Dobutamine-Atropine Stress Echocardiography for the Detection of Coronary Artery Disease in Patients With Left Ventricular Hypertrophy

Importance of Chamber Size and Systolic Wall Stress

Steven C. Smart, MD; Thomas Knickelbine, MD; Fayaz Malik, MD; Kiran B. Sagar, MD

Background—Left ventricular hypertrophy is a heterogeneous disorder with distinct morphologies. Changes in wall thickness, left ventricular chamber diameter, and mass alter systolic wall stress of the left ventricle and may influence ischemic threshold. Thus, the goal of this study was to investigate the effect of the different patterns of left ventricular hypertrophy on the accuracy of dobutamine-atropine stress echocardiography.

Methods and Results—Three-hundred eighty-six patients underwent multistage dobutamine-atropine stress echocardiography and diagnostic angiography. Echocardiograms were measured for mean and relative wall thicknesses, chamber size, left ventricular mass, and end-systolic wall stress. The patterns of ventricular hypertrophy were concentric hypertrophy (increased wall thickness and mass), eccentric hypertrophy (normal wall thickness and increased mass), and concentric remodeling (increased wall thickness and normal mass). The overall sensitivity, specificity, and accuracy of dobutamine-atropine stress echocardiography for the detection of coronary artery disease were 85%, 87%, and 86%, respectively. Increased left ventricular mass index alone did not affect accuracy. Sensitivity was markedly reduced (36%) only in those with concentric remodeling. The univariate predictors of false-negative studies were single-vessel left circumflex disease, increased wall thickness, small chamber size, hyperdynamic ejection fraction, and left ventricular concentric remodeling. Multivariate predictors were concentric remodeling (P<0.0001; odds ratio, 13.5), left ventricular ejection fraction >2 SD above normal (P<0.0001), and single-vessel left circumflex disease (P<0.0007; odds ratio, 7.6). Sensitivity was excellent in patients with small ventricles and normal wall thickness and in those with normal or large chambers regardless of wall thickness.

Conclusions—Dobutamine-atropine stress echocardiography is an accurate test in most patients with left ventricular hypertrophy, but it is insensitive in the small subset with concentric remodeling. (Circulation. 2000;101:258-263.)

Key Words: hypertrophy ■ echocardiography ■ coronary disease

Left ventricular (LV) hypertrophy has heterogeneous morphologies with variable changes in LV mass, volume, wall thickness, diameter, systolic wall stress, and coronary flow reserve.1–6 By definition, the adaptive variations in wall thickness and ventricular size result in different systolic meridional wall stress, which may alter the threshold for demand-based ischemia2 and may impair the capacity of dobutamine atropine stress echocardiography to detect coronary artery disease.

LV hypertrophy has no influence on the accuracy of exercise stress echocardiography.7,8 However, the effect of LV hypertrophy on the accuracy of dobutamine-atropine stress echocardiography remains unclear, especially in relation to LV wall thickness, chamber diameter, and systolic meridional wall stress. In the present study, we postulated that LV morphology, specifically wall thickness/diameter, and systolic meridional wall stress significantly influence the accuracy of dobutamine-atropine stress echocardiography to detect coronary artery disease. The specific aim of the study was to determine the effect of LV mass, wall thickness, chamber size, and systolic meridional wall stress on the sensitivity and specificity of dobutamine-atropine stress echocardiography.

Methods

Patient Selection

Between July 1992 and June 1996, 386 patients with known or suspected coronary artery disease underwent both dobutamine-atropine stress echocardiography and diagnostic coronary angiography within 1 month of each other at the Milwaukee County Medical Complex. All patients gave informed consent. Exclusion criteria were recent myocardial infarction (<1 month), unstable angina, severe hypertension (blood pressure >220 mm Hg or diastolic
TABLE 1. Mean±SD of Measured Values in 100 Normal Dobutamine Echocardiograms

<table>
<thead>
<tr>
<th></th>
<th>Diastolic MWT, cm</th>
<th>Systolic MWT, cm</th>
<th>RWT, cm</th>
<th>LV Mass, g</th>
<th>Mass Index (BSA), g/m²</th>
<th>LVID, cm</th>
<th>LVSD, cm</th>
<th>SV, mL</th>
<th>Systolic Circumferential Wall Stress, dyne/cm²</th>
<th>Systolic Meridional Wall Stress, dyne/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=100)</td>
<td>0.8±0.1</td>
<td>1.2±0.1</td>
<td>0.37±0.06</td>
<td>148±37</td>
<td>80±20</td>
<td>4.6±0.5</td>
<td>3.3±0.5</td>
<td>52±16</td>
<td>198±48</td>
<td>72±18</td>
</tr>
<tr>
<td>Men (n=50)</td>
<td>0.9±0.1</td>
<td>1.2±0.1</td>
<td>0.36±0.06</td>
<td>164±33*</td>
<td>82±17</td>
<td>4.8±0.4</td>
<td>3.4±0.4</td>
<td>59±16</td>
<td>204±51</td>
<td>74±19</td>
</tr>
<tr>
<td>Women (n=50)</td>
<td>0.8±0.1</td>
<td>1.1±0.1</td>
<td>0.37±0.06</td>
<td>137±35</td>
<td>78±22</td>
<td>4.5±0.5</td>
<td>3.2±0.4</td>
<td>54±19</td>
<td>193±44</td>
<td>71±17</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; LVSD, systolic LV diameter; and SV, stroke volume.

*P<0.0001 vs women.

Statistical Analysis
Continuous data are expressed as mean±SD. The $\chi^2$ analysis or Fisher’s exact test was used to compare categorical data. Continuous data were compared by multway ANOVA and Bonferroni’s t test. Hemodynamic changes during dobutamine-atropine echocardiography were compared by repeated-measures ANOVA and Bonferroni’s t test. Linear and sigmoidal (Chapman 3-parameter) regression analyses were used to compare the relationships of sensitivity, specificity, and wall stress (SigmaPlot 4.0, SPSS, Inc). Stepwise multiple logistic regression analysis was used to identify independent causes of false-negative and false-positive results. A 2-tailed value of $P<0.05$ was significant.

Results

Patient Data
The 386 patients enrolled in the study had a mean age of 61±12 years. There were 133 women and 253 men. One hundred twenty patients were treated with $\beta$-adrenergic blocking agents, 127 with calcium channel blockers, and 169 with nitrates or other vasodilators. Hypertension was documented in 242 patients.

Dobutamine Infusion
The mean peak dose of dobutamine was 26±12 $\mu$g·kg$^{-1}$·min$^{-1}$. Atropine (0.2 to 2.0 mg) was used in 176 patients (46%). Resting heart rate, systolic blood pressure, and rate-pressure product were 71±13 bpm, 134±23 mm Hg, and 9563±418 mm Hg/min, respectively. Mean peak heart rate, systolic blood pressure, and rate-pressure product increased to 127±17 bpm, 142±37 mm Hg, and 18150±5103 mm Hg/min, respectively. End points for peak dose were heart rate >120 bpm in 310 patients, severe anginal chest pain in 18, maximum dose in 32, nonsustained ventricular tachycardia (5 to 8 beat runs) in 7, hypotension in 6, hypertension in 3, multiple inducible wall motion abnormalities at a submaximal heart rate in 7, and severe nausea or vomiting in 3.

Coronary Angiography
Coronary angiography detected significant coronary artery disease in 280 patients (73%). There were 169 patients with multivessel coronary artery disease and 111 with single-vessel disease. Of these 111 patients, 87 had stenosis ≥70% and 24 had stenosis between 50% and 69%. Of the patients with single-vessel disease, 38 had left anterior descending disease, 21 had left circumflex disease, and 52 had right coronary artery disease.

Dobutamine Echocardiographic Data
There were 122 normal and 264 abnormal stress echocardiograms. The sensitivity and specificity of wall motion abnor-
malities for detecting coronary artery disease were 85% (238 of 280) and 87% (92 of 106), respectively. The positive predictive values of fixed resting and induced wall motion abnormalities were 97% (60 of 62) and 94% (178 of 190), respectively. The negative predictive value of a normal dobutamine-atropine stress echocardiogram or sustained improvement in all vascular territories was 69% (92 of 134).

Sensitivity was higher ($P<0.05$) for multivessel disease (88%, 149 of 169) than single-vessel disease (80%, 89 of 111) and for single-vessel disease and $\geq 70\%$ stenosis (87%, 76 of 87) than single-vessel disease and 50% to 69% stenosis (54%, 13 of 24). Sensitivity was 85% (44 of 52) in single-vessel right coronary artery disease, 84% (32 of 38) in single-vessel left anterior descending disease, but only 62% (13 of 21, $P<0.05$) in single-vessel left circumflex disease.

Figure 3 compares sensitivity and specificity of dobutamine-atropine stress echocardiography in the 3 different types of hypertrophy, patients with normal wall thickness and small chamber size, and those with normal wall thickness and chamber size. The accuracy of dobutamine-atropine stress echocardiography was compromised only in the small subset of patients with concentric remodeling. Specificity was not affected by any of the hypertrophy patterns. Sensitivity was not altered by concentric or eccentric hypertrophy but was markedly reduced by concentric remodeling ($P<0.01$ versus all other groups). Sensitivity was preserved in patients with small chamber sizes and normal wall thickness.

Low meridional and circumferential wall stress was the only factor that distinguished patients with concentric remodeling from other groups. Figure 4 plots the relationship of resting LV systolic meridional (top) and circumferential (bottom) wall stress and accuracy. Sensitivity was correlated ($P<0.0001$) with both meridional and circumferential wall stress by a sigmoidal relationship ($r=0.98$ and 0.97, respectively). In patients with normal or high meridional wall stress ($>40$ dynes/cm$^2$), sensitivity was high (88%, 150 of 170). In patients with low meridional wall stress ($\leq 40$ dynes/cm$^2$), sensitivity was low (54%, 26 of 48) and steeply decreased to 0 at a wall stress of 15 dynes/cm$^2$. In patients with normal or high circumferential wall stress ($>100$ dynes/cm$^2$), sensitivity was high (92%, 158 of 177). In patients with low meridional wall stress ($\leq 100$ dynes/cm$^2$), sensitivity was low (44%, 18 of 41) and steeply decreased to 0 at a wall stress of $\leq 40$ dynes/cm$^2$. Specificity did not correlate ($P>0.2$) with resting meridional or circumferential wall stress ($r=0.163$ and 0.017, respectively).

Multivariate Analysis of Data

The univariate causes of false-negative studies were increased wall thickness, small chamber size, concentric remodeling, increased relative wall thickness, low global rest-
ing LV wall stress, small diastolic volume, high LVEF, single-vessel coronary artery disease, and single-vessel left circumflex coronary artery disease. The multivariate predictors of false-negative studies were concentric remodeling ($P<0.000001$) and single-vessel coronary artery disease ($P=0.0007$). The univariate causes of false-positive studies were induced wall motion abnormalities, wall motion abnormalities isolated in a single vascular territory, and isolated wall motion abnormalities of the basal inferior and lateral walls. The only independent cause of false-positive studies

### TABLE 2. Echocardiographic Measurements and Clinical Data According to Hypertrophy Type

<table>
<thead>
<tr>
<th>Hypertrophy Type</th>
<th>Concentric Hypertrophy (n=93)</th>
<th>Concentric Remodeling (n=45)</th>
<th>Small Chamber, Normal WT (n=16)</th>
<th>LV Eccentric Hypertrophy (n=14)</th>
<th>Normal Chamber, WT (n=144)</th>
<th>LV Resting Wall Motion Abnormality (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall thickness, diastole, cm</td>
<td>1.2±0.2†‡§</td>
<td>1.3±0.2†‡§</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>Wall thickness, systole, cm</td>
<td>1.7±0.3†‡§</td>
<td>1.8±0.2†‡§</td>
<td>1.3±0.1</td>
<td>1.2±0.2</td>
<td>1.2±0.2</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>LV diameter, diastole, cm</td>
<td>4.9±0.6†§</td>
<td>3.7±0.4†‡</td>
<td>3.8±0.2†‡</td>
<td>5.8±0.5†</td>
<td>5.0±0.4</td>
<td>6.0±0.8†</td>
</tr>
<tr>
<td>LV diameter, systole, cm</td>
<td>3.6±0.7†§</td>
<td>2.6±0.4†‡</td>
<td>2.7±0.2†‡</td>
<td>4.5±1.0†</td>
<td>3.6±0.5</td>
<td>5.4±0.9†</td>
</tr>
<tr>
<td>RWT</td>
<td>0.51±0.09†‡</td>
<td>0.70±0.11†‡§</td>
<td>0.48±0.05†‡</td>
<td>0.32±0.04</td>
<td>0.35±0.05</td>
<td>0.32±0.09</td>
</tr>
<tr>
<td>LV mass index (BSA), g/m²</td>
<td>142±40†§</td>
<td>103±30†‡</td>
<td>65±13†‡</td>
<td>135±15†</td>
<td>86±17</td>
<td>143±40†</td>
</tr>
<tr>
<td>Meridional wall stress, dyne/cm²</td>
<td>52±22†</td>
<td>32±10*†‡§</td>
<td>52±13†‡</td>
<td>114±35†</td>
<td>77±27</td>
<td>140±59†</td>
</tr>
<tr>
<td>Circumferential wall stress, dyne/cm²</td>
<td>147±68†</td>
<td>84±25*†‡§</td>
<td>125±31†‡</td>
<td>262±89</td>
<td>200±76</td>
<td>380±264†</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>110±49†§</td>
<td>54±19*†‡</td>
<td>51±11†‡</td>
<td>174±52†</td>
<td>117±32</td>
<td>202±93†</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>62±22†§</td>
<td>33±12†‡</td>
<td>32±8†‡</td>
<td>84±19†</td>
<td>63±19</td>
<td>54±22</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>58±10†</td>
<td>61±10†</td>
<td>62±8†</td>
<td>52±7†</td>
<td>59±9</td>
<td>28±8†</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±13</td>
<td>63±11</td>
<td>61±13</td>
<td>63±11</td>
<td>59±11</td>
<td>62±12</td>
</tr>
<tr>
<td>Female sex, % (n)</td>
<td>30 (28)</td>
<td>51 (23)†</td>
<td>63 (10)†</td>
<td>36 (5)</td>
<td>28 (41)</td>
<td>35 (26)</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>72 (67)†</td>
<td>76 (34)†</td>
<td>50 (8)</td>
<td>79 (11)†</td>
<td>71 (74)</td>
<td>65 (48)</td>
</tr>
<tr>
<td>β-Blocker, % (n)</td>
<td>33 (31)</td>
<td>18 (8)</td>
<td>19 (3)</td>
<td>21 (3)</td>
<td>28 (41)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>128±18</td>
<td>130±18</td>
<td>127±11</td>
<td>125±13</td>
<td>127±17</td>
<td>128±17</td>
</tr>
<tr>
<td>Peak SBP, mm Hg</td>
<td>144±42</td>
<td>148±36</td>
<td>155±41</td>
<td>137±33</td>
<td>141±34</td>
<td>140±37</td>
</tr>
</tbody>
</table>

WT indicates wall thickness; BSA, body surface area; HR, heart rate; and SBP, systolic blood pressure. Values are mean±SD.

*P<0.05 vs concentric hypertrophy; †P<0.05 vs normal mass and wall thickness; ‡P<0.05 vs eccentric hypertrophy; §P<0.05 vs small LV chamber and normal WT.

**Figure 2.** Sensitivity and specificity according to LV diameter (LVD), wall thickness (WT), and RWT in patients with normal resting wall motion. >2SD indicates >2 SD above normal mean; <2SD, <2 SD below normal mean. P<0.01 vs normal or low wall thickness; §P<0.01 vs normal or high LV diameter; |P<0.01 vs normal or low RWT.

**Figure 3.** Sensitivity and specificity in patients with normal resting wall motion and normal LV diameter (LVD) and wall thickness (WT), normal wall thickness with small diameter, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy in patients. P<0.01 vs all other subsets.
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increased wall thickness, the pattern called concentric remodeling. This study shows that patients with small LV chamber size and increased wall thickness was 0.1 cm, respectively. In a cohort of 100 patients, the variabilities in chamber size and wall thickness were 0.1 and 0.2 cm, respectively. In a cohort of 60 patients, the concordance between M-mode and 2D measurements of wall thickness was small wall motion abnormalities of the basal inferior or lateral wall (P<0.000001).

**Intraobserver and Interobserver Variabilities**

Intraobserver and interobserver variabilities of wall motion analysis were minimal in a representative subset of 60 patients, including 40 patients with and 20 patients without coronary artery disease. The interpretations of the 2 investigators regarding the presence or absence of wall motion abnormalities agreed in 92% (55 of 60). Intraobserver variability was assessed by 1 investigator. The 2 readings were concordant regarding the presence or absence of wall motion abnormalities in 97% (58 of 60).

Intraobserver variability of echocardiographic measurements was assessed in the same cohort of patients. The mean variabilities in chamber size and wall thickness were 0.1 and 0.1 cm, respectively. In a cohort of 100 patients, the correlation coefficient, y intercept, and slope of the relationship between M-mode and 2D measurements of wall thickness were 0.94, 0, and 0.99±0.004, respectively. These values for chamber size were 0.96, 0, and 1.00±0.004, respectively.

**Discussion**

This study shows that patients with small LV chamber size and increased wall thickness, the pattern called concentric remodeling, exhibit an excessively high number of false-negative studies in the presence of significant angiographic coronary stenoses. Concentric remodeling was the strongest univariate and multivariate predictor of false-negative studies. In contrast, sensitivity was preserved in patients with small chamber size and normal wall thickness, concentric and eccentric hypertrophy. The presence of hypertension or increased LV mass index alone did not affect accuracy. Although adjunctive measures, such as the addition of intravenous atropine to augment heart rate response in patients taking β-blocker therapy, have been shown to overcome decreases in sensitivity during dobutamine stress echocardiography, LV morphological patterns may represent the most important absolute limitation of its detection of coronary stenoses.

Ganau et al reported that LV hypertrophy occurred in 3 morphological patterns in a series of 165 hypertensive patients: increased ventricular mass and wall thickness as typical concentric hypertrophy, increased mass and normal wall thickness as eccentric hypertrophy, and increased wall thickness and normal LV mass as concentric remodeling. Chamber size is normal or large in concentric hypertrophy, large in eccentric hypertrophy, and small in concentric remodeling. These more direct definitions of specific patterns of hypertrophy may be needed in evaluations of the accuracy of stress echocardiography. Marwick et al reported that the accuracy of exercise echocardiography is not impaired in patients with LV hypertrophy. The definition of hypertrophy used, however, was increased LV mass index. The present study is concordant with these findings in that an absolute increase in LV mass index did not affect accuracy. However, our study demonstrates a significant reduction in sensitivity of dobutamine stress echocardiography in a small subset of patients with LV hypertrophy, concentric remodeling. Marwick et al reported that increased wall thickness (defined as wall thickness >1.2 mm) did not alter the sensitivity (73% versus 72%) or specificity (94% versus 83%) of dobutamine stress echocardiography. However, chamber size and LV mass were not documented, the peak heart rate was only 109±25 bpm, and atropine was not used. In the present study, sensitivity was decreased most prominently in patients with the combination of increased wall thickness and small LV chamber in concentric remodeling. Small chamber size in the absence of increased wall thickness was not associated with false-negative studies. In the present study, atropine was frequently used (44% of patients), the peak heart rate was higher (128±17 bpm), and the percentage of patients with increased wall thickness was higher (48%) than Marwick et al used.

The sensitivity of dobutamine stress echocardiography for detection of coronary artery disease has been shown to range from 76% to 96%. Previous studies have identified submaximal stress, single-vessel disease, distal coronary artery disease, female sex, and β-adrenergic blocker therapy as potential causes of false-negative studies. Specificity of dobutamine stress echocardiography has ranged from 60% to 95%. Inadequate endocardial visualization, myocardial ischemia caused by microvascular disease, and wall motion abnormalities unrelated to coronary artery disease (cardiomyopathy or left bundle-branch block) have been hypothesized to cause false-positive studies. Bach et al reported that the primary causes of false-positive dobutamine echocardiogra-
phy were female sex, wall motion abnormalities of the basal segments of the posterior circulation, and intermediate coronary stenoses ≥40%; however, fewer women were included in the present study. Patients with concentric remodeling commonly have hypertension and a high probability of microvascular coronary artery disease and impaired coronary flow reserve.23 In our study patients, neither concentric remodeling nor hypertension was a cause of false-positive results. These observations suggest that although microvascular coronary disease can lead to angina in patients with normal coronary arteries,4 these patients do not manifest significant clinically detectable wall motion abnormalities during the peak stress phase of dobutamine-atroventricular stress echocardiography.

One hypothesis to explain why small chamber size and increased wall thickness caused false-negative studies may be that these patients have an increased threshold for demand ischemia and induced wall motion abnormalities. A consequence of the marked increase in myocardial wall thickness and decrease in LV chamber size is reduced systolic wall stress and myocardial displacement during stress. The results of the present study demonstrate that reduced systolic wall stress causes sensitivity to plummet. Furthermore, hyperdynamic wall motion is common in these patients. Thus, ischemic segments that become hypokinetic or akinetic during stress may remain visually undetected because of minimal excursion distances and “tethering” from adjacent hyperdynamic segments.

Overestimation of noncritical stenosis by the caliper technique may contribute to reduced sensitivity5; however, only 24 of 111 (22%) of patients with single-vessel disease in the present study had a stenosis from 50% to 69%. Patients with intermediate coronary stenosis (40% to 70%) often do not have impaired coronary flow reserve.3 Sensitivity may be reduced in these patients, but this factor did not account for the reduced sensitivity in concentric remodeling patients. Therefore, our conclusions regarding the sensitivity of dobutamine-atroventricular stress echocardiography remain valid.

Sharp et al11 reported a sensitivity of 83% and specificity of 71% in patients with dilated cardiomyopathy. Sensitivity of dobutamine stress echocardiography for detection of triple-, double-, and single-vessel disease was 100%, 83%, and 69% respectively. In our study, in patients with concentric remodeling (LVEF, 61%), sensitivity was 36% and specificity was 89% (Figure 3). In the group with eccentric hypertrophy and reduced LVEF, specificity was significantly reduced, similar to the results reported by Sharp et al.11

In conclusion, dobutamine-atroventricular stress echocardiography may not be the ideal test for the small subset of patients with small LV chamber, increased wall thickness, and high relative wall thickness, a pattern recognized as concentric remodeling, especially the extreme cases. In contrast, dobutamine-atroventricular stress echocardiography remains an accurate diagnostic test in patients with eccentric hypertrophy, those with typical concentric hypertrophy, and even those with small chambers but normal wall thickness.

References
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