=0.009 and r=-0.21; P<0.001, respectively) in the overall sample (Figure 1B and 1C). Among women, there was no significant relationship between LVMI and METs (P=0.11), whereas RWT remained significantly associated with METs (r=-0.17; P=0.031). Among men, both LVMI and RWT were significantly associated with METs (r=-0.26 and -0.23, respectively; P≤0.001 for each). These associations between the individual components of geometry and achieved METs were no longer statistically significant after adjusting for age in sex-stratified analyses or after adjusting for age and sex in the entire sample.
Systolic blood pressure, heart rate, and ejection fraction each increased from rest to exercise overall ($P<0.001$) and within each geometry group (all $P<0.01$; Table 2). However, the magnitude of observed changes with exercise differed among geometry groups (Figure 2). The increase in systolic blood pressure with exercise tended to be smaller in CH compared with NL ($P=0.06$), despite the higher peak blood pressures reached in CH. The heart rate response to exercise was significantly attenuated in CH compared with NL, even after adjusting for $\beta$-blockade ($P=0.001$) or excluding all of the subjects on $\beta$-blockers ($P=0.015$). Despite similarly increased LV mass in EH and CH, exercise heart rate response was preserved in EH ($P=0.7$ compared with NL; $P=0.04$).
compared with CH). Augmentation of ejection fraction with exercise was blunted in CH, even after accounting for medications (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers; \( P=0.004 \)). The increase in echo-estimated filling pressures (E/e’ ratio) with exercise was similar among geometry groups (\( P=0.40 \)), as was the increase in the individual velocities of early mitral inflow (E; \( P=0.50 \)) or early mitral annular motion (e’; \( P=0.93 \)).

Discussion

This is the largest study to date examining the relationships between LV geometry and exercise capacity. In low-risk adults free of valvular heart disease, myocardial ischemia, or arrhythmias, LV geometry was related to exercise tolerance. Compared with normal geometry, those with CH had the worst exercise capacity, whereas those with CR or EH had intermediate levels of exercise intolerance. This relationship remained significant even after adjusting for age and sex. Intriguingly, poor exercise performance in CH was related to decreased heart rate and LV systolic (ejection fraction) reserve responses with exercise, even after accounting for medications. These findings support the notion that ventricular remodeling plays a role in the pathogenesis of functional decline in patients with structural heart disease.

Importance of Ventricular Remodeling

The importance of LV geometry has been recognized for decades.\(^{19,20}\) LV remodeling is known to play a central role in the pathophysiology of cardiovascular disease.\(^{8}\) According to the classic paradigm, a stimulus for remodeling, typically pressure overload, causes myocytes to increase in width, thereby normalizing the pressure-induced increase in wall stress by Laplace law.\(^{19}\) In some patients, the predominant stimulus to LV hypertrophy is volume overload, with resultant EH.\(^{21}\) The adaptive increase in myocardial mass, however, may be associated with maladaptive alterations and LV dysfunction. Indeed, the prognostic impact of LV geometric patterns on cardiovascular events has been extensively described.\(^{22,23}\) Recent studies have raised serious questions with the notion that hypertrophic remodeling may ever be “adaptive,”\(^{24,25}\) leading some investigators to suggest that hypertrophic remodeling in itself represents an important therapeutic target.\(^{26}\)

Cardiac Geometry and Exercise Capacity

Although abnormal geometry is clearly associated with increased cardiovascular outcomes, surprisingly few data have been published regarding the impact of LV geometry on physiology, exercise capacity, and reserve function. Two previous studies examined the association between LV geometry and exercise capacity.\(^{5,7}\) Tomiyama et al\(^{1}\) studied a male population with hypertension (N=192; mean age: 42 to 45 years) and found that, among the 4 geometric groups, CH was associated with reduced treadmill exercise time compared with normal geometry. In addition, men who developed CH during 3 years of follow-up demonstrated a reduction in exercise time. Pierson et al\(^{7}\) studied 89 hypertensive adults (44% men; mean age: 46 to 48 years) and similarly found shorter exercise treadmill time in CH compared with any other geometric pattern. Importantly, peak exercise oxygen

<table>
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<th>Parameter</th>
<th>NL</th>
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<th>EH</th>
<th>CH</th>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<td>128±20</td>
<td>128±18</td>
<td>133±20†</td>
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<tr>
<td>Heart rate, bpm</td>
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<td>74±13</td>
<td>70±14</td>
<td>73±12</td>
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<tr>
<td>Ejection fraction, %</td>
<td>59±8</td>
<td>67±11</td>
<td>62±5‡</td>
<td>51±12‡</td>
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</tbody>
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\(^*P\) value is for comparison across groups using 1-way ANOVA.
\(†P<0.01\) for all within-group comparisons of stress vs rest by paired t tests.
\(‡P<0.05\) vs NL adjusting for age.
consumption was also measured in the latter study and shown to be lower in CH than in CR or normal geometry.

Examining the separate components of RWT and LV mass in multivariate analysis adjusting for age and sex, Pierson et al. demonstrated an independent effect of LV mass indexed to height, but not RWT, on peak exercise oxygen consumption. A sex-stratified analysis was not available in this study but was performed in a study by Gharavi et al., where LV mass predicted maximal VO2 in hypertensive men but not women, an interesting finding also observed in the current study. Although RWT was not examined in the previous study, we further found that, despite a lack of association with LV mass in women, increasing RWT was still associated with decreasing exercise capacity in women, suggesting that LV "shape relative to size" may be a more important determinant of exercise performance in women than "absolute LV size." However, none of these associations between individual components of LV geometry and exercise capacity remained statistically significant after accounting for age in men and women in our study, and further studies are warranted.

In aggregate, our data are consistent with the previous data and extend the findings to older subjects in the largest study of its kind to date. The large sample size in this study provided statistical power to detect even modest (r<0.2) associations of potential physiological significance. Similarly, modest associations of known clinical importance include the correlation between severity or duration of systemic hypertension and the degree of LV hypertrophy. The large number of subjects in the current study also allowed adjustment for important covariates (age, sex, and medications) to yield clinically meaningful results. Clinical characteristics and distribution of LV geometry patterns in this sample closely resemble those observed in population-based studies from the Olmsted County, Minn, general community of subjects typically at risk of heart failure with preserved ejection fraction (HFrEF). Abnormal Systolic and Heart Rate Reserve in CH

The current data suggest that impaired systolic and chronotropic reserves may contribute to reduced exercise capacity in adults with CH. Similar findings have been observed in other populations with cardiovascular disease. Patients with HFrEF often display CH, and hypertensive heart disease is considered a precursor condition to HFrEF. In previous studies comparing hypertensive controls with patients with HFrEF, blunted increases in ejection fraction with peak exercise, as well as attenuated chronotropic responses, were demonstrated in HFrEF. Although a direct association with LV geometry was not investigated in these previous studies, HFrEF patients had smaller LV volumes and increased LV mass compared with hypertensive controls with predominantly CH. More recent studies from this group have again shown that contractile reserve is attenuated in HFrEF compared with hypertensives, even during submaximal effort. These findings lead to the speculation that "occult" systolic dysfunction may be present at rest in CH, despite the preservation of ejection fraction and chamber contractility, and that this systolic dysfunction becomes apparent with exercise stress. Indeed, it is known that the increase in RWT in CR allows normal circumferential shortening at the endocardi um and preservation of ejection fraction, even when midwall myocardial shortening is depressed, and that midwall LV shortening is inversely related to LVMI under resting conditions.

Clinical Implications

The current results suggest that hypertrophic remodeling in itself may contribute to exercise disability by impairing systolic and chronotropic reserve function. The observation across studies of a progressive impairment from normal geometry to CH to HFrEF suggests that upstream therapies targeting hypertrophic remodeling may prevent the progression of asymptomatic hypertension (stage B) to symptomatic heart failure (stage C). These data lend support to the use of anti-remodeling strategies to preserve or improve exercise tolerance in future trials. Intriguingly, aerobic exercise itself has been shown to have a beneficial effect on ventricular remodeling. This "physiological" remodeling is manifested as EH in athletes and serves as an adaptive response to enhance exercise performance. Attenuation of LV concentricity by exercise training, without affecting LV mass, has been elegantly demonstrated in animal models of hypertension.

In this regard, it is of interest that chronotropic response was relatively preserved in EH compared with CH despite a similar use of β-blockers in both groups in the current study. In addition, although EF responses to exercise were similar, an increase of 6% in EH represents a larger absolute increase in stroke volume because of the larger end-diastolic volume in EH. We speculate that both of these mechanisms may potentially contribute to better exercise tolerance in EH. Importantly, we cannot discern "pathological" from "physiological" eccentric remodeling in this study, and the EH
group likely included both types of patients. It may be that any benefits from physiological EH were offset by pathological EH. This deserves further study.

Limitations
Invasive measurements and expiratory gas analysis were not available in this study. However, echocardiography is a well-established clinical tool to assess LV function, and METs provide a reasonable measure of exercise capacity that has been validated and widely applied in previous studies. Although it would be preferable to hold all patients at peak workload to obtain all measurements, this was not feasible because of limiting symptoms of dyspnea and fatigue. All of the groups were examined with the same protocol (imaging achieved immediately after peak), and there was no systematic disparity among geometry groups in the way heart rate and blood pressure decayed during early recovery ($P>0.05$ for all of the group comparisons with Dunnett test). Ejection fraction varies inversely with afterload, and there may have been differences in the change in LV loading during exercise among the geometry groups. Nonetheless, the change in systolic blood pressure during exercise was lowest in CH and EH patients, arguing against afterload mismatch as an explanation for the impaired EF response in these patients. The large SDs of $E/e'$ measurements during exercise may have limited our inability to detect a statistically significant difference. The notable increase in left atrial size across geometry groups suggests an increasing diastolic burden across groups; the contribution of left atrial function to exercise capacity deserves further study.

Perspectives
Among low-risk patients referred for exercise echocardiography, abnormal ventricular geometry was associated with impaired exercise performance. Patients with CH displayed the most impaired exercise capacity, in association with reduced systolic and chronotropic reserve. These results support the notion that ventricular remodeling influences cardiovascular performance with exercise and may serve as a novel therapeutic target to prevent or treat functional decline in patients with structural heart disease.

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Disclosures
None.

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