Prediction of Outcomes in Hypertensive Patients With Suspected Coronary Disease

Thomas H. Marwick, Colin Case, Stephen Sawada, Charles Vasey, James D. Thomas

Abstract—Stress echocardiography has been shown to improve the diagnosis of coronary artery disease in the presence of hypertension, but its value in prognostic evaluation is unclear. We sought to determine whether stress echocardiography could be used to predict mortality in 2363 patients with hypertension, who were followed for up to 10 years (mean 4.0±1.8) for death and revascularization. Stress echocardiograms were normal in 1483 patients (63%), 16% had resting left ventricular (LV) dysfunction alone, and 21% had ischemia. Abnormalities were confined to one territory in 489 patients (21%) and to multiple territories in 365 patients (15%). Cardiac death was less frequent among the patients able to exercise than among those undergoing dobutamine echocardiography (4% versus 7%, \(P<0.001\)). The risk of death in patients with a negative stress echocardiogram was <1% per year. Ischemia identified by stress echocardiography was an independent predictor of mortality in those able to exercise (hazard ratio 2.21, 95% confidence intervals 1.10 to 4.43, \(P=0.0001\)) as well as those undergoing dobutamine echo (hazard ratio 2.39, 95% confidence intervals 1.53 to 3.75, \(P=0.0001\)); other predictors were age, heart failure, resting LV dysfunction, and the Duke treadmill score. In stepwise models replicating the sequence of clinical evaluation, the results of stress echocardiography added prognostic power to models based on clinical and stress-testing variables. Thus, the results of stress echocardiography are an independent predictor of cardiac death in hypertensive patients with known or suspected coronary artery disease, incremental to clinical risks and exercise results. (Hypertension. 2002;39:1113-1118.)

Key Words: hypertension, essential ■ stress ■ echocardiography ■ coronary artery disease ■ mortality

Hypertension and coronary artery disease (CAD) are often associated, reflecting common origins in lifestyle and the role of hypertension as a risk factor for CAD. The presence of hypertension may cloud the diagnosis of CAD because chest pain and dyspnea, as well as stress-induced ST-segment changes, may be due to hypertensive heart disease even in the absence of CAD. However, although stress echocardiography has been shown to improve the diagnosis of CAD in hypertensive patients,\(^1\)\(^-\)\(^3\) its value in prognostic evaluation is unclear.

The assessment of risk using functional testing may facilitate decision making regarding coronary revascularization for prognostic purposes. For example, such interventions should not be considered if the yearly risk of cardiac death is <1%.\(^4\) In unselected patients without a history of hypertension, the risk of death from coronary disease may be stratified by features in the clinical history, resting ventricular function, exercise capacity, and the presence and extent of ischemia at stress echocardiography.\(^5\)\(^,\)\(^6\) Despite the high prevalence of hypertension among patients presenting with chest pain, there are few available data regarding the validity of this approach in the hypertensive population. However, given the effects of hypertensive heart disease on resting and stress ST-segment changes in the absence of epicardial coronary disease, as well as reduced exercise capacity, there are grounds for suspecting that standard approaches may be ineffective. We therefore sought to determine whether stress echocardiography using exercise (ExE), when feasible, or dobutamine echo (DbE) could be used to predict mortality.

Methods

Patient Population

This multicenter cohort study involved 2363 patients with diagnosed or treated hypertension and known or suspected coronary disease, who undertook stress echocardiography at 3 large, expert laboratories between 1988 and 1994. ExE was performed in patients who were considered able to exercise, and DbE was performed in those unable to exercise or where there was a question regarding myocardial viability. Clinical, exercise, and echocardiographic data of these patients were obtained prospectively, and follow-up was obtained up to 10 years later. The study was approved by the Institutional Review Board, informed consent was obtained before testing, and the procedures followed were in accordance with institutional guidelines.

The mean age of the group was 62±12 years, and 49% of the patients were women. Hypertension was defined by a systolic blood pressure (BP) ≥140 mm Hg, a diastolic BP ≥90 mm Hg, or by antihypertensive drug therapy. The clinical characteristics of patients in the study are summarized in Table 1. Studies were performed for the investigation of anginal symptoms in nearly half of the ExE group and rather fewer of the DbE group, although the latter had more patients with previous myocardial infarction.
Stress Testing
Exercise echocardiography was performed in 1043 patients who were considered likely to exercise maximally during treadmill testing. Most were able to perform the Bruce protocol, but other protocols were selected in accordance with the age and functional capacity of patients. The preparation of the patient and the endpoints of the test were consistent with current guidelines. In addition to the separate evaluation of exercise capacity, chest pain, and ST-segment changes, these variables were combined into the Duke treadmill score, a composite index of risk that has been well validated in nonhypertensive populations.

Dobutamine echocardiography was performed in the remaining 1320 patients who were unable to exercise or had a history of myocardial infarction or regional wall motion abnormalities that led to questions about the presence of viable myocardium. Dobutamine was infused during continuous clinical, electrocardiographic, and echocardiographic monitoring, using a standard incremental dose protocol from 5 to 40 μg/kg per minute. The preparation and endpoints of this protocol have been previously described.

Echocardiography
A standard 2D echo was performed at rest in all patients. Resting images were archived in digital format, as well as on videotape. The imaging was repeated during dobutamine stress and at peak exercise and saved in digital format to permit side-by-side comparison of the rest and stress images.

Studies were interpreted independently of clinical, stress, or angiographic data by experienced observers who had been trained in the performance of the technique. Relying left ventricular function was qualitatively evaluated by an experienced observer as normal, mild, moderately, or severely reduced, based on assessment of the extent of abnormal wall motion. Stress echocardiograms were interpreted by comparison of rest and stress images using the quad-screen digital display, with review of video-tape if desired. Segments were designated as normal if they showed normal resting function with no deterioration induced by stress. Ischemia was defined by the presence of new or worsening dysfunction in response to stress, and infarction was defined by akinesis or dyskinesis at rest. Myocardial segments were combined into vascular territories for the purpose of expressing the extent of abnormal wall motion. The apex, anteroseptal, septal, and anterior walls were attributed to the left anterior descending, the lateral to the left circumflex, and the inferior and basal septal to the right coronary. The posterior wall was attributed to the circumflex or right coronary if either was abnormal; in patients with isolated posterior wall abnormalities, these were ascribed to the left circumflex. The results were made available to the physicians responsible for the patient.

Follow-Up
Follow-up data were gathered by clinic review or telephone contact with the patient or patient’s physician after 4.0 ± 1.8 years (range 1 month to 10 years). The primary endpoint was cardiac mortality. Patients were removed from further follow-up at the time of noncardiac death, coronary bypass surgery, or coronary angioplasty, but these were not identified as events.

Statistical Analysis
Differences between survival curves based on individual variables were compared with the log-rank test. The association of various clinical, stress-testing, and imaging findings on outcomes was investigated using a Cox proportional hazards model, and factors significant at the P < 0.05 level were entered into a forward stepwise model to assess the effects of ischemia on outcome, independently of clinical, exercise, and resting echocardiographic variables. A series of models was used to investigate the prognostic value of ischemia incremental to clinical data and resting left ventricular (LV) function. Analyses were performed using SPSS statistical software (SPPS Inc), and probability values < 0.05 were considered to be statistically significant, except for multiple comparisons where significant probability values were defined by the Bonferroni method.

Results
Resting and Stress Echocardiography
The results of exercise testing are summarized in Table 2. Resting left ventricular function was normal in 1755 patients (74%) and mildly reduced in 371 (16%), and showed moderate or worse dysfunction in 211 (9%) and severe LV dysfunction in the remainder. No inducible ischemia was identified in 1839 patients (78%); of those with a positive study, 350 of 526 (67%) had abnormal function restricted to a single vascular territory. Thus, no abnormality at either rest or stress (ie, a completely normal study) was reported in 1483 patients (63%), and in patients with an abnormal result, rest and stress-induced wall motion abnormalities were restricted to a single territory in 489 of 880 (56%).

Outcomes
Patients undergoing ExE were followed over 4.5 ± 1.6 years, compared with 3.5 ± 2.0 years follow-up for patients under-
going DbE. Cardiac death occurred in 136 patients (6%), including 39 patients in the ExE and 97 in the DbE group (4% versus 7%, P<0.001). Myocardial infarction occurred in 33 ExE and 59 DbE patients (3% versus 5%, P=NS). Noncardiac deaths were recorded in 60 of the ExE and 325 of the DbE patients, and 279 were censored from follow-up at the time of revascularization.

The association of stress echocardiography findings with outcome is illustrated in Figure 1. For both exercise and dobutamine stress, the annualized cardiac mortality associated with a normal test was <1%; although mortality was greater in the dobutamine group. The presence of scar, ischemia, and a combination of both were all associated with risk; Figure 2 illustrates the association of risk with increasing extent of abnormal wall motion at rest and stress.

Prediction of Mortality With Stress Echocardiography

Among patients who were able to exercise, cardiac mortality was independently associated with heart failure, resting LV dysfunction, a moderate- or high-risk Duke treadmill score (but not the categorical analysis of the ST segment), and the presence of ischemia (Table 3). A series of models was developed to investigate the incremental value of each step of the risk evaluation in the prediction of outcome (Figure 3). The clinical model (age, heart failure, history of infarction) was strengthened by the addition of the Duke treadmill score (P<0.001), the addition of resting LV function data (P<0.0001), and finally, by the addition of stress data (P<0.001).

Among patients undergoing dobutamine stress, cardiac mortality was predicted by age and the performance of an abnormal stress echocardiogram (Table 4). The incremental

Figure 1. Association of stress echocardiography findings with outcome. The annualized cardiac mortality associated with a normal test was <1% for both exercise and dobutamine stress. The presence of scar, ischemia, and a combination of both were all associated with risk.

Figure 2. Association of risk with increasing extent of abnormal wall motion at rest and during stress.
models showed that the addition of resting LV function added significantly to the power of the clinical model ($P<0.0001$) and that the finding of ischemia added little incremental information (Figure 4).

**Discussion**

The results of this longitudinal study indicate that stress echocardiography is a useful prognostic tool in hypertensive patients. A normal study with either exercise or dobutamine is a marker of low risk ($<1\%$ per year). Ischemia or an abnormal stress echocardiogram is an independent predictor of cardiac death in hypertensive patients, and the level of risk is related to the extent of abnormality. Although the Duke treadmill score is also an independent predictor of cardiac mortality, the risk allocated on the basis of an abnormal stress echocardiogram is incremental to these findings. In patients studied using dobutamine stress, an abnormal study is an independent predictor of cardiac death, but the impact of ischemia is overwhelmed by the importance of resting LV dysfunction in these patients, who are more likely to have previous infarction.

**Assessment of CAD in Patients With Hypertension and LV Hypertrophy**

A significant number of patients with coronary artery disease have coexistent hypertension. Many of these patients complain of anginal pain, but although this may be due to coronary artery disease, other causes include abnormal coronary flow reserve, vascular dysfunction, and LV outflow obstruction. Unfortunately, the usual noninvasive techniques for the diagnosis of coronary artery disease may be unreliable in these patients. False-positive ST-segment depression has been recognized for many years. A number of previous studies have shown that stress echocardiography is more reliable for the diagnosis of coronary artery disease than the standard ST-segment interpretation in patients with hypertension and LV hypertrophy. However, the shortcomings of ST-segment analysis may reflect the limitations of using a single cutoff of ST-segment depression, and this may be addressed by assessment of ST segment as a continuous variable, for example using the ST/heart-rate slope or a multivariate score such as the Duke treadmill score. Myocardial perfusion imaging may also present inaccuracies because of false-positive and negative results caused by disturbed coronary flow reserve, partial volume issues, and reduced exercise capacity, although there are reports of more favorable accuracy. The definitive study for the comparison of stress echocardiography with single-photon emission computed tomography (SPECT) was reported by Fragasso, who compared dobutamine stress echocardiography with dipyridamole stress 99mTc-MIBI stress/rest myocardial perfusion imaging.

**Table 3. Predictors of Cardiac Mortality in Patients Undergoing Exercise Stress**

<table>
<thead>
<tr>
<th>Predictors of Cardiac Death</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td>Log Rank</td>
<td>$P$</td>
<td>Hazard Ratio (95% CI)</td>
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<tr>
<td>Age</td>
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<td></td>
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<tr>
<td>60–70 years</td>
<td>0.95</td>
<td>0.33</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>8.30</td>
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<tr>
<td>Men</td>
<td>0.39</td>
<td>0.53</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.31</td>
<td>0.02</td>
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<tr>
<td>Smoking</td>
<td>0.18</td>
<td>0.76</td>
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<tr>
<td>Medical therapy</td>
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<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>0.27</td>
<td>0.60</td>
</tr>
<tr>
<td>Ca channel blocker</td>
<td>0.41</td>
<td>0.52</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>7.25</td>
<td>0.007</td>
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<tr>
<td>Coronary vasodilators</td>
<td>1.51</td>
<td>0.22</td>
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<tr>
<td>Previous myocardial infarction</td>
<td>18.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12.81</td>
<td>0.003</td>
</tr>
<tr>
<td>Resting LV dysfunction</td>
<td>45.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duke score moderate/high</td>
<td>10.13</td>
<td>0.0015</td>
</tr>
<tr>
<td>Ischemia</td>
<td>20.73</td>
<td>&lt;0.0001</td>
</tr>
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</table>

Figure 3. The incremental value of each step of the risk evaluation in relation to the prediction of outcome, using exercise echocardiography. The clinical model (heart failure, history of infarction) was strengthened by the addition of the Duke treadmill score ($P<0.001$), resting LV function data ($P<0.0001$), and, finally, stress echo data ($P<0.001$).
cardial single-photon emission computed tomography in 101 patients with hypertension, chest pain, and a positive-exercise ECG, who underwent coronary angiography. The sensitivity of dobutamine stress echocardiography (88%) and dipyridamole perfusion scintigraphy (98%) were comparable, but the specificity of the echocardiographic technique was superior (80% versus 36%). To our knowledge, no studies have examined the prognostic application of myocardial perfusion imaging in hypertensive patients.

Assessment of Prognosis
In patients whose symptoms are minimal or controlled on medical therapy, the main indications for coronary revascularization are prognostic. Although angiographic assessment of the left ventricle or coronary angiograms have been used to identify the highest levels of risk, this is not feasible for all patients, and a technique for the noninvasive assessment of risk would be desirable. The identification of low risk would enable the exclusion of many patients from further invasive investigation. Patients with a yearly risk of cardiac death <1% are not likely to have the natural history of their disease altered by coronary revascularization.

Nuclear imaging can accurately identify patients at low risk of cardiac events in unselected populations. Recent studies with exercise and dobutamine echocardiography have shown the yearly event rate with a negative test to be of the order of 1% per year. The results of this study of hypertensive patients are consistent with the data obtained in nonhypertensive patients. Previous studies have shown that patients who have events despite a negative test tend to be older, have a history of heart failure, exercise to low workload, or have anginal symptoms or left ventricular hypertrophy.

The presence of an abnormal stress echocardiogram indicates that the patient is at risk of cardiac death. The risk of patients undergoing dobutamine stress is greater than that of patients who are able to exercise, reflecting the risk previously described caused by inability to exercise, as well as the prevalence of previous infarction. Other clinical and exercise variables, such as age, the presence of heart failure or previous infarction, and the exercise score are also contributors to the level of risk. This risk can be stratified according to the type (Figure 1) and extent of abnormality (Figure 2), an effect analogous to the correlation of the extent and severity of perfusion defects with the outcomes of

### Table 4. Predictors of Cardiac Mortality in Patients Undergoing Dobutamine Stress

<table>
<thead>
<tr>
<th>Predictors of Cardiac Death</th>
<th>Univariate</th>
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<th></th>
<th></th>
<th>Multivariate</th>
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<td></td>
<td>Log Rank</td>
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<td>Hazard Ratio (95% CI)</td>
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<td></td>
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<td></td>
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<tr>
<td>60–70 years</td>
<td>4.55</td>
<td>0.03</td>
<td>1.70 (0.96–2.99)</td>
<td>0.07</td>
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<tr>
<td>&gt;70 years</td>
<td>9.21</td>
<td>0.002</td>
<td>2.34 (1.33–4.11)</td>
<td>0.003</td>
<td></td>
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<tr>
<td>Men</td>
<td>4.00</td>
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<td>Diabetes</td>
<td>0.06</td>
<td>0.80</td>
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<tr>
<td>Medical therapy</td>
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<td>Digoxin therapy</td>
<td>6.10</td>
<td>0.01</td>
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<tr>
<td>Beta blockers</td>
<td>1.31</td>
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<td>0.52</td>
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<td>Diuretics</td>
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<tr>
<td>Coronary vasodilators</td>
<td>1.51</td>
<td>0.22</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>3.53</td>
<td>0.06</td>
<td></td>
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<td></td>
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<tr>
<td>Resting LV dysfunction</td>
<td>18.67</td>
<td>&lt;0.0001</td>
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<tr>
<td>Low workload (RPP)</td>
<td>11.75</td>
<td>0.0006</td>
<td>1.81 (1.16–2.80)</td>
<td>0.008</td>
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<td>Ischemia</td>
<td>4.43</td>
<td>0.04</td>
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<tr>
<td>Abnormal DbE (rest or stress)</td>
<td>18.35</td>
<td>&lt;0.0001</td>
<td>2.39 (1.53–3.75)</td>
<td>0.0001</td>
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RPP indicates rate-pressure product.

Figure 4. The incremental value of each step of the risk evaluation in relation to the prediction of outcome, using dobutamine echocardiography. The incremental models showed that the addition of resting LV function added significantly to the power of the clinical model (P<0.0001). Despite the independent association of an abnormal dobutamine stress result with outcome, the finding of ischemia did not add incremental information.
patients studied using SPECT. Multivariate analysis of our data showed ischemia or the finding of an abnormal stress echocardiogram to be an independent predictor of mortality in hypertensive patients, and all of these data are consistent with previous reports in unselected patients with both exercise and dobutamine echocardiography.

Limitations
The development of ischemia may reflect reduced myocardial blood flow caused by conduit or resistance vessel disease, or both. In the absence of angiography, it is not clear that the source of ischemia is amenable to revascularization, so that, although the study identifies patients with ischemia as being at risk of cardiac death, it is likely, but not certain, that this risk is treatable.

Left ventricular hypertrophy is an important determinant of outcome in hypertensive patients. This study was focused on the predictive value of stress echo rather than resting LV parameters. However, further study is required to examine the relative effects and possible interaction of LV hypertrophy and ischemia on outcome.

Perspectives
The results of this study indicate that stress echocardiography is a useful tool for estimating the risk of cardiac death in hypertensive patients with known or suspected coronary artery disease, just as it is in nonhypertensive patients. The absence of ischemia indicates that the risk of death is too low to justify coronary revascularization, and in this situation coronary angiography is usually unnecessary. If the test is positive, the ability to identify a spectrum of risk in hypertensive patients may support the selection of patients for coronary revascularization.

Stress echocardiography is clearly superior to exercise testing for this risk assessment process, but although myocardial scintigraphy has been problematic from a diagnostic standpoint in this group, the relative prognostic value of the 2 imaging techniques in hypertensive patients warrants further study. Finally, although stress echocardiography is shown to provide useful information in patients with suspected coronary disease, the study does not pertain to the screening of asymptomatic hypertensive patients.

Acknowledgments
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References
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