Comparison of Stress/Rest Myocardial Perfusion Tomography, Dipyridamole and Dobutamine Stress Echocardiography for the Detection of Coronary Disease in Hypertensive Patients With Chest Pain and Positive Exercise Test

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OBJECTIVES
Although different noninvasive tests have been proposed for detecting coronary artery disease (CAD) in patients with hypertension and chest pain symptoms, the relative performance of the available techniques has not been systematically assessed.

BACKGROUND
Patients with hypertension frequently complain of chest pain and exhibit ischemic-like ST segment changes on the exercise electrocardiogram (ECG). However, the specificity of such changes for predicting significant CAD is very low, because these patients often exhibit a normal coronary angiogram.

METHODS
In 101 patients with hypertension, chest pain and positive exercise ECG, we performed stress/rest myocardial single photon emission computed tomography with 99mTc-MIBI, dipyridamole and dobutamine stress echocardiography and coronary angiography. All patients had normal global ventricular function and 57 had left ventricular hypertrophy. All were kept on ACE inhibitors during the study period.

RESULTS
No patients had significant side effects during perfusion scintigraphy. Dose-limiting side effects were observed in five patients with dipyridamole and in seven patients with dobutamine. Only 56% of study patients exhibited significant CAD. Sensitivity, specificity, accuracy, positive and negative predictive values were, respectively, 98%, 36%, 71%, 67% and 94% for perfusion scintigraphy, 61%, 91%, 74%, 90% and 64% for dipyridamole and 88%, 80%, 85% and 83% for dobutamine stress echocardiography.

CONCLUSIONS
This study shows that stress echo in patients with hypertension yields a satisfactory diagnostic accuracy for identifying significant epicardial CAD. Our results indicate that dobutamine might be superior to dipyridamole. The low specificity of myocardial scintigraphy probably relates to the fact that this method traces perfusion abnormalities, not necessarily caused by epicardial CAD, possibly due to microvascular disease and not causing obvious wall motion abnormalities. (J Am Coll Cardiol 1999;34:441–7) © 1999 by the American College of Cardiology

In patients with arterial hypertension, the accurate diagnosis of coronary artery disease (CAD) bears important therapeutic and prognostic implications. Both diseases may result in similar clinical events and frequently occur in the same patient (1,2). Yet, the noninvasive detection of CAD in hypertensive patients with chest pain remains an unresolved issue (2). The use of exercise electrocardiography is limited by the low specificity of the test, regardless of whether hypertension is associated with left ventricular hypertrophy or not (3). Moreover, although myocardial perfusion scintigraphy has been proposed as a more specific alternative, its specificity is far from being ideal (4–7). Recently, both dipyridamole and dobutamine stress echocardiography have been proposed as useful tools for the diagnosis of CAD in hypertensive patients (8,9). However, comparative studies using all the previously cited techniques have not been performed. The aim of the present study was to assess the relative diagnostic performance of rest/stress myocardial perfusion scintigraphy, dipyridamole and dobutamine stress
emission computed tomography (SPECT) acquisitions at peak exercise and 48 h postexercise, at rest. Single photon Tc-MIBI tracer (925 MBq) was given intravenously with or without angina.

Positive exercise test and were submitted to the following investigations, which were performed in the order in which they are presented. Each patient gave his or her written informed consent.

Study population. We studied 101 consecutive patients (55 men, aged 61 ± 10 years, range 45 to 76) with arterial hypertension (duration from diagnosis 22 ± 20 months, range 2 to 120) referred to our cardiology outpatient clinic for rest or effort typical angina and a positive exercise test. None of the patients had had a previous myocardial infarction. To avoid interference with the study investigations, all antiischemic drugs, such as nitrates, beta-adrenergic blocking agents and calcium antagonists, were discontinued for the entire study duration. To control blood pressure during the study period, patients were given ACE inhibitors or diuretics as necessary. All study subjects had a reproducibly positive exercise test and were submitted to the following investigations, which were performed in the order in which they are presented. Each patient gave his or her written informed consent.

Stress-rest myocardial perfusion imaging. Treadmill exercise was performed following the modified Bruce protocol; the 12-lead electrocardiogram (ECG) and the blood pressure (cuff sphygmomanometer) were recorded at rest and every minute during exercise and recovery. The following criteria were used for discontinuing the test: 1) achievement of the maximal predicted heart rate; 2) occurrence of ≥2.0 mm rectilinear or downsloping ST-segment depression on at least one precordial or two peripheral leads, with or without angina; 3) severe dyspnea or fatigue; 4) repetitive ventricular arrhythmias; and 5) a greater than 10-mm Hg decrease in systolic blood pressure at any exercise step. For all tests, total exercise time and rate–pressure product (RPP) at peak exercise were analyzed. A test was considered positive in the presence of ≥1.0 mm rectilinear or downsloping ST-segment depression, calculated from baseline levels, on at least one precordial or two peripheral leads, with or without angina.

Myocardial perfusion imaging was performed with 99m-Tc-MIBI. The tracer (925 MBq) was given intravenously peak exercise and 48 h postexercise, at rest. Single photon emission computed tomography (SPECT) acquisitions were performed 90 min after tracer injection, with a large field of view, single-head rotating gamma camera (Starcam 400 AC; General Electric, Milwaukee, Wisconsin). Sixty-four angular projections (64 × 64 matrix) were obtained in approximately 40 min over 360°. Transaxial slices, 6.2 cm thick, were reconstructed using a filtered back projection algorithm with a Butterworth filter (cutoff frequency = 0.4 cycles/pixel). No correction for attenuation was performed.

Interpretation of scintigraphic images. From the raw scintigraphic data, horizontal long-axis, vertical long-axis and short-axis tomograms were reconstructed and reported independently by two experienced observers, unaware of each patient’s identity and angiographic findings. The left ventricular myocardium was divided into six segments: anterior, apical, septal, inferior, posterior and lateral. Images were displayed in random order and graded using a four-point score (0 = normal, 1 = moderate uptake reduction, 2 = severe uptake reduction, 3 = absent uptake). A test was considered positive when there was ≥1 point score change between rest and stress images in at least two adjacent tomographic slices. In case of disagreement, a majority decision was taken by including a third observer.

Stress echocardiography. Dobutamine and dipyridamole stress echocardiography were performed on separate days in random order. Dobutamine was infused intravenously (i.v.) with a mechanical pump, starting with a dose of 5 μg/kg/min and increasing the rate at 3-min intervals to 10, 20, 30 and 40 μg/kg/min. During the infusion, the 12-lead ECG was monitored continuously and recorded on paper every 2 min. Blood pressure was measured by sphygmomanometer at 3-min intervals. Test end points were: 1) achievement of peak dobutamine dose; 2) attainment of 85% of the maximal predicted heart rate; 3) development of severe angina or ST-segment depression ≥2 mm; 4) appearance of a new abnormality in systolic wall motion or wall thickening; and 5) occurrence of severe side effects. The latter included hypertension (systolic pressure >220 mm Hg, diastolic pressure >120 mm Hg), hypotension (>30 mm Hg fall of systolic pressure), dyspnea, significant ventricular or supraventricular arrhythmia (≥6 beats supraventricular tachycardia or ≥3 beats ventricular tachycardia) and nausea/vomiting.

Dipyridamole was infused at 0.56 mg/kg over 4 min. In the event of a negative test, a further 0.28-mg/kg dose was given in 2 min. The maximal cumulative dose was therefore 0.84 mg/kg. Aminophylline (up to 240 mg i.v. over 3 min), was readily at hand. The 12-lead ECG and blood pressure were recorded at 1-min intervals during the whole investigation.

All study subjects had adequate transthoracic acoustic windows. Studies were performed with an ultrasound system (Sonos 2500; Hewlett-Packard, Andover, Massachusetts) equipped with a 2.5/2.0-MHz transducer and were recorded on half-inch VHS tape. Images were also digitized.
at each stage from four views, using a commercially available stress program (Sonos 2500 ultrasound system; Hewlett-Packard). R-Wave triggering was used to capture a representative cardiac cycle in each view at 30 frames per second. The first 400 ms of the selected cycle were displayed in a continuous-loop format to evaluate systolic wall thickening without the potential confounding influence of diastolic septal motion. The generated cineloops were recorded on VHS tape and stored on a rewritable optical disk (Hewlett-Packard) for later review.

Each subject was examined in the left lateral decubitus. Standard M-mode measurements were obtained at the papillary muscle level. Left ventricular mass was calculated by Devereux and Reichek’s formula and normalized for body surface (left ventricular mass index [LVMI] in g/m²) (10). The LVMI obtained in study patients was compared with the value obtained from an age- and gender-matched control group in our echocardiography database.

Echocardiographic image processing and analysis. Two-dimensional echocardiograms were recorded continuously during both dobutamine and dipyridamole administration. In the baseline studies, as well as during stress, all standard echocardiographic views were obtained whenever possible. Both analog and digital images were interpreted by two independent investigators who had no knowledge of patients’ status. The left ventricle was divided into 16 segments as previously described (11). For each segment, systolic wall motion and thickening were visually graded with the following semiquantitative scoring system: 1 = normal or hyperkinesia; 2 = hypokinesia; 3 = akinesia; and 4 = dyskinesia. Inadequately visualized segments were not scored. A test result was considered positive when the wall motion score increased by one grade or more at peak stress. In positive dobutamine tests, the dobutamine infusion time (minutes) was also determined as the time interval from the beginning of drug infusion to the occurrence of stress-induced asynergy.

To compare SPECT and echocardiographic images, the left ventricle was also divided into six major segments: anterior, apical, septal, inferior, posterior and lateral.

Coronary angiography. All patients underwent coronary angiography and left ventriculography by the Judkins technique. Ventriculography was performed in the 30° right anterior oblique and 60° left anterior oblique views. Coronary arteries were selectively injected in multiple views and, to avoid overestimation of coronary stenosis due to vasoconstriction, left and right coronary injections were also performed after intracoronary administration of nitroglycerine (100 μg, as a bolus). End-diastolic cine frames were selected for optimal stenosis visualization and magnified 5×. Eccentric stenoses were evaluated in two orthogonal views. A normal arterial segment was identified immediately proximally and distally to the lesion and measured with an electronic caliper. The minimal stenosis diameter was also measured and severity was expressed as percent reduction of normal diameter. Significant CAD was considered >50% reduction in luminal diameter of at least one major epicardial vessel.

Statistical analysis. When not in absolute numbers, data are reported as mean ± 1 standard deviation. Statistical significance was evaluated by the Student t test or a chi-square test when indicated. A p value <0.05 was considered significant. Bonferroni’s correction for multiple testing was performed where appropriate.

RESULTS

Clinical data. Of the 101 patients studied, 57 (56%) had significant coronary disease, and the remaining 44 (44%) exhibited either angiographically smooth coronary arteries (34 patients) or minor vessel wall irregularities (10 patients). Twenty patients had one-vessel, 26 had two-vessel and the remaining 11 had three-vessel disease. Duration of hypertension from diagnosis was 23 ± 22 months in CAD patients and 21 ± 18 months in patients with normal coronary arteries (p = NS).

Of the 57 patients with CAD, 14 exhibited a normal resting electrocardiogram, 5 had left ventricular hypertrophy, 1 had left anterior hemiblock and 39 had different degrees of ST abnormalities. Of the patients with normal coronary arteries, 17 had a normal resting electrocardiogram, 2 had left ventricular hypertrophy, 7 had left anterior hemiblock and 20 had various degrees of ST-T abnormalities. Although left ventricular hypertrophy was not a frequent finding on the surface ECG, mean left ventricular mass index (LVMI) was greater than in a matched group of normal controls (116 ± 42 vs. 90 ± 17 g/m², p < 0.05).

When analyzed separately, patients with CAD showed a

Table 1. Exercise Parameters Recorded on Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Pred. HR</th>
<th>RPP 1 mm</th>
<th>Time 1 mm</th>
<th>Time max</th>
<th>Recovery</th>
<th>ST max</th>
<th>Leads</th>
<th>Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCA</td>
<td>87 ± 16</td>
<td>23,216 ± 6637</td>
<td>26,495 ± 4893</td>
<td>509 ± 143</td>
<td>647 ± 175</td>
<td>238 ± 125</td>
<td>1.6 ± 0.6</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>CAD</td>
<td>83 ± 11</td>
<td>21,612 ± 4869*</td>
<td>24,885 ± 4990</td>
<td>434 ± 203</td>
<td>562 ± 193*</td>
<td>345 ± 182*</td>
<td>1.7 ± 0.7</td>
<td>2.8 ± 0.9</td>
</tr>
</tbody>
</table>

Angina = patients reporting chest pain on exercise testing; CAD = coronary artery disease; Leads = number of leads showing diagnostic ST segment depression; NCA = normal coronary arteries; pred HR = percent of maximal predicted heart rate; Recovery = time for ECG recovery (s); RPP 1 mm and RPP max = rate-pressure product at 1-mm ST segment depression and at peak exercise (mm Hg × beats/min); ST max = maximal ST segment depression (mm); Time 1 mm and Time max = time to 1-mm ST segment depression and total exercise duration (s).

* p < 0.05.
greater LVMI than those with normal coronary arteries (130 ± 48 vs. 101 ± 24 g/m², p < 0.05). In the latter, LVMI was not significantly different from the control group.

The mean blood pressure values obtained just before performing the three tests, were 151 ± 19/88 ± 9 mm Hg in patients with CAD, and 151 ± 19/89 ± 9 mm Hg in patients with normal coronary arteries (p = NS). At peak exercise (at the time of perfusion scintigraphy), these values increased to 192 ± 21/96 ± 12 and 189 ± 23/99 ± 12 mm Hg, respectively (p = NS).

Exercise performance was significantly better in patients with normal coronary arteries, as evidenced by higher RPPs at 1-mm ST segment depression and peak exercise, longer exercise duration and shorter recovery time (Table 1).

**Noninvasive detection of coronary artery disease.** Dipyridamole and dobutamine stress echocardiograms and perfusion scintigrams identified, respectively, 35, 50 and 56 of the 57 patients with CAD, with a relative sensitivity of 61%, 88% and 98%. The three tests correctly identified, respectively, 40, 35 and 16 of the 44 patients with normal coronary arteries, yielding a specificity of 91%, 80% and 36%.

The negative predictive value was highest (94%) for methoxy-isobutyl-isonitrile (MIBI), while the positive predictive value was greatest for dipyridamole (90%). Dobutamine had similar positive and negative predictive value (85% to 83%). As a result, overall diagnostic accuracy for dipyridamole-dobutamine and perfusion scintigraphy was 74%, 84% and 71%, respectively. The results of the tests were concordant in 46 patients (32 with CAD and 12 with normal coronary arteries). The relative performance of the three tests are shown in Table 2 and Figure 1. The sensitivity to predict the presence of single, double and triple vessel disease was 31%, 69% and 82% for dipyridamole, 85%, 88% and 91% for dobutamine and 95%, 100% and 100% for MIBI, respectively. Dobutamine infusion time was 13.2 ± 3.7, 13.6 ± 3.1 and 12.9 ± 2.9 µg/kg in one-, two- and three-vessel disease, respectively (p = NS). The sensitivity of the three tests to detect isolated left anterior descending coronary disease (five patients, mean percent stenosis 71 ± 21%) was 40%, 80% and 100%, respectively. These figures were 78%, 93% and 96%, respectively, when left anterior descending coronary disease was present in patients with multivessel disease (Tables 3 and 4).

**Concordance of tests.** Ten patients with normal coronary arteries and 25 with CAD had resting wall motion abnormalities in 21 and 87 segments, respectively. Eight (38%) and 44 (51%) of these dysfunctioning segments also showed resting underperfusion on the resting MIBI scan in five patients with normal coronary arteries and in 22 patients with CAD. Stress-induced MIBI perfusion defects and dobutamine-induced wall motion abnormalities were observed in the same segments in six patients with normal coronary arteries (seven segments) and in 40 patients with CAD (70 segments). Dipyridamole-induced wall motion abnormalities and stress-MIBI perfusion defects were observed in the same segments in two patients with normal coronary arteries (three segments) and in 28 patients with CAD (44 segments). Finally, all three tests were positive and concordant in two patients with normal coronary arteries (three segments) and in 25 patients with CAD (37 segments). All tests were negative in four patients with normal coronary arteries and in none of CAD patients. Overall, they gave concordant results in 31 patients (31%).

**Figure 1.** Histogram showing sensitivity (SENS), specificity (SPEC), accuracy (ACC), negative (NPV) and positive (PPV) predictive value of dipyridamole (Dip), dobutamine (DOB) stress echocardiography, and myocardial perfusion scintigraphy (MIBI), for the detection of CAD, in hypertensive patients with chest pain and positive exercise test. Open bars: MIBI; solid bars: Dip; striped bars: DOB.
Side effects and ECG responses during stress-echo. Of the 101 patients studied, 5 (5%) had significant side effects with dipyridamole and 7 (7%) with dobutamine. The maximal dipyridamole dose could be administered in 48 patients with coronary disease (84%) and in 39 patients with normal coronary arteries (89%); in the two groups, mean administered dobutamine dose was 28 ± 8 μg and 31 ± 8 μg (p = NS), respectively.

The percent of maximal predicted heart rate achieved during dobutamine was 77 ± 10 and 74 ± 11% (p = NS) in patients with normal coronary arteries and CAD, respectively. With exercise (at the time of perfusion scintigraphy), the percent of the predicted heart rate achieved was 87 ± 16% and 83 ± 11%, respectively (p < 0.0001 for both groups, exercise vs. dobutamine). Four of the seven patients with coronary disease who had a negative dobutamine test achieved >85% of maximal predicted heart rate; the remaining three patients could not terminate the protocol because of repetitive ventricular ectopic beats.

The presence of angina and ST-segment depression during stress echocardiography were significantly more frequent in patients with coronary disease than in patients with normal coronary arteries. Accordingly, angina and ST-segment depression were more likely to appear during a positive stress echocardiogram (Table 5).

### DISCUSSION

In hypertensive patients, the distinction between anginal symptoms caused by CAD and those caused by hypertension is important, because treatment goals and management may be different. If the presence of epicardial CAD can be excluded by noninvasive means, the risks and expense of coronary arteriography can be avoided. However, the use of exercise stress testing for determining the probability of obstructive epicardial CAD in hypertensive patients lacks specificity (2,3). Undiagnosed hypertrophy may be present even in the absence of ECG signs (12), and exercise-induced diagnostic ST-segment depression may result from transmural flow redistribution due to increased left ventricular mass rather than to obstructive epicardial CAD (13). This is why a number of noninvasive investigations have been proposed, in an attempt to overcome the limitations of exercise testing.

### Comparison of noninvasive tests.

The results of our study confirm the poor diagnostic accuracy of the exercise ECG, because 44 patients with a positive test had angiographically normal coronary arteries. Both dipyridamole and dobutamine stress echocardiography yielded a superior diagnostic accuracy. Specifically, and in keeping with previous investigations (14,15), dipyridamole exhibited very high specificity with a relatively low sensitivity for the detection of CAD. Conversely, dobutamine yielded high sensitivity (88%) with satisfactory specificity (80%).

The discrepancy between the results obtained by the two stressors probably relates to the mechanisms by which they cause ischemia. Dipyridamole induces transmural flow redistribution via inhibition of adenosine breakdown, which causes arteriolar vasodilation and subendocardial "steal." Therefore, this agent causes ischemia almost exclusively by altering coronary hemodynamics in the presence of critical epicardial disease. Indeed, in our study, the sensitivity of the test progressively increased with the progression of coronary disease extent. This suggests that the greater the impairment of coronary hemodynamics, the more likely dipyridamole is to cause ischemia. Dobutamine increases myocardial oxygen consumption by sympathetic stimulation that causes heart rate and contractility to increase (16–18). Like dipyridamole, this agent causes arteriolar coronary dilation (and transmural flow redistribution), due to metabolic stimulation and increased ATP breakdown; in addition, it causes...
oxygen demand to increase. Therefore, it is not surprising that this agent yields a greater sensitivity for detecting epicardial coronary disease, with very little loss in specificity and greater diagnostic accuracy. Furthermore, the ability of dobutamine stress echocardiography to detect epicardial coronary stenoses was not apparently related to the extent of the disease. In fact, the sensitivity of the test did not significantly increase with the progression of disease severity, as also evidenced by similar dobutamine infusion times in patients with one-, two- or three-vessel disease. This finding is at variance with previous reports, which showed a direct relation between dobutamine sensitivity and the extent of CAD (18). It is possible that in our selected population of hypertensive patients, the likelihood of a positive test may have somewhat increased due to a reduction of the ischemic threshold induced by greater LVMI or coexisting microvascular abnormalities, regardless the extent of CAD.

Therefore, when patients with hypertension, chest pain and a positive exercise test are elected to undergo further diagnostic stratification with stress echocardiography, dobutamine rather than dipyridamole should be considered as the first-choice pharmacologic stressor. Although the addition of atropine at peak pharmacologic stimulation has been shown to improve the diagnostic accuracy of both dipyridamole and dobutamine stress echocardiography, the diagnostic accuracy of dobutamine remains higher (19,20). Exercise may represent a valid alternative to pharmacologic stressors, possibly yielding even better diagnostic accuracy than dobutamine when performed by expert echocardiographers (15).

Significance of perfusion abnormalities. The diagnostic value of dobutamine stress echo also appears to be better than that of MIBI perfusion scintigraphy. Indeed, and in agreement with previous studies (4–7), stress-rest myocardial perfusion scintigraphy frequently yielded false-positive results, possibly due to microvascular abnormalities (21,22). Indeed, microvascular dysfunction, which has been previously hypothesized as the cause of ST-segment abnormalities during dipyridamole administration in patients with arterial hypertension and chest pain (8), may be the cause of inhomogeneous myocardial perfusion both at rest and during stress. Increased medial thickness has been reported in coronary arterioles from hypertensive patients undergoing endomyocardial biopsy (23). This could explain the reduction in coronary reserve and maximal flow capacity consistently observed in these patients, whose flow response to atrial pacing is blunted and is further decreased by the administration of ergonovine (24). Thus, besides structural alterations, the microvasculature may also show functional derangements leading to abnormal vasoconstriction in response to vasoactive stimuli. The reduction in coronary flow reserve is unrelated to the presence of left ventricular hypertrophy (25). Accordingly, we found no relation between left ventricular mass and exercise-induced perfusion defects, which further supports the hypothesis that a microvascular disorder is present in the coronary circulation of patients with hypertension.

The simple scrutiny of these figures should be enough to allow the conclusion that in patients with hypertension, angina and a positive exercise test, stress-rest myocardial perfusion scintigraphy does not allow an accurate prediction of obstructive epicardial coronary disease. When noninvasive assessment is envisaged, stress echocardiography should be preferred.

Conclusions. Chest pain is a common complaint among hypertensive patients. Hypertension and coronary disease may present with symptoms and signs that are clinically indistinguishable. A positive exercise ECG is not reliably predictive of obstructive epicardial CAD, and should prompt the physician to pursue additional noninvasive testing. For this purpose, stress echocardiography appears to be the most valuable tool. Among pharmacologic stressors, dobutamine stress echocardiography should be the first choice. Myocardial perfusion imaging yields a very low specificity, and therefore does not help in excluding the presence of epicardial coronary disease in hypertensive patients with chest pain and a positive exercise test. However, carefully performed prospective studies on the prognostic significance of perfusion defects in hypertensive patients with chest pain and positive exercise test are not available. Long-term follow up of such patients would merit major consideration.

Acknowledgment
We thank Orietta Parmesan for her kind secretarial assistance.

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REFERENCES