Left Ventricular Hypertrophy Influences Cardiac Prognosis in Patients Undergoing Dobutamine Cardiac Stress Testing

Charaslak Charoenpanichkit, MD; Timothy M. Morgan, PhD; Craig A. Hamilton, PhD; Eric L. Wallace, DO; Killian Robinson, MD; William O. Ntim, MB, ChB; W. Gregory Hundley, MD

Background—This study was performed to determine the utility of dobutamine stress test results for predicting myocardial infarction (MI) and cardiac death in patients with chest pain and left ventricular hypertrophy (LVH).

Methods and Results—Three hundred fifty-three participants with a mean±SD age of 64±12 years (54% men) underwent dobutamine cardiovascular magnetic resonance stress testing and then were followed up for 6±2 years (mean±SD; range, 0.5–11.5) to assess the post–dobutamine cardiovascular magnetic resonance stress test occurrence of MI or cardiac death. LV mass and the presence or absence of ischemia were determined; LVH was defined as an LV mass index >96 g/m² in men and >77 g/m² in women. LVH was present in 62 participants (18% of the men and 17% of the women, P = 0.90). Seventy-one (20%) participants experienced an MI or cardiac death during follow-up. The MI and cardiac death rate was more frequent in those with versus without LVH (32% vs 17%, P = 0.009). In multivariable analysis that accounted for the presence of preexisting coronary artery disease, hypertension, diabetes, stress-induced ischemia, and reduced LV ejection fraction, LVH was an independent predictor of MI and cardiac death (hazard ratio = 1.99; 95% CI, 1.13–3.50; P = 0.02).

Conclusions—LVH is predictive of future MI and cardiac death in patients with or without inducible ischemia during dobutamine cardiac stress testing. As a result, LVH should be reported in those referred for dobutamine cardiac stress tests, particularly in those without inducible ischemia, in whom one would otherwise assume a favorable cardiac prognosis. (Circ Cardiovasc Imaging. 2010;3:392-397.)

Key Words: hypertrophy • MRI • myocardial infarction

I n those with chest pain referred for dobutamine stress testing, the absence of inducible ischemia has been shown to confer a low risk of future adverse cardiac events. More recently, left ventricular hypertrophy (LVH), a strong, independent predictor of cardiovascular events and all-cause mortality, has become a relatively frequent finding in patients with chest pain referred for noninvasive dobutamine cardiac stress testing. At present, it is unknown whether the absence of inducible LV wall motion (LVWM) abnormalities indicative of ischemia (that normally carries a favorable prognosis in the absence of LVH) confers a negative cardiac prognosis in patients with LVH. The purpose of this study was to determine the importance of LVH in patients with chest pain referred for dobutamine cardiovascular stress testing procedures.

Clinical Perspective on p 397

Methods

Our study was approved by the institutional review board at the Wake Forest University School of Medicine, and all participants provided informed consent. Between 1997 and 2004, 562 dobutamine cardiovascular magnetic resonance (DCMR) studies were performed to diagnose inducible ischemia in which LVWM was visualized throughout testing and LV mass could be measured from the acquired images. Patients’ routine use of medications, including β-receptor antagonists, was unaltered before testing. Comprehensive demographic data regarding health status and medication use were collected at the time of testing. For the purposes of our study, prior myocardial infarction (MI), hypertension, diabetes, and hypercholesterolemia were defined according to previously published criteria. The study was designed as a prospective cohort analysis in which cardiac outcomes were assessed after participants received stress DCMR.

DCMR Procedure

DCMR was performed according to previously published techniques with single-slice, multiphase gradient-echo images of the left ventricle acquired on a Horizon 1.5-T whole-body imaging system (General Electric Medical Systems) at rest and then after dobutamine was infused to achieve 80% of the maximum predicted heart rate response for age. Image parameters included a 256×128 matrix, a 35- to 48-cm field of view, a 10-ms repetition time, a 4-ms echo time, a 20° flip angle, an 8-mm slice thickness, and a 40-ms temporal resolution. Images were analyzed during and directly after the examination with the use of a software program designed for display of DCMR results in a multiview, synchronized format. Inducible
LVWM abnormalities were defined as deterioration of LVWM (with the exception of akinesia to dyskinesia) in any myocardial segment observed in 2 orthogonal planes of the left ventricle during infusion of dobutamine. The resting LV ejection fraction (LVEF) was measured with a biplane area-length technique. LV mass was calculated from wall thickness measurements according to a truncated ellipsoid technique that was indexed to body surface area (BSA). Papillary muscle mass was included in the LV cavity but excluded from the LV mass determination. According to previously published techniques, threshold values of LV mass (96 g/m² and 77 g/m² in men and women, respectively) were used to define LVH. Alternative analyses were also performed that defined LVH according to values indexed by height.

Follow-Up
Personnel blinded to the DCMR stress testing results contacted each subject (or if deceased, an immediate family member) to determine whether cardiac events had occurred since their DCMR test. The date of the contact was used to calculate follow-up times. All events were confirmed by review of the participants’ medical records or death certificates. Hard events were defined as MI (angina of ≥30 minutes’ duration and either a ≥2-mm and 1-mm ST-segment elevation in men and women, respectively, in 2 consecutive ECG leads or detection of a rise in cardiac biomarkers (troponin I) with at least 1 value >99th percentile of the upper reference limit, or cardiac death (death in the presence of acute coronary syndrome, significant cardiac arrhythmia, or refractory congestive heart failure)). ECG, enzymatic, or autopsy data were used to substantiate cardiac events, including (when available) cardiac mortality.

Statistical Analysis
Differences in baseline characteristics stratified by LVH were compared with χ² and Student’s t tests for categorical and continuous characteristics, respectively. Kaplan–Meier methods were used to estimate the probability of hard cardiac events as a function of 5 years of follow-up, and unadjusted differences were compared with the log-rank test, with weight given during these 5 years. Multivariable Cox proportional-hazards regression models were constructed to identify independent predictors of the time to cardiac events. Factors known to predict cardiovascular events that were recorded were included in the model. The risk of a given variable was expressed by a hazard ratio (HR) with corresponding 95% CIs. Variables were considered significant if the null hypothesis of no contribution could be rejected at the 5% 2-sided level of significance. In addition to the primary analysis of comparing time to hard events between those with and without LVH, secondary analyses estimated the increase risk associated with LVH in subgroups defined by prior MI, ischemia, and LVEF <40%, although preliminarily there was thought to be somewhat insufficient power to detect clinically important HRs with the number of events per subgroup.

Results
Of the 362 patients who underwent DCMR and had follow-up, 9 underwent immediate (within 4 weeks) coronary artery revascularization and were excluded from further analysis to avoid the possibility of a hard event resulting from a revascularization procedure. This exclusion resulted in a study population of 353 participants; LVH was present in 62 participants, or 17.6%, of the study population, including 18% of the men and 17% of the women (P=0.90). The demographic and clinical characteristics of the participants are shown in Table 1. The age (63 vs 64 years, P=0.80), sex (men 55% vs women 54%, P=0.90), and body mass index (31 vs 31 kg/m²; P=0.91) were similar between those with and without LVH.

Fifty-four participants (37 with inducible ischemia, 12 on receipt of maximal stress, and 5 with angina) did not achieve 80% of the maximum predicted heart rate response for age. Participants with LVH exhibited more diabetes mellitus; prior history of MI, congestive heart failure, and smoking were similar between the groups. Hypertension was prevalent in all study participants and trended higher in those with LVH. Overall, renin-angiotensin–converting enzyme inhibitors were prescribed more frequently in participants with LVH (26% vs 48%, P=0.003). Both participant groups did not
women, even after accounting for BSA (75 versus 105 g/m². LV mass was greater in men than in
averaged 69 ± 22 g/m² in patients without LVH versus 105 ± 19 g/m² in patients with
LVH (P < 0.001). Compared with those without LVH, patients with LVH had a lower LVEF (48 ± 14% vs 57 ± 12%, P < 0.001) and a higher prevalence of inducible ischemia during DCMR (48% vs 27% with ischemia, P = 0.001). In 27% of patients (17 of 62) with LVH, the resting wall motion was normal, whereas in patients without LVH, 49% (136 of 279) had no segmental wall motion abnormalities (P = 0.02).

During a mean ± SD follow up of 6.2 ± 2 years (range, 0.5 to 11.5), 138 participants, or 39%, experienced at least 1 cardiac event. Of these 138 participants, 71 (51%) experienced a hard event (including 32 subjects with nonfatal MIs and 39 subjects with cardiac death). The hard cardiac event rate at 5 years was greater in patients with LVH than in those without LVH (32% vs 14%, P = 0.009). Men and women with LVH had similar 5-year hard cardiac event rates (20% vs 16%, P = 0.31). As shown in Figure 1, LVH was associated with a reduced event-free survival for hard events (P < 0.0085).

As shown in Figure 2, among participants with a history of prior MI, the risk of hard cardiac events was greater in participants with LVH (HR = 2.34; P = 0.01; 5-year hard event value of 48% vs 23% without LVH); for those without prior MI, the risk of hard events was also higher in those with LVH (HR = 2.31; P = 0.05; 5-year event rate of 22% vs 10% in those without LVH). Among participants with or without inducible ischemia, participants with LVH experienced more hard cardiac events (HR = 1.88 [5-year event rate of 41% vs 23% in those without LVH] and HR = 2.67 [5-year event rate of 28% in those without ischemia vs 11% in those without LVH]); however, it was only statistically significant in the nonischemic group (P = 0.08 and P = 0.01, respectively; Figure 3). When analysis was performed to evaluate participants with an LVEF ≥40% or <40%, the incidence of hard cardiac events was higher in participants with LVH for both groups (HR = 2.21 [5-year event rate of 27% vs 13% in those without LVH] and HR = 1.94 [5-year event rate of 54% vs 30% in those without LVH]), but it was only statistically significant in those with an LVEF ≥40% (P = 0.02 and P = 0.19, respectively; Figure 4).

The univariable and multivariable HRs for cardiac events are displayed in Table 2. After adjustment for age, sex, body mass index, and other risk factors for cardiac events, LVH, inducible ischemia, and prior history of MI were independent predictors of an increased risk of hard cardiac events. Eight subjects exhibited a biphasic response during dobutamine stress. The incidence of hard events at 5 years was 40% in these 8 subjects compared with a 26% incidence (P = 0.61 for difference) of hard events in individuals with ischemia who did not exhibit a biphasic response.

When LV mass indexed to BSA was treated as a continuous rather than a dichotomous variable, there remained a

![Figure 1. Kaplan–Meier survival curves for MI and cardiac death in participants with chest pain referred for dobutamine stress testing, stratified by LVH. Compared with patients without LVH, event-free survival was reduced in participants with LVH.](http://circimaging.ahajournals.org/)

![Figure 2. Kaplan–Meier survival curves for MI and cardiac death in participants receiving dobutamine stress testing with or without a history of prior MI, stratified by LVH. Compared with patients without a history of prior MI and LVH, event-free survival was significantly reduced in participants with LVH.](http://circimaging.ahajournals.org/)

![Figure 3. Kaplan–Meier survival curves for MI and cardiac death in participants receiving dobutamine stress testing with or without inducible ischemia, stratified by LVH. Compared with participants without inducible ischemia and LVH, event-free survival was significantly reduced in participants with LVH. Note the reduced event-free survival in participants with LVH and no ischemia relative to those without LVH but with inducible ischemia.](http://circimaging.ahajournals.org/)
significant association between LV mass and cardiac events \((P<0.03)\). Analyses were performed to determine whether different indices of LV mass were predictive of cardiac events after accounting for the results of dobutamine stress. As shown in Table 3, all measures of LVH were predictive of MI or cardiac death.

### Discussion

The major finding of this study relates to the importance of LVH in individuals with chest pain who are referred for dobutamine stress tests. The results of this study indicate that LVH is an independent predictor of cardiovascular events in patients with chest pain referred for dobutamine stress testing. This is true regardless of whether LV mass is indexed to BSA or height. Importantly, in those without inducible LV WM abnormalities indicative of ischemia during dobutamine stress, the presence of LVH portends a poor cardiac prognosis. This finding is important, given that in the absence of inducible LV WM abnormalities indicative of ischemia, often termed a “negative” stress test result, these negative dobutamine stress results are frequently used to ascribe a low risk of future MI or cardiac death. The results of this study indicate clearly that individuals with chest pain and LVH who have no inducible LV WM abnormalities during dobutamine testing continue to be at risk of MI and cardiac death.

The presence of LVH has been shown to reduce the sensitivity of LV WM analyses assessed during dobutamine stress testing for identifying inducible ischemia due to >50% coronary arterial luminal narrowing. Recently, our group identified that increased LV end-diastolic wall thickness was associated with MI and cardiac death in individuals with a resting LVEF >55% and no inducible LV WM abnormalities indicative of ischemia after intravenous dobutamine. Participants in the current study included those with chest pain referred for dobutamine stress testing to identify LV WM abnormalities indicative of inducible ischemia. All variables known to be associated with a risk of cardiovascular events recorded in our dataset were included in our models to predict MI or cardiac death. Inclusion of all variables was performed to avoid bias by simply selecting variables that might have reached statistical significance. In this study, we recognize that there is insufficient power to detect HRs of 1.0 to 2.0

| Table 3. Relation of Different Indices of LV Mass to MI and Cardiac Death |
|------------------|------------------|------------------|
|                  | Unadjusted Model |                 |
|                  | HR (95% CI)      | \(P\) Value     |
| LV mass, g       | 1.005 (1.00–1.01) | 0.03            |
| LV mass/BSA, g/m^2 | 1.019 (1.019–1.03) | <0.001         |
| LV mass/height, g/m | 3.17 (1.40–7.19)     | 0.005          |
| LV mass/height >1 or <1 g/m | 2.23 (1.30–3.82)     | 0.003          |

Table 2. Relation of LV Mass to MI and Cardiac Death

<table>
<thead>
<tr>
<th>Model</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>(P) Value</td>
<td>HR (95% CI)</td>
<td>(P) Value</td>
</tr>
<tr>
<td>LVH (g/m^2)*</td>
<td>2.59 (1.51–4.43)</td>
<td>&lt;0.001</td>
<td>1.99 (1.13–3.50)</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>3.20 (1.78–5.76)</td>
<td>&lt;0.001</td>
<td>1.90 (0.98–3.69)</td>
<td>0.06</td>
</tr>
<tr>
<td>Inducible ischemia</td>
<td>2.44 (1.47–4.05)</td>
<td>&lt;0.001</td>
<td>1.87 (1.06–3.31)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>1.53 (0.91–2.57)</td>
<td>0.10</td>
<td>1.56 (0.90–2.71)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.36 (0.81–2.28)</td>
<td>0.24</td>
<td>0.85 (0.48–1.50)</td>
<td>0.57</td>
</tr>
<tr>
<td>BMI</td>
<td>0.97 (0.94–1.01)</td>
<td>0.16</td>
<td>0.98 (0.93–1.02)</td>
<td>0.28</td>
</tr>
<tr>
<td>Prior Q-wave MI</td>
<td>2.95 (1.76–4.93)</td>
<td>&lt;0.001</td>
<td>2.72 (1.59–4.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.01 (0.60–1.67)</td>
<td>0.98</td>
<td>1.04 (0.61–1.76)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.36 (0.76–2.43)</td>
<td>0.30</td>
<td>1.28 (0.68–2.40)</td>
<td>0.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.30 (0.78–2.18)</td>
<td>0.31</td>
<td>0.86 (0.49–1.51)</td>
<td>0.60</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.49 (0.90–2.47)</td>
<td>0.12</td>
<td>1.35 (0.79–2.33)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

BMI indicates body mass index. Other abbreviations are as defined in text.

*LVH was defined as an LVMi >96 g/m^2 and 77 g/m^2 in men and women, respectively.
within subgroups of individuals with LVH who exhibited a significant HR for cardiac events within our multivariate model. Importantly, however, we were able to determine that LVH is an independent predictor of adverse cardiovascular events within our multivariable model that includes known predictors for cardiovascular events.

Results of this study indicate that LVH should be reported in individuals referred for dobutamine wall motion stress testing. As shown in Figure 3, the adverse prognosis associated with LVH in individuals without inducible ischemia was similar to those without LVH and inducible ischemia. Of note, the poor prognosis of those with LVH, but without ischemia, is also similar to populations with ischemia reported in other magnetic resonance imaging stress studies. The results of this study raise important concerns for individuals who develop hyperdynamic wall motion responses during dobutamine echocardiography or cine magnetic resonance but concomitantly exhibit LVH. Data from this study indicate that these individuals, while exhibiting no apparent inducible wall motion abnormalities to suggest an adverse prognosis, do indeed continue to have an adverse prognosis related to the presence of LVH.

Because image data for participants in this study were acquired primarily before the year 2000, newer, more rapid acquisitions of myocardial perfusion or delayed enhancement were not used during the stress cine magnetic resonance protocol. For this reason, we were unable to determine whether myocardial fibrosis or dobutamine-induced perfusion defects were present in our study participants. As demonstrated by Kwong et al, the presence of delayed enhancement in patients with chest pain referred for dobutamine stress testing may serve as a marker of an adverse cardiac prognosis. Perhaps other imaging or biomarkers could be used to identify those at risk for future cardiac events in patients with chest pain and LVH who are currently referred for dobutamine wall motion stress tests.

In this study, we performed analyses that stratified our measures of LV mass based on sex. Several studies have performed similar analyses owing to discrepancies in both heart and body size in men versus women. In these studies, women with LVH were found to have a higher risk of adverse outcomes compared with men. In our study, those of either sex and with LVH exhibited an increase in adverse cardiac outcomes. Differences between our results and prior studies may be due to the fact we enrolled few black women, cardiac outcomes. Differences between our results and prior studies may be due to the fact we enrolled few black women, and many of the men had known coronary artery disease. Both of these conditions elevate the risk of cardiac events. The results of this study and others indicate that women with LVH and chest pain referred for dobutamine stress testing exhibit an elevated risk of cardiac events in the presence of LVH. Several criteria have been used previously to define LVH. We found that a higher LV mass indexed to BSA predicted a 2.1-fold risk of subsequent cardiovascular events. In addition to expressing LVH as a dichotomous variable, we performed analyses with LVH as a continuous variable. The relation between LV mass and increased cardiovascular risk was continuous, even down to values below the conventional cutoff for echocardiographically detected LVH (nominally, at least 125 g/m² in men and at least 110 g/m² in women). Previously, Schillaci et al have shown a powerful relation between LV mass and risk of cardiovascular events over a wide range of LV mass values, even below the current “upper normal” limits.

We found that LVMI exhibited similar prognostic importance, whether indexed to BSA or height. We also assessed the LV mass to height ratio of ≥1 or <1 g/cm and found a positive association for those with an LVMI ≥1 and future cardiovascular events (Table 3). This relatively easily remembered metric could be useful in further clinical studies.

Study Limitations
We recognize the following limitations to our study. First, the majority of our patients were white. Reliable evaluation of the relation of ethnicity with respect to LV mass and cardiovascular events during dobutamine stress testing will require additional study. Second, research has demonstrated reversal of LVH in patients receiving various antihypertensive medications. Unfortunately, the role of medications during the time between DCMR and participants’ events could not be addressed effectively in our study because information about medication use was limited to that at the time of the DCMR examination. Third, spoiled gradient-echo sequences were used at the time of data collection with DCMR. We are uncertain how results obtained with steady-state free precession techniques would compare with those in this study. Fourth, studies on multislice determinations of LV volume or mass or with perfusion or late gadolinium enhancement techniques were not performed. Further studies with these methodologies may offer additional prognostic information on subjects with suspected LVH. Fifth, the study’s main goal was to estimate the association between LVH and MI or cardiac death. It was not designed with optimal power to detect potentially important HRs when participants were further divided into subgroups.

Clinical Implications and Conclusion
Patients with chest pain syndromes and LVH who may or may not exhibit inducible wall motion abnormalities indicative of ischemia during dobutamine stress testing are at high risk for future MI or cardiac death. LVH should be reported in patients referred for dobutamine stress testing, and one should not assume a low future risk of MI and cardiac death in patients with LVH who do not exhibit inducible LVWM abnormalities indicative of ischemia during intravenous dobutamine stress testing.

Source of Funding
The current research was supported in part by National Institutes of Health grants R01HL076438, MOI-RR071225, and P30AG21332.

Disclosures
None.

References


---

CLINICAL PERSPECTIVE

Inducible left ventricular (LV) wall motion abnormalities (due to flow-limiting epicardial coronary artery disease) observed during dobutamine stress testing are used to identify individuals with myocardial ischemia and those at risk for future cardiovascular events. Previously, it has been shown that patients with concentric LV remodeling or hypertrophy who may have flow-limiting coronary artery disease do not exhibit inducible LV wall motion abnormalities during dobutamine stress testing. In this study, we examined the prognostic utility of the absence of dobutamine-induced wall motion abnormalities for predicting future myocardial infarction or cardiac death. The results indicate that those individuals with LV hypertrophy and no inducible wall motion abnormalities during dobutamine stress testing exhibit the same adverse cardiovascular prognosis as individuals with inducible wall motion abnormalities indicative of ischemia who do not have LV hypertrophy. These findings suggest that one should identify LV hypertrophy during dobutamine stress studies and not assume a favorable cardiovascular risk profile in the absence of inducible wall motion abnormalities when LV hypertrophy is present. In this situation, one should consider other forms of testing to ascertain cardiovascular risk.
Left Ventricular Hypertrophy Influences Cardiac Prognosis in Patients Undergoing Dobutamine Cardiac Stress Testing
Charaslak Charoenpanichkit, Timothy M. Morgan, Craig A. Hamilton, Eric L. Wallace, Killian Robinson, William O. Ntim and W. Gregory Hundley

Circ Cardiovasc Imaging. 2010;3:392-397; originally published online May 4, 2010;
doi: 10.1161/CIRCIMAGING.109.912071
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue,
Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/3/4/392

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/