Thallium-201 Stress Imaging in Hypertensive Patients

DOUGLAS S. SCHULMAN, CHARLES K. FRANCIS, HENRY R. BLACK, AND FRANS J. TH. WACKERS

SUMMARY To assess the potential effect of hypertension on the results of thallium-201 stress imaging in patients with chest pain, 272 thallium-201 stress tests performed in 133 hypertensive patients and 139 normotensive patients over a 1-year period were reviewed. Normotensive and hypertensive patients were similar in age, gender distribution, prevalence of cardiac risk factors (tobacco smoking, hyperlipidemia, and diabetes mellitus), medications, and clinical symptoms of coronary disease. Electrocardiographic criteria for left ventricular hypertrophy were present in 16 hypertensive patients. Stepwise probability analysis was used to determine the likelihood of coronary artery disease for each patient. In patients with mid to high likelihood of coronary disease (>25% probability), abnormal thallium-201 stress images were present in 54 of 60 (90%) hypertensive patients compared with 51 of 64 (80%) normotensive patients. However, in 73 patients with a low likelihood of coronary disease (<25% probability), abnormal thallium-201 stress images were present in 21 patients (29%) of the hypertensive group compared with only 5 of 75 (7%) of the normotensive patients (p<0.001). These findings suggest that in patients with a mid to high likelihood of coronary artery disease, coexistent hypertension does not affect the results of thallium-201 exercise stress testing. However, in patients with a low likelihood of coronary artery disease, abnormal thallium-201 stress images are obtained more frequently in hypertensive patients than in normotensive patients.

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KEY WORDS • exercise testing • hypertension • thallium 201 • myocardial perfusion imaging • treadmill exercise testing • coronary artery disease

SINCE hypertension is a major risk factor for the development of coronary artery disease, the reliability of stress testing for the evaluation of chest pain in patients with abnormal blood pressure elevation is an important clinical concern. Interpretation of routine exercise treadmill testing with electrocardiographic monitoring may be limited in these patients by the presence of baseline electrocardiographic abnormalities associated with left ventricular hypertrophy, medication effects, left bundle branch block, or advanced age.1-3 Furthermore, in a study of hypertensive patients with chest pain, exercise radionuclide angiography was found to be an inadequate screening test for coronary artery disease because of the frequent occurrence of false-positive responses.4 Since stress-induced thallium-201 myocardial defects are a more specific indicator of abnormal regional myocardial perfusion than are electrocardiographic or hemodynamic criteria, exercise testing with thallium-201 imaging may be a more useful test in hypertensive patients. Therefore, thallium-201 stress imaging may be more suited than other diagnostic techniques for the identification of ischemia.5 There is little information concerning the effects of hypertension and possibly associated left ventricular hypertrophy on thallium-201 imaging in patients evaluated for chest pain. To assess the effects of hypertension on the results of thallium-201 stress testing, we reviewed our experience over a 1-year period with normotensive and hypertensive patients who were referred for exercise testing with thallium-201 imaging. The patients were categorized according to their likelihood of having coronary artery disease. We hypothesized that hypertensive patients would have a higher incidence of abnormal thallium-201 imaging than would their normotensive counterparts.
Patients and Methods

Studies of 273 consecutive patients referred for thallium-201 exercise stress testing from December 1983 through November 1984 were reviewed. Before exercise, information regarding cardiac risk factors, including history of hypertension, diabetes, tobacco smoking, hyperlipidemia, and family history of ischemic heart disease, was obtained. Historical or electrocardiographic evidence of myocardial infarction, coronary bypass surgery, angina pectoris, or atypical chest pain was also ascertained. One patient was excluded from analysis. This patient was injected with thallium-201 before reaching a required end point of chest pain, electrocardiographic abnormalities, arrhythmia, or heart rate (≥120 beats/min).

The hypertensive study group was composed of 133 patients with a mean blood pressure of 137/91 mm Hg. They had had documented hypertension (diastolic pressure ≥ 90 mm Hg) for at least 2 years and/or were receiving antihypertensive medications for established hypertension but were normotensive at the time of testing. There were 101 men and 32 women, with a mean age of 58 years. Ninety-four of the hypertensive patients were receiving drug treatment, while 39 remained untreated. Mean resting blood pressure was 135/90 mm Hg in the treated and 140/94 mm Hg in the untreated hypertensive patients. There were 139 patients with no history of hypertension or antihypertensive treatment. They had a mean blood pressure of 126/82 mm Hg, which was not significantly different from that of hypertensive patients. There were 109 men and 30 women, with a mean age of 55 years. The clinical characteristics of the patients in both groups are shown in Table 1.

Likelihood of Coronary Artery Disease

Patients were categorized according to their likelihood of having coronary artery disease using stepwise probability analysis, since coronary arteriography was not performed in most patients. The likelihood of coronary artery disease was based on the patient's age, gender, symptoms, and electrocardiographic changes during exercise. In patients with baseline ST segment changes (including left ventricular hypertrophy), further exercise-induced depression of more than 1.5 mm at 0.08 second after the J point was considered an abnormal response. Patients with a history of myocardial infarction, diagnostic Q waves on electrocardiogram, coronary arteriographically demonstrated luminal narrowing exceeding 75%, or prior coronary artery bypass surgery with previous infarction were categorized as 100% likelihood. Patients with prior coronary artery bypass surgery without a history of infarction were categorized using stepwise probability analysis as in other patients. An arbitrary cutoff point of 25% likelihood was chosen for the purpose of analysis in the present study. Patients with a greater than 25% probability of coronary artery disease were categorized as having a mid to high likelihood of coronary artery disease, and patients with 25% or less probability, as having a low likelihood of coronary artery disease.

With the use of these criteria, 60 of 133 hypertensive patients (45%) and 64 of 139 normotensive patients (46%; $p = $NS) had a mid to high likelihood of coronary artery disease, while 73 hypertensive patients (55%) and 75 normotensive patients (54%; $p = $NS) had a low likelihood of coronary artery disease.

Thallium-201 Stress Imaging

All patients exercised upright on a motor-driven treadmill using the standard Bruce protocol. Exercise was discontinued because of the development of limiting symptoms, electrocardiographic abnormalities, or dysrhythmia. Thallium-201 (2 mCi) was injected 1 minute before termination of exercise. Cardiac images were obtained using a gamma camera (Siemens LEM, Erlangen, West Germany) interfaced with a minicomputer (MDS A2, Ann Arbor, MI, USA). The gamma camera was equipped with a high-resolution parallel-hole collimator. The energy window was symmetrically set (20%) over the 80 keV photo-peak of thallium-201. Imaging was started within 5 minutes after injection of the radiopharmaceutical in the left anterior oblique, anterior, and left lateral projections. Each image was acquired for 10 minutes. Images were obtained for identical times 4 hours later (delayed imaging). Thallium-201 images were processed for computer quantification using the Cedars-Sinai Planar Thallium-201 Software (MDS A2). The digitized unprocessed (analog equivalent) images and circumferential profiles of all patients were analyzed independently by two experienced observers who had no knowledge of clinical data or stress test results. One of the following criteria was used to define an abnormal thallium-201 study:

1. Fixed defect: Any 18-degree segment of the poststress profile falling below the lower limit of normal on any of three views, without a change in relative thallium-201 distribution at 4-hour delayed imaging.
2. Reversible defect: A defect present on the post-exercise image, but with normal thallium-201 distribution at 4-hour delayed imaging.
3. Partially reversible defect: A postexercise defect that has improved at 4-hour delayed imaging, but is still below the lower limit of normal.
4. Abnormal washout: Any 18-degree segment of the washout profile falling below the lower limit of normal in any of three views. Low washout was only considered abnormal if the

<table>
<thead>
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<th>Characteristic</th>
<th>Hypertensive (n = 133)</th>
<th>Normotensive (n = 139)</th>
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<tbody>
<tr>
<td>Mean age (yr)</td>
<td>58</td>
<td>55</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>101:32</td>
<td>109:30</td>
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<tr>
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<td>13</td>
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<td>Smoker</td>
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<td>33</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>62</td>
<td>68</td>
</tr>
<tr>
<td>Left ventricular hypertrophy*</td>
<td>16</td>
<td>0†</td>
</tr>
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</table>

*By electrocardiogram.
†$p<0.05$, compared with number of hypertensive subjects.
patient achieved an exercise heart rate of at least 120 beats/min. In this study, one patient who did not reach a peak exercise heart rate of at least 120 beats/min and had only washout abnormalities on the thallium-201 study was a priori excluded.

Statistical Analysis

The results of thallium-201 exercise tests in patients with and without hypertension were compared in the subgroups with a mid to high likelihood of coronary artery disease and those with a low likelihood of coronary artery disease. In addition, the results of thallium-201 testing in treated versus untreated hypertensive patients were compared. Chi-square analysis was used to test the difference in incidence in subgroups. The difference in clinical factors, blood pressure, and exercise time in patients with and without hypertension was compared by unpaired t test. A p value of less than 0.05 was considered significant.

Results

The groups did not differ significantly in age, gender distribution, or major coronary risk factors, including tobacco smoking, hyperlipidemia, and diabetes mellitus (Table 1). The medications received by patients in each group are shown in Table 2. Of note is that β-blocker therapy was comparable in both groups. The prevalence of clinical coronary disease was also comparable in both groups and is shown in Table 3. The percentage of patients with angina pectoris, prior myocardial infarction with and without bypass surgery, and bypass surgery alone was not significantly different between groups. In the mid to high likelihood category, 57% of the hypertensive and 56% of the normotensive patients had a history of myocardial infarction or of coronary bypass surgery and myocardial infarction. The distribution of likelihood of coronary artery disease by probability analysis in the hypertensive and normotensive groups was similar in both groups (Table 4).

The exercise performance was comparable in hypertensive and normotensive groups. Duration of exercise and workload were not significantly different between groups. Mean exercise time was 8.7 ± 2.1 minutes in hypertensive patients and 8.9 ± 2.2 minutes in normotensive patients (p = NS). Peak exercise systolic blood pressure was 182 ± 14 mm Hg in hypertensive patients compared with 178 ± 12 mm Hg in normotensive patients (p = NS). Peak exercise heart rate was 141 ± 12 and 137 ± 11 beats/min in the hypertensive and normotensive patients, respectively (p = NS).

Overall, 75 patients with hypertension and 56 patients without hypertension had abnormal thallium-201 stress images. The distribution of the various types of abnormal thallium-201 images is shown in Table 5. Patients with a mid to high likelihood of coronary artery disease were more likely to have abnormal thallium-201 perfusion images than patients with low likelihood of coronary artery disease, independent of the presence or absence of hypertension (Table 6). Fifty-

<table>
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<th>Medication</th>
<th>Hypertensive (n = 133)</th>
<th>Normotensive (n = 139)</th>
</tr>
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<tr>
<td>β-blockers only</td>
<td>14</td>
<td>24</td>
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<tr>
<td>Diuretics only</td>
<td>30</td>
<td>0</td>
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<tr>
<td>Nitrates only</td>
<td>5</td>
<td>6</td>
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<tr>
<td>Calcium entry blockers only</td>
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<td>19</td>
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<tr>
<td>β-blockers and nitrates</td>
<td>0</td>
<td>10</td>
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<td>9</td>
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<tr>
<td>Calcium blockers, nitrates, and β-blockers</td>
<td>8</td>
<td>6</td>
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<table>
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<th>Types of Abnormal Thallium-201 Stress Images</th>
<th>Hypertensive (n = 133)</th>
<th>Normotensive (n = 139)</th>
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</thead>
<tbody>
<tr>
<td>Fixed defect</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Reversible defect</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Partially reversible defect</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Abnormal washout only</td>
<td>5 (1)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent patients whose washout abnormality was diffuse. CAD = coronary artery disease.

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four of 60 (90%) hypertensive patients with mid to high likelihood of coronary artery disease had abnormal thallium-201 perfusion images, while 51 of 64 (80%) of normotensive patients with mid to high likelihood of coronary disease had abnormal images ($p = NS$). However, in patients with a low likelihood of coronary artery disease, hypertensive patients had a higher incidence of abnormal thallium-201 stress images (Table 7). Abnormal thallium-201 perfusion scans were present in 21 (29%) of hypertensive patients and in 5 (7%) of normotensive patients with a low likelihood of coronary artery disease ($p < 0.001$). All these patients showed reversible defects or abnormal washout, or both. The patients in the mid to high likelihood group had various abnormalities (see Table 5). Fifty-six of 94 (60%) treated and 19 of 39 (49%) untreated hypertensive patients had abnormal thallium-201 scans ($p = NS$; Table 8).

**Discussion**

This study demonstrates that significantly more patients with hypertension and low likelihood of coronary artery disease have abnormal thallium-201 stress test results than do normotensive patients with a comparable low likelihood of coronary artery disease. As expected, in patients with a mid to high likelihood of coronary artery disease, the frequency of abnormal thallium-201 images was high and not different between normotensive and hypertensive patients. These findings might indicate that hypertension may independently produce myocardial changes and changes in perfusion that are detected by thallium-201 stress imaging. The scintigraphic abnormalities in the low likelihood hypertensive group consisted of reversible defects on planar imaging or abnormal washout on quantitative analysis, or both. These findings are consistent with reversible exercise-induced inhomogeneity of myocardial blood flow. The precise pathophysiology underlying this phenomenon is uncertain. Although these scintigraphic abnormalities in thallium images are highly specific for obstructive coronary artery disease and ischemia in nonhypertensive patients, it is possible that the pattern may not be specific for ischemia, especially coronary artery disease, in hypertensive patients. In the latter group of patients, relative regional hypoperfusion and redistribution conceivably might occur without ischemia. Clinical follow-up, studies of myocardial metabolism in hypertensive patients, and thallium-201 kinetic studies in experimental models of hypertrophy may further delineate the underlying pathophysiology.

As the clinical characteristics of the two patient groups were not significantly different, our observations cannot be explained by differences in the normotensive and hypertensive populations. The groups were comparable with respect to conventional risk factors for coronary artery disease. The distribution of diabetes, tobacco smoking, and hyperlipidemia were similar in hypertensive and normotensive groups and appear unrelated to the results of thallium-201 stress imaging. The number of patients receiving β-blockers, nitrates, calcium entry blockers, and various combinations of these drugs was also similar in both groups. As expected, the use of diuretics was significantly greater in the hypertensive group. An analysis of treated versus untreated hypertensive patients revealed no differences in resting blood pressure or in the results of thallium-201 scintigraphy.

Electrocardiographic criteria for left ventricular hypertrophy were present only in 16 patients in the hypertensive group. This finding did not correlate with the results of thallium-201 stress imaging. Echocardiographic assessment of left ventricular hypertrophy has been shown to be a more sensitive technique for the assessment of left ventricular hypertrophy but was performed in only a small number of patients. Folmer...
et al. demonstrated that echocardiographic left ventricular hypertrophy may not correlate with thallium-201 perfusion abnormalities. The frequency distribution of mid to high and low likelihood of coronary disease, as determined by probability analysis of clinical characteristics, was comparable in both hypertensive and normotensive groups. In the mid to high likelihood group, myocardial infarction or coronary bypass surgery and myocardial infarction was present in more than half of the hypertensive and the normotensive patients. The remaining patients in the mid to high likelihood group, with chest pain only, had a greater than 25% probability of coronary artery disease. In this study we employed the 25% level as an arbitrary demarcation point to separate patients with mid to high likelihood from those with low likelihood. We sought to ensure that classification in the low likelihood group would be specific for patients without coronary artery disease. We realized that by choosing the 25% cutoff, some patients without coronary artery disease are likely to be categorized in the mid to high likelihood group. As shown in Table 4, the majority of coronary artery disease patients had probability scores of greater than 75%.

The increased prevalence of abnormal thallium-201 stress test results in the low likelihood group is greater than that generally reported. The abnormal thallium-201 perfusion study results may have been related to undetected coronary artery disease in hypertensive patients, increased oxygen demand caused by increased left ventricular mass, inadequate coronary reserve, altered hemodynamics, or to a combination of these or other, as yet unrecognized, factors. The increased incidence of abnormal stress test results in hypertensive patients in the absence of angiographic coronary artery disease noted in earlier radionuclide ventriculographic studies and the trends observed in the present study of thallium perfusion may reflect supply-demand imbalance independent of coronary anatomy.

Although the current study cannot discriminate among the various possibilities, we speculate that abnormal coronary vascular reserve in the hypertensive patients may have played a role in the abnormalities observed. In experimental models of hypertrophy, coronary vascular reserve is decreased and coronary vascular resistance is increased. This abnormal vasodilative capacity can lead to endocardial ischemia during stress secondary to hypoperfusion. Similar changes in coronary vascular reserve occur in right but not left ventricular blood flow in an experimental model of right ventricular hypertrophy. Therefore, hypertrophy itself, rather than coronary perfusion pressure, changes in coronary arteries, or humoral or neural factors, mediates this response. Likewise, patients with left ventricular hypertrophy also have abnormal coronary vasodilative capacity. Similar to experimental preparations, abnormal coronary reserve can cause ischemia in patients during stress. Therefore, abnormal coronary vascular reserve in our low likelihood hypertensive patients could have led to relative regional hyperperfusion or ischemia during exercise and abnormal thallium-201 images.

It is unlikely that the abnormal scans in the low likelihood hypertensive patients represent false-positive results. Although abnormal images in these patients may not signify coronary artery disease, it likely reveals exercise-induced inhomogeneity of myocardial blood flow. Recent studies have shown inadequate coronary vascular reserve in patients with abnormal thallium-201 stress images or exercise radionuclide ventriculograms and normal coronary angiograms. Some of these patients have been shown to have true myocardial ischemia, as judged by myocardial lactate production during pacing-induced stress.

In summary, this study indicates that in a mixed population of patients referred for thallium-201 exercise testing, those with a low likelihood of coronary artery disease and hypertension were more likely to have abnormal thallium-201 test results than were their normotensive counterparts. The diagnostic accuracy of routine exercise treadmill exercise testing has been shown to be enhanced when performed in conjunction with radionuclide studies. The diagnostic capability of radionuclide ventriculography, however, may be diminished in some groups of patients. Myocardial perfusion imaging with thallium-201 may be better suited for the evaluation of hypertensive patients. However, decreased diagnostic accuracy has also been reported for thallium-201 imaging in patients with chest pain syndromes without obstructive epicardial coronary artery disease and in patients with aortic stenosis and normal coronary arteries. Thus, although some hypertensive patients in the low likelihood group may have had occult coronary artery disease, abnormal coronary vascular reserve or other pathophysiological mechanisms may cause true ischemia. This ischemia may account for the thallium-201 scintigraphic abnormalities found in this and other studies.

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Thallium-201 stress imaging in hypertensive patients.
D S Schulman, C K Francis, H R Black and F J Wackers

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