Left Ventricular Hypertrophy

Prediction of Mortality in Patients With Left Ventricular Hypertrophy by Clinical, Exercise Stress, and Echocardiographic Data

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OBJECTIVES
This study evaluated the clinical, exercise stress test, and echocardiographic predictors of mortality and cardiac events in patients with left ventricular hypertrophy (LVH).

BACKGROUND
Left ventricular hypertrophy is associated with an increased risk of cardiovascular morbidity and mortality.

METHODS
Symptom-limited treadmill exercise echocardiography was performed for evaluation of coronary artery disease in 483 patients (age, 66 ± 11 years; 281 men) with LVH. End points during follow-up were all-cause mortality and hard cardiac events (cardiac death and nonfatal myocardial infarction [MI]).

RESULTS
Forty-six patients died and 14 had nonfatal MI. The cumulative mortality rate was higher in patients with abnormal exercise echocardiography (3% vs. 0.4% at one year, 11.7% vs. 3.7% at three years, and 18.3% vs. 9.5% at five years, p < 0.001). In a sequential multivariate analysis model of clinical, exercise test, and rest and exercise echocardiographic data, incremental predictors of mortality were workload (hazard ratio [HR], 0.5; 95% confidence interval [CI], 0.3 to 0.9), rate pressure product (HR, 0.7; 95% CI, 0.5 to 0.9), left ventricular (LV) mass index (HR, 1.4; 95% CI, 1.1 to 1.8), and failure to increase ejection fraction (EF) with exercise (HR, 2.1; 95% CI, 1.1 to 3.8). Predictors of cardiac events were history of coronary artery bypass grafting (HR, 2.6; 95% CI, 1.2 to 5.4), lower exercise rate-pressure product (HR, 0.6; 95% CI, 0.5 to 0.8), resting wall motion score index (HR, 1.4; 95% CI, 1.1 to 1.8), and failure to increase EF with exercise (HR, 3.3; 95% CI, 1.6 to 6.9).

CONCLUSIONS
In patients with LVH, LV mass index and EF response to exercise are independent predictors of mortality, incremental to clinical and exercise test data and resting LV function. A normal exercise echocardiogram predicts a relatively low mortality rate during the following three years.
Abbreviations and Acronyms

- CAD = coronary artery disease
- ECG = electrocardiogram/electrocardiographic
- EF = ejection fraction
- LV = left ventricle/ventricular
- LVH = left ventricular hypertrophy
- METs = metabolic equivalents
- MI = myocardial infarction

METHODS

Patients. The population of this study was selected from patients referred between 1990 to 1995 for exercise echocardiography for the diagnosis or functional evaluation of CAD. Patients were included if they had an increased mean LV wall thickness (>11 mm) (15). Exclusion criteria were left bundle branch block, significant valvular heart disease, or previous valve surgery. The final population of the study consisted of 483 patients. The Institutional Review Board approved the study.

Data regarding patients' history and risk factors were entered in our computerized database at the time of the exercise echocardiogram. Hypercholesterolemia was defined as total cholesterol >200 mg/dl or use of a cholesterol-lowering agent. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medication. Diabetes mellitus was defined by the presence of a fasting blood glucose concentration ≥140 mg/dl or requirement for insulin or orally administered hypoglycemic agents.

Exercise echocardiography. Patients underwent symptom-limited treadmill exercise testing according to the Bruce protocol in 83%, Naughton protocol in 10%, and modified Bruce protocol in 7%. Standard blood pressure and 12-channel ECG monitoring were performed. Two-dimensional echocardiographic images were obtained from the parasternal and apical windows at rest and immediately after exercise. Left ventricular septal thickness, posterior wall thickness, and chamber size were measured at rest in the parasternal long-axis view at end diastole. Mean wall thickness was defined as the average of septal and posterior wall thicknesses. Left ventricular mass was calculated using Troys method, and measurements were made in accordance with the American Society of Echocardiography criteria (16) as follows: LV mass (g) = 1.04 [(IVS + LVDD + PWT)² - (LVDD)²], where IVS is interventricular septal thickness in cm, LVDD is left ventricular diastolic diameter, and PWT is left ventricular posterior wall thickness in cm. The result was then corrected by the following equation (17) to correlate with necropsy mass: LV mass (g) = 0.8 (LV mass) + 0.6. The LV mass was indexed by body surface area using normal limits from the Framingham Heart study. Left ventricular mass index >116 g/m² in men and >104 g/m² in women was considered abnormal (18). Patients who had normal LV mass index were considered to have concentric remodeling (19).

Interpretation of images. Both digitized and videotape-recorded images were used for interpretation of the studies (20). Ejection fraction (EF) at rest was measured using a previously validated (21) modification of the method of Quinones et al. (22) or by visual estimation (23) and at exercise by visual estimation. Regional wall motion was assessed semiquantitatively by an experienced echocardiographer blinded to clinical information. Wall motion at rest and with exercise was scored 1 through 5 according to a 16-segment model (24). Regional wall motion score index was determined at rest and peak exercise as the sum of the segmental scores divided by the number of visualized segments. This method has been previously validated in our laboratory (25). The development of new or worsening wall motion was considered indicative of myocardial ischemia. A wall motion abnormality present at rest and unchanged with exercise was classified as fixed. Exercise echocardiography results were defined as abnormal if there was ischemia or fixed wall motion abnormalities (11). The exercise ECG was considered positive for ischemia if there was horizontal or downsloping ST-segment depression of ≥1 mm at 80 ms after the J point, nondenstrophic if the baseline ST-segment was abnormal, or negative for ischemia in the absence of the criteria described above. Workload was measured in metabolic equivalents (METs).

Intraobserver and volumetric validation. In a sample of 25 tests randomly selected to represent a range of responses, image qualities, and LV mass index, two independent observers determined the EF at rest and with exercise. An independent observer measured EF at rest and with exercise using the modified biplane Simpson method (Image Vue, Nova Microsonics, Allendale, New Jersey).

Follow-up. Follow-up was obtained by mailed questionnaires and scripted telephone interviews. Events were verified by contacting the patients' primary physician and reviewing medical records and death certificates. The end points considered were all-cause mortality and hard cardiac events defined as nonfatal myocardial infarction (MI) and cardiac death. Sudden death occurring without another explanation was included as cardiac death. Coronary revascularization procedures during the follow-up period were also noted. Patients who had coronary angioplasty or coronary artery bypass surgery before other events were censored at the time of revascularization in the analysis of hard cardiac events.

Statistical analysis. Continuous variables were reported as mean ± SD, and categorical variables as percentages. The level of agreement (interobserver and intermethod) for exercise EF was assessed by the method of Bland and Altman. Cohen's kappa statistic was used to assess the level of agreement for the subjective categorization of the EF response to exercise (increased vs. unchanged or decreased) and the intermethod categorization of the EF response. Univariable and multivariable association of clinical and exercise echocardiographic variables with the end points were assessed in the Cox proportional hazards framework.
The results of these analyses were summarized as hazard ratios with corresponding 95% confidence intervals. The incremental value of exercise stress and echocardiographic information over clinical data for the prediction of points of interest was assessed in four modeling steps. The first step consisted of fitting a multivariable model of only clinical data. Exercise ECG and hemodynamic variables were added in a stepwise forward selection manner to the clinical model. Rest echocardiographic variables were then added to this model in a stepwise forward selection manner. In the final step, exercise echocardiographic variables were added.

RESULTS

Clinical data. The mean age was 66 ± 11 years. There were 281 men. Risk factors for CAD were hypertension in 443 patients (92%), diabetes mellitus in 81 patients (17%), hypercholesterolemia in 266 patients (55%), and smoking in 255 patients (53%). Sixty-seven patients (14%) had a previous MI, and 70 (14%) underwent previous myocardial revascularization. Typical anginal pectoris was present in 106 patients (22%), and 166 patients (34%) had atypical chest pain. Left ventricular hypertrophy on baseline ECG was present in 281 men. Risk factors for CAD were hypertension in 266 patients (55%), and smoking in 255 patients (53%). In 21 patients, revascularization was performed within 3 months after the exercise stress test. Patients who underwent revascularization had a higher prevalence of abnormal exercise echocardiogram (73% vs. 45%, p = 0.0001) and new or worsening wall motion abnormalities (63% vs. 31%, p = 0.0001) and more frequently had exercise-induced ST-segment depression (40% vs. 16%, p < 0.0001).

Echocardiographic data. Resting wall motion abnormalities were present in 163 patients (34%). The LV mass index was increased in 354 patients (73%), and 129 patients (27%) had concentric remodeling. The mean LV mass index was 139 ± 40 gm/m². Ejection fraction was 60 ± 8% at rest and 66 ± 11% after exercise (p = 0.001). Exercise-induced wall motion abnormalities (regional ischemia) occurred in 169 patients (35%). Of these, 96 patients also had resting wall motion abnormalities. The exercise echocardiogram was considered normal in 247 patients (51%).

Interobserver and intermethod variation. There was 100% interobserver agreement (kappa = 1.0) for the subjective categorization of the EF response to exercise. Two observers, one using volumetrics and the other visual assessment, agreed on the EF response to exercise in 96% of the cases (kappa = 0.78 ± 0.14). The interobserver difference in the subjective assessment of exercise EF was 0.4 ± 7 (95% limits of agreement −3%, 3%). The mean difference between the visually estimated exercise EF and volumetric assessment was 0.2 ± 1.0 (95% limits of agreement −4%, 3%).

Outcome. During a median follow-up of 3 years (range, 1 day to 7.6 years), 46 patients died. Death was due to cardiac causes in 20 patients; malignancies in 11 patients; stroke in 5 patients; renal failure in 5 patients; infection in 2 patients; and chronic obstructive pulmonary disease, suicide, and trauma each occurring in 1 patient. Fourteen patients had nonfatal MI. A total of 33 hard cardiac events were noted. An additional patient with cardiac death was not included as he underwent myocardial revascularization after the test.

The cumulative mortality rate was higher in patients with abnormal, compared with patients with normal, exercise echocardiography (3% vs. 0.4% at one year, 11.7% vs. 3.7% at three years, and 18.3% vs. 9.5% at five years, p = 0.02).

Clinical, ECG, and hemodynamic variables associated with the risk of mortality and hard cardiac events in the univariate analysis are listed in Table 1. Predictors of events in the in the incremental multivariate analysis models are presented in Tables 2 (all-cause mortality) and 3 (hard cardiac events).

Revascularization procedures. During the follow-up period, 60 patients (12%) underwent coronary revascularization. In 21 patients, revascularization was performed within 3 months after the exercise stress test. Patients who underwent revascularization had a higher prevalence of abnormal exercise echocardiogram (73% vs. 45%, p < 0.0001) and new or worsening wall motion abnormalities (63% vs. 31%, p < 0.0001), and more frequently had exercise-induced ST-segment depression (40% vs. 16%, p < 0.0001).

DISCUSSION

In this study we evaluated the role of clinical, exercise stress, and echocardiographic data in the prediction of mortality and nonfatal MI in 483 patients with LVH and suspected or known CAD. During a median follow-up of 3 years, events occurred in 60 patients and included 46 deaths, 20 of which were due to cardiac causes, and 14 nonfatal MIs. Independent predictors of outcome were studied by an incremental multivariate analysis model that took into consideration the clinical data and the sequence of noninvasive studies (exercise stress test, resting echocardiogram, and exercise echocardiogram), which the physician may order to improve risk stratification.

Among clinical parameters, a history of coronary artery bypass grafting was independently associated with increased risk hard cardiac events. Age, gender, and other risk factors were not predictive of outcome. This demonstrates the difficulties that confront the physician who attempts to risk-stratify patients with LVH using clinical predictors alone. Perhaps the risk associated with LVH was high enough to account for the lack of additional impact of other
In the second step of the incremental multivariate analysis, exercise echocardiographic data were added. Left ventricular mass index was incremental to clinical and exercise stress testing data in the prediction of all-cause mortality, independent of exercise capacity and resting LV function. These findings may be explained by the possibility that patients with a larger LV mass index had more severe target-organ damage with a higher probability of dying of cardiac causes, strokes, and renal failure. The severity of resting LV dysfunction (presented as wall motion score index) was incremental to clinical and exercise stress testing data in the prediction of hard cardiac events. The presence of more severe resting LV dysfunction is an established risk for death from subsequent heart failure or fatal arrhythmias. Furthermore, extensive wall motion abnormalities are a marker of extensive CAD with the associated high risk of cardiac death and nonfatal MI. This may explain the association between a higher wall motion score index and the risk of hard cardiac events in this study.

In the third step, exercise echocardiographic data were added. Failure to increase EF with exercise was predictive of mortality and hard cardiac events, and was incremental to clinical data, exercise hemodynamics, resting LV function, and LV mass index. Presence of exercise-induced wall motion abnormalities was not predictive of outcome. Subtle changes of regional function may be more appreciable than subtle changes of regional function. Poor EF response to

### Table 1. Univariate Association of Clinical, Exercise Stress Test, and Echocardiographic Variables With Risk of Hard Cardiac Events and All-Cause Mortality

<table>
<thead>
<tr>
<th>Clinical/Exercise Parameters</th>
<th>Hard Cardiac Events</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi-Square</td>
<td>Hazard Ratio (CI)</td>
</tr>
<tr>
<td>History of CAD</td>
<td>10.2</td>
<td>3.06 (1.54–6.08)</td>
</tr>
<tr>
<td>History of angina</td>
<td>6.8</td>
<td>2.6 (1.27–5.3)</td>
</tr>
<tr>
<td>% of predicted HR achieved</td>
<td>13.3</td>
<td>0.25 (0.12–0.53)</td>
</tr>
<tr>
<td>Exercise HR</td>
<td>18.8</td>
<td>0.74 (0.66–0.82)</td>
</tr>
<tr>
<td>Exercise rate pressure product</td>
<td>21.5</td>
<td>0.16 (0.07–0.35)</td>
</tr>
<tr>
<td>Left ventricular mass index</td>
<td>4.5</td>
<td>1.08 (1.01–1.16)</td>
</tr>
<tr>
<td>Rest EF</td>
<td>14</td>
<td>0.54 (0.35–0.74)</td>
</tr>
<tr>
<td>Exercise EF</td>
<td>31.1</td>
<td>0.54 (0.48–0.66)</td>
</tr>
<tr>
<td>Failure to increase EF</td>
<td>22.6</td>
<td>0.19 (0.1–0.38)</td>
</tr>
<tr>
<td>Exercise WMA</td>
<td>5.4</td>
<td>2.35 (1.14–4.86)</td>
</tr>
<tr>
<td>New WMA (ischemia)</td>
<td>3.6</td>
<td>1.9 (0.97–3.84)</td>
</tr>
<tr>
<td>% of ischemic segments</td>
<td>7.2</td>
<td>1.85 (1.18–2.88)</td>
</tr>
<tr>
<td>% Rest WMSI</td>
<td>17.4</td>
<td>5.6 (2.5–12.7)</td>
</tr>
<tr>
<td>% Exercise WMSI</td>
<td>19</td>
<td>4.7 (2.35–9.5)</td>
</tr>
</tbody>
</table>

*Per 10 U increment; †Per 1,000 U increment; ‡Per 25% increment (4 of 16 segments); §Per 1 U change. CAD = coronary artery disease; CI = confidence interval; EF = ejection fraction; HR = heart rate; WMA = wall motion abnormalities; WMSI = wall motion score index.

### Table 2. Independent Predictors of All-Cause Mortality Using Four-Step Model

<table>
<thead>
<tr>
<th>Models</th>
<th>Parameters</th>
<th>Hazard Ratio (95% CI)*</th>
<th>p Value</th>
<th>Model Chi-Square‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Age†</td>
<td>1.0 (0.7–1.5)</td>
<td>0.95</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Male gender</td>
<td>1.5 (0.8–2.9)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Known CAD</td>
<td>1.3 (0.7–2.4)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Clinical + exercise stress</td>
<td>METs†</td>
<td>0.5 (0.3–0.9)</td>
<td>0.01</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Rate pressure product†</td>
<td>0.7 (0.5–0.9)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Clinical, exercise stress +</td>
<td>Left ventricular mass</td>
<td>1.4 (1.1–1.9)</td>
<td>0.007</td>
<td>45</td>
</tr>
<tr>
<td>rest echocardiography +</td>
<td>index†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical, exercise stress, rest</td>
<td>Failure to increase ejection</td>
<td>2.1 (1.1–3.8)</td>
<td>0.02</td>
<td>51</td>
</tr>
<tr>
<td>echocardiography +</td>
<td>fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exercise echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Information is based on final model fit; †Hazard ratio and 95% CI per 1 SD change in covariate; ‡Degrees of freedom for testing improvement in model fit over previous model is equal to the number of variables presented within modeling increments. CAD = coronary artery disease; CI = confidence interval; METs = metabolic equivalents.
exercise may reflect more extensive disease and, consequently, a more adverse prognosis than regional abnormalities alone. Furthermore, a poor EF response to exercise may indicate diffuse microvascular abnormalities in patients with LVH (26,27). Impaired EF response to exercise was previously demonstrated as a marker of adverse prognosis, although the specificity for the diagnosis of CAD was low (28,29).

**Event rate in patients with normal exercise echocardiogram.** Patients with a normal exercise echocardiogram in this study had a significantly lower mortality rate (0.4% vs. 3% at one year, 3.7% vs. 11.7% at three years, and 9.5% vs. 18% at five years) and hard cardiac event rate (0.8% vs. 3.4% at one year, 3.8% vs. 8.6% at three years, and 6.9% vs. 15.8% at five years, \( p < 0.001 \)) as compared with patients with an abnormal exercise echocardiogram. However, the relatively low risk status of patients with a normal exercise echocardiogram was maintained only to three years. A follow-up study after three years may be useful to reassess the risk status of these patients; further studies are required to establish this as a recommendation.

**Myocardial ischemia.** Myocardial ischemia (new or worsened wall motion abnormalities) was univariately associated with increased risk of cardiac events. However, the relative risk was marginal when compared with the risk associated with the presence and extent of resting wall motion abnormalities. This may be explained by the possibility that some of the resting wall motion abnormalities represent myocardial ischemia rather than infarction. This contention is supported by the fact that 34% of patients in this study had resting wall motion abnormality, although a history of previous MI was obtained in only 14%. Some of these wall motion abnormalities may be the consequence of hypertensive heart disease or the advanced phase of remodeling of a hypertrophied ventricle and may occur in the absence of significant CAD. Finally, revascularization procedures were more frequently performed in patients with ischemia. Although the results of the test may be a source of bias in referral to revascularization, it is possible that prognosis has been improved in some of these patients by revascularization, thus limiting the value of ischemia in predicting hard cardiac events.

**Previous studies.** To our knowledge, the prognostic value of stress echocardiography in patients with LVH has not been previously studied. Recent studies have demonstrated that the specificity of stress echocardiography for the diagnosis of CAD is maintained in patients with LVH (15,30). Few studies have established a comparison between various stress testing modalities for the diagnosis of CAD using angiography as gold standard in patients with LVH. These studies reported controversial results with some indicating a similar accuracy between both techniques (30) and others indicating a higher specificity of stress echocardiography (10). It is noteworthy that the presence of myocardial perfusion and wall motion abnormalities in the absence of significant CAD may represent a disease beyond angiographic detection, with independent prognostic implications. A recent study utilizing dual isotope myocardial perfusion single photon emission computed tomography in patients with ECG evidence of LVH demonstrated that the summed stress score of perfusion abnormalities added incremental prognostic information after adjusting for clinical parameters. The impact of LV mass on prognosis was not evaluated in that study (31).

Levy et al. (18) reported risk of event in terms of each increment of 50 gm/m of LV mass, consistent with the results of this study. Our study showed additionally that this risk is incremental to resting LV function, hemodynamic response to exercise, and functional capacity. Previous studies have demonstrated that patients with concentric LV hypertrophy have the highest event rate as compared with other patterns of LVH (19,32–34). In our study cardiac events occurred less frequently in patients with concentric remodeling. However, the pattern of hypertrophy was not an independent predictor of outcome when LV mass index was considered as a continuous variable.

**Study limitations.** A limitation of the study is that 24% of patients were receiving beta-blocker therapy at the time of the exercise stress test, which may have resulted in underestimation of the role of ischemia by ECG and/or echocardiographic detection, with independent prognostic implications.
diography in the prediction of outcome. Assessment of EF in this study was performed by subjective visual analysis. However, the current echocardiographic methods used for quantitative assessment of EF have limitations because these assume a geometric model. Nevertheless, we found a good agreement between visual and volumetric assessment in a randomly selected subset of patients in this study. The use of visual estimation of EF in stress echocardiographic studies has previously been validated by our group (21) as well as by other investigators (35). Finally, the number of cardiac events in this study was relatively low, which may explain the lack of independent association of LV mass index with these events. The low event rate may reflect a lower risk status in a population able to perform an exercise stress test and, possibly, improved outcome with medical treatment. Further studies are needed to assess predictors of events during longer-term follow-up.

Conclusions. It is concluded that LV mass index and EF response to exercise are independent predictors of mortality in patients with LVH. The associated risk is incremental to clinical data, exercise capacity, hemodynamic response to exercise, and resting LV function. A normal exercise echocardiogram predicts a relatively low mortality and cardiac event rate during the subsequent three years.

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