Dipyridamole Echocardiography in Essential Hypertensive Patients with Chest Pain

EUGENIO PICANO, ALESSANDRA RENATA LUCARINI, FABIO LATTANZI, ALESSANDRO DISTANTE, VIRGILIO DI LEGGE, ANTONIO SALVETTI, AND ANTONIO L'ABBATE

SUMMARY The exercise-electrocardiography test shows limited feasibility and diagnostic accuracy for the noninvasive detection of coronary artery disease in hypertensive patients. Recently, the dipyridamole-echocardiography test (two-dimensional echocardiographic monitoring with dipyridamole infusion, up to 0.84 mg/kg over 10 minutes) has been proposed as an exercise-independent method for the diagnosis of coronary artery disease. The diagnostic usefulness of the exercise-electrocardiography test and the dipyridamole-echocardiography test was evaluated in 63 consecutive inpatients with history of chest pain, essential hypertension, and no previous myocardial infarction. The criterion of positivity for the exercise-electrocardiography test was a horizontal or downsloping ST segment shift exceeding 0.1 mV and for the dipyridamole-echocardiography test, a transient dysynergy of contraction. Fifteen patients could not perform a diagnostic exercise-electrocardiography test because of an inability to exercise adequately (two patients), severe hypertension in spite of full antihypertensive therapy (six patients), or excessive blood pressure rise at the first step of the exercise-electrocardiography test (seven patients). Five patients could not perform the dipyridamole-echocardiography test because of a poor acoustic window. The overall feasibility was 76% for the exercise-electrocardiography test and 92% for the dipyridamole-echocardiography test (p < 0.05). All 43 patients who performed both tests underwent coronary angiography; 30 had significant coronary artery disease (>70% lumen reduction of at least 1 major coronary vessel). Sensitivity was 67% for both the exercise-electrocardiography test and the dipyridamole-echocardiography test (p = NS); specificity was 46% for the exercise-electrocardiography test and 92% for the dipyridamole-echocardiography test (p < 0.05). Thus, the dipyridamole-echocardiography test represents a good diagnostic alternative to the exercise-electrocardiography test in symptomatic hypertensive patients, as it has a similar sensitivity and higher feasibility and specificity for the detection of coronary artery disease. (Hypertension 12: 238-243, 1988)

KEY WORDS • coronary artery disease • essential hypertension • dipyridamole • echocardiography

SINCE hypertension is a major risk factor for the development of coronary artery disease (CAD), the reliability of stress testing for the evaluation of chest pain in patients with abnormal blood pressure elevation is an important clinical problem. The exercise-electrocardiography test (EET) is the most widely used clinical tool for the diagnosis of CAD.1 However, its use in patients with arterial hypertension is limited by various factors: 1) safety (severe hypertension is a formal contraindication to exercise testing), 2) feasibility (marked blood pressure rise can be found in the first steps of exercise, precluding the execution of the test and therefore the performance of a diagnostic EET), and 3) specificity (ST segment depression is often found in the absence of angiographically assessed CAD, thus, dramatically lowering the diagnostic accuracy of EET in this subset of patients). This is particularly true in the presence of left ventricular hypertrophy, which makes an EET uninterpretable.2 Unfortunately, alternative stressing procedures, such as exercise radionuclide angiography3 and thallium-201 stress imaging,4 were found to be inadequate screening tests for CAD because of the frequent occurrence of false-positive responses.

As a non-exercise-dependent method of detecting CAD, dipyridamole stress testing is gaining popularity. It has been proposed in combination with...
12-lead electrocardiography, thallium-201 imaging, and more recently, with two-dimensional echocardiography. In particular, with the high dose dipyridamole-echocardiography test (DET), the diagnostic end-point is represented by a transient dyssynergy of contraction, a more specific marker of myocardial ischemia than are ST segment changes. Furthermore, this test does not require an ability to exercise and does not induce a marked hypertensive reaction (rather it induces a mild hypertension). Theoretically, it might be more feasible and accurate than the EET for the diagnosis of CAD in a population of hypertensive patients with chest pain. Thus, the aim of this study was to evaluate the relative feasibility and diagnostic accuracy of the DET versus the EET in the diagnosis of angiographically assessed CAD in essential hypertensive patients. Both diagnostic tests were also evaluated in a normotensive group with similar clinical symptoms of CAD.

Patients and Methods

Sixty-three consecutive inpatients (44 men, 19 women; mean age, 54 ± 9 years) were considered initially. Inclusion criteria were 1) history of chest pain (typical or atypical, either at rest or on effort) and 2) arterial hypertension (diastolic blood pressure > 95 mm Hg). Exclusion criteria were 1) history or electrocardiographic evidence of previous myocardial infarction (since in this subset the diagnosis of CAD was known from the outset), 2) cardiac failure, 3) congenital or valvular heart disease, 4) documented cardiomyopathy, and 5) bundle branch block. Seventeen patients (27%) of the patients (48 men, 12 women; mean age, 53 ± 9 years) were considered while not receiving therapy. Both diagnostic tests were also evaluated in a normotensive group with similar clinical symptoms of CAD.

Exercise-Electrocardiography Test

Patients with resting diastolic blood pressure greater than 130 mm Hg in spite of full antihypertensive therapy were not subjected to the EET. All remaining patients performed a multistage upright bicycle ergometer test, with an initial load of 25 W and subsequent increments of 25 W every 2 minutes. A 12-lead electrocardiogram and blood pressure determination were performed at baseline and every minute thereafter. Criteria for interrupting the test were severe chest pain, diagnostic ST segment shift, fatigue, excessive blood pressure rise (systolic blood pressure > 280 mm Hg; diastolic blood pressure > 140 mm Hg), limiting dyspnea, or maximal predicted heart rate in the absence of ischemia.

Electrocardiographic tracings were considered diagnostic for myocardial ischemia when there was an ST segment shift of at least 0.10 mV, 0.08 second after the J point compared with baseline. Electrocardiographic tracings were analyzed visually by an experienced cardiologist, blind to angiographic and DET findings.

Dipyridamole-Echocardiography Test

Two-dimensional echocardiographic and 12-lead electrocardiographic monitoring were performed in combination with a dipyridamole infusion of 0.56 mg/kg over 4 minutes followed by 4 minutes of no dose and then 0.28 mg/kg in 2 minutes. The cumulative dose was therefore 0.84 mg/kg over 10 minutes.

Aminophylline (240 mg), which promptly reverses the effects of dipyridamole, was readily at hand. During the procedure, the blood pressure and the electrocardiogram were recorded each minute. The electrocardiographic criteria for ischemia during this test were the same as during the exercise stress test. Two-dimensional echocardiograms were obtained continuously during and up to 20 minutes after dipyridamole administration. A commercially available wide-angle phased-array imaging system (Model 77020, Hewlett-Packard, Palo Alto, CA, USA; 2.5- and 3.5-MHz transducers) was used. In the baseline studies, all standard echocardiographic views were obtained when possible. During the test new areas of abnormal wall motion were identified on multiple views by rapidly moving the ultrasound transducer through various positions. After an optimal position for the observation of abnormal wall motion was established, the transducer was held stationary throughout the remainder of the study and the recovery period.

The videotapes were analyzed by two independent observers. When there was a disagreement about the results (positivity vs negativity), a third observer reviewed the study and the subsequent majority judgment was binding. None of the three observers had access to angiographic and exercise stress test findings before the interpretation of the videotapes. Segmental anatomy and wall motion were assessed in a qualitative manner as previously reported. Wall motion was graded as hyperkinetic, normal, hypokinetic, akinetic, or dyskinetic. The grading of the asynergy and the regional localization of the asynergy were decided by consensus between the two observers. The positivity of the test was linked to detection of a transient asynergy of contraction.

Intraobserver variability was assessed by one of the investigators (F.L.) repeating the evaluation of 10 studies in hypertensive patients, selected at random, 1 month after the first interpretation and without knowledge of the first evaluation.
Angiographic Study

Patients underwent biplane left ventriculography and selective right and left coronary arteriography, using either the Judkins or the Sones technique. Multiple views of each coronary artery were obtained, including craniocaudal views. A vessel was considered to have significant obstruction if its diameter was narrowed by 70% or more with respect to the prestenotic tract. Two independent observers, blind to the results of the EET and the DET, analyzed coronary angiograms.

Statistical Analysis

Values are expressed as means ± SD. Differences between the results of the EET and the DET were compared using the chi-square test; a Fisher’s exact test was used when appropriate. A p value below 0.05 was considered statistically significant. For both tests, sensitivity, specificity, predictive value of positive and negative test results, and accuracy in detecting angiographically assessed CAD were calculated according to standard definitions.13

Results

Feasibility of Exercise-Electrocardiography and Dipyridamole-Echocardiography Tests

Hypertensive Group

An adequate EET result could be obtained in 48 of 63 patients (76%; Table 1). Testing in the remaining 15 patients was ruled out due to 1) severe hypertension in resting conditions under full medical therapy (six patients); 2) excessive blood pressure rise in the very first step of exercise, which precluded the administration of the test and therefore the achievement of at least 80% of the age and sex-related target heart rate (seven patients); and 3) inability to exercise, due to lack of motivation or physical reasons (two patients). An adequate DET result could be obtained in 58 of 63 patients (92%; Table 2). Testing in the remaining five patients was ruled out due to a poor acoustic window in resting conditions. Thus, a total of 43 hypertensive patients performed both tests.

Normotensive Group

An adequate EET result was obtained in 55 of 60 normotensive patients (92%). Testing in the remaining five patients was ruled out because of an inability to exercise, a lack of motivation (three patients), and physical reasons (two patients; see Table 1). An adequate DET result was obtained in 56 of 60 patients (93%; see Table 2). The remaining four patients had to be ruled out due to a poor acoustic window in resting conditions. Thus, a total of 51 normotensive patients performed both tests.

Clinical Characteristics

The two groups of patients (hypertensive and normotensive) who could perform both provocative tests did not differ significantly in age or gender distribution or in the prevalence of risk factors other than arterial hypertension (Table 3). Sixteen patients in the hypertensive group had echocardiographic evidence of left ventricular hypertrophy; eight of them had electrocardiographic left ventricular hypertrophy, and three also had resting ST-segment and T-wave repolarization changes. Eleven patients in the hypertensive group underwent both provocative tests while taking their usual antihypertensive medications, but the other 32 hypertensive patients and the whole normotensive group were not taking any medications at the time of the study.

Comparison of Test Results with Angiographic Findings

A comparison with angiographic findings was performed, for both groups, in the subset of patients who could perform both provocative tests.

Hypertensive Group

At coronary angiography, 13 patients had nonsignificant and 30 had significant CAD; 10 of these had single-vessel, 14 had double-vessel, and 6 had triple-vessel disease. The DET showed a specificity of 92% (12 of 13 patients), the EET, of 46% (6 of 13 patients; p < 0.05; Figure 1). One of the seven patients with a false-positive EET result was receiv-

### Table 1. Exercise Stress Test Findings in Hypertensive and Normotensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (%)</th>
<th>Normotensive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility</td>
<td>76 (48/63)</td>
<td>92* (55/60)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>67 (20/30)</td>
<td>72 (28/39)</td>
</tr>
<tr>
<td>Specificity</td>
<td>46 (6/13)</td>
<td>75* (9/12)</td>
</tr>
</tbody>
</table>

Number of patients is shown in parentheses. *p < 0.05, compared with hypertensive values.

### Table 2. Dipyridamole-Echocardiography Test Findings in Hypertensive and Normotensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (%)</th>
<th>Normotensive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility</td>
<td>92 (38/63)</td>
<td>93 (56/60)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>67 (20/30)</td>
<td>71 (28/39)</td>
</tr>
<tr>
<td>Specificity</td>
<td>92 (12/13)</td>
<td>100 (12/12)</td>
</tr>
</tbody>
</table>

Number of patients is shown in parentheses.

### Table 3. Clinical Characteristics of Patients Who Performed Both Provocative Tests

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (n = 43)</th>
<th>Normotensive (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52 ± 8</td>
<td>53 ± 8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>30:13</td>
<td>41:10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Smoker</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>30</td>
<td>39</td>
</tr>
</tbody>
</table>

Age is shown as means ± SD.
DIPYRIDAMOLE ECHOCARDIOGRAPHY IN ISCHEMIC HYPERTENSION/Picano et al. 241

Feasibility, sensitivity, and specificity

**Figure 1.** Histograms representing the comparative feasibility, sensitivity, and specificity of the exercise-electrocardiography test (EET) versus the diprydamole-echocardiography test (DET) for the diagnosis of coronary artery disease in hypertensive patients.

**Figure 2.** Histograms representing the relative sensitivity and specificity of the diprydamole-electrocardiography test (D-ECG) and the exercise-electrocardiography test (EET) for the diagnosis of coronary artery disease in hypertensive patients.

Of the 21 patients with positive DET results, 8 had regional hypokinesia, 11 had akinesia, and 2 had dyskinesia. The transient asynergy mainly involved the septum in eight, the anterolateral wall in four, the inferoposterior wall in six, and the apex in three patients.

Except for the single false-positive result (in a patient with posterior hypokinesia), in all patients there was a good correspondence between the location of the transiently asynergic region and the presence of marked stenosis in the coronary artery feeding that region. The asynergy appeared in 14 patients after the lower (0.56 mg/kg in 4 minutes) diprydamole dose (time range: from 0–4 minutes after the low dose infusion). In seven patients the asynergy appeared during or soon after the onset of the infusion of the higher diprydamole dose (time range: 0–6 minutes after the end of the full diprydamole dosage: 0.84 mg/kg in 10 minutes). In all patients, the asynergy was promptly reversed (usually within 2 minutes) by aminophylline infusion.

The assessment of positivity versus negativity in the 43 studies analyzed was unanimous in 40. In the remaining three studies there was a split decision. The intraobserver agreement was 100% in the 10 studies reanalyzed by the same observer. This high level of interobserver and intraobserver agreement was made possible by several factors:

- The quality of echocardiographic tracings was as good after diprydamole administration as in baseline conditions; the readers agreed in advance not to record minor degrees of hypokinesia; primary reliance was placed on changes from baseline to peak diprydamole, and the investigators had previous experience in joint reading.

When the only electrocardiographic criterion was diprydamole test positivity, the specificity was 46% (p = NS vs EET) and the sensitivity was 53% (p = NS vs EET; Figure 2). The predictive value of a positive test result was 95% for the DET and 74% for the EET (p < 0.01). The predictive value of a negative test result was 55% for the DET and 38% for the EET (p = NS). Accuracy was 74% for the DET and 60% for the EET (p < 0.05).

Chest pain during the diprydamole test occurred in 20 patients: 12 had CAD, 8 had no CAD. Of the eight patients without CAD, six also had electrocardiographic evidence of ischemia during diprydamole testing. Of these six patients, three had echocardiographic evidence of left ventricular hypertrophy.

**Normotensive Group**

At coronary angiography, 12 normotenstive patients had no significant and 39 had significant CAD; 14 of these had single-vessel, 20 had double-vessel, and 5 had triple-vessel disease. The specificity was 100% (12 of 12 patients) for the DET and 75% (9 of 12 patients) for the EET (p < 0.05). The sensitivity was 71% (28 of 39 patients) for the DET and 72% (27 of 39 patients) for the EET (p = NS). The predictive value of a positive test result was 100% for the DET and 90% for the EET (p < 0.01). The predictive value of a negative test result was 52% for the DET and 45% for the EET (p = NS); accuracy was 78 and 73%, respectively (p = NS). When the only electrocardiographic criterion was diprydamole test positivity, the specificity was 85% (p = NS vs EET) and the sensitivity was 56% (p = NS vs EET). Chest pain during the diprydamole test occurred in 28 patients; 25 had CAD and 3 had no CAD. Of these three patients, one also had electrocardiographic evidence of ischemia.

**Side Effects During the Dipyridamole-Echocardiography Test**

Sixty-four patients (68%) of the 94 who performed both tests experienced some side effects during the diprydamole test. Some patients experienced more than 1 side effect. Side effects in order of frequency were headache (33%), flushing (19%), nausea (9%).
Eighty patients received aminophylline (80–240 mg over 1–3 minutes) to stop ischemia or to abate side effects in negative test results. No patient had marked hypotension. No significant differences in the frequency of side effects could be recorded between the two groups (Table 4). In all patients, the side effects were mild, well tolerated by the patient, and reversed by aminophylline, when given; therefore, we completed the test in all patients.

Discussion

Clinical Implications

In our population of essential hypertensive patients with history of chest pain without previous myocardial infarction, the DET was more feasible and specific than the EET for the diagnosis of CAD. The EET was less feasible and less specific in the hypertensive group than in the normotensive group, whereas the DET offered similar diagnostic information, with a comparable feasibility, in the normotensive and hypertensive groups. The sensitivity of the DET in the hypertensive population of this study was 67%. In a series of 324 patients with history of chest pain, we reported a 75% sensitivity for angiographically assessed CAD.14 The slightly lower DET sensitivity found here can be explained on the basis of the enrollment criteria of this study, which included normal regional and global resting left ventricular function, with no previous myocardial infarction. Furthermore, in this study a relatively large number of CAD patients (10 of 30) had single-vessel disease. In comparative studies on the same patient population, the DET sensitivity was similar to that for exercise-thallium scintigraphy,15 dipyridamole-thallium scintigraphy,16 and exercise echocardiography.17

The main limitation of the DET is the requirement of an acceptable acoustic window, which is found in more than 90% of patients with state of the art echocardiographic instruments.12 Dipyridamole infusion does not cause a marked stress-induced hypotensive reaction and can be performed safely14 in patients with severe hypertension, in whom an exercise stress test is contraindicated.1,2 Although dipyridamole induces ischemia through nonphysiological mechanisms, it can localize the myocardium at risk in the same way as does physiological stress, such as exercise.17,18

Comparison with Previous Studies

Our findings are consistent with previous studies showing that the sensitivity of high dose dipyridamole-electrocardiography is similar to that of the EET.8 Its main limitation is a relatively low specificity, particularly in the group with arterial hypertension or left ventricular hypertrophy (or both).6,8 This limitation is also associated with the EET.1–2 In this study, we have shown that the mechanical marker of dipyridamole-induced ischemia (which is exploited for DET positivity) is much more specific than are ST segment changes for the detection of angiographically assessed CAD. Not surprisingly, this high specificity is not affected by the presence of arterial hypertension or left ventricular hypertrophy (or both).

Pathophysiological Meaning

A significant number of patients with false-positive EET results also had ST segment depression during the DET in the presence of normal left ventricular function. They also had chest pain during both the EET and the DET. This entity of echocardiographically silent myocardial "ischemia" closely recalls the pattern that we have described as Syndrome X.19 Certainly, this effect may simply be the expression of the unreliability of the electrocardiographic marker of ischemia in some conditions, such as female gender and left ventricular hypertrophy. Alternatively, however, Osterspey et al.8 have suggested that dipyridamole-induced ST segment depression may indicate a reduced coronary reserve, even in the presence of normal coronary arteries.

Syndrome X and left ventricular hypertrophy may share a common pathophysiological mechanism, since in both states a reduction of coronary reserve in the presence of angiographically normal epicardial coronary arteries has been described.20,21 A common nosographic allocation of the two conditions in the syndrome of microvascular angina has been proposed.22 In this regard, it is also interesting that a considerable number of asymptomatic essential hypertensive patients show ST segment depression during the DET in the absence of any regional or global left ventricular dysfunction.23 Further studies are needed, however, to establish the role of the DET in this condition.

Acknowledgment

We are indebted to Ms. Antonella Distante for skillful secretarial assistance.

Table 4. Side Effects Experienced During the Dipyridamole-Echocardiography Test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (%)</th>
<th>Normotensive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Flushing</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Other (dizziness, dyspnea, etc.)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting, hypotension, persistent myocardial ischemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total incidence of side effects</td>
<td>67</td>
<td>69</td>
</tr>
</tbody>
</table>
References


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