Dipyridamole Stress Echocardiography for Risk Stratification in Hypertensive Patients With Chest Pain

Lauro Cortigiani, MD; Emilio A. Paolini, MD; Eugenio Nannini, MD

Background—The noninvasive prognostic assessment of coronary artery disease (CAD) in hypertensive patients represents an unresolved task to date. In this study, we investigated the value of dipyridamole stress echocardiography in risk stratification of hypertensive patients with chest pain and unknown CAD.

Methods and Results—Dipyridamole stress echocardiography was performed in 257 hypertensives (110 men; age, 63±9 years) complaining of chest pain and without a history of CAD. No major complications occurred. Four tests were interrupted prematurely because of side effects, with 98.4% feasibility of test. A positive echocardiographic response was found in 72 patients (27 during the low-dose [≤0.56 mg/kg] and 45 during the high-dose [≥0.56 mg/kg]). During the follow-up (32±18 months), 27 cardiac events occurred: 3 deaths, 8 infarctions, and 16 cases of unstable angina. Moreover, 27 patients underwent coronary revascularization. At multivariate analysis, the positive echocardiographic result (OR, 5.5; 95% CI, 1.4 to 16.6) was the only predictor of hard cardiac events (death, infarction). Considering spontaneous cardiac events (death, infarction, and unstable angina) as end points, the positive echocardiographic result (OR, 4.2; 95% CI, 1.8 to 9.6) and family history of CAD (OR, 4.2; 95% CI, 1.5 to 6.9) were independently associated with prognosis. The 3-year survival rates for the negative and the positive populations were, respectively, 97% and 87% (P=0.0019) considering hard cardiac events and 96% and 74% (P=0.0000) considering spontaneous cardiac events.

Conclusions—Dipyridamole stress echocardiography is safe, highly feasible, and effective in risk stratification of hypertensives with chest pain and unknown CAD. At present, it represents an attractive option for prognostic assessment of this clinically defined population. (Circulation. 1998;98:2855-2859.)

Key Words: echocardiography ■ dipyridamole ■ prognosis ■ hypertension ■ coronary disease

The noninvasive prognostic assessment of hypertensive patients with chest pain is a particularly important goal in daily clinical practice, because hypertension is one of the major cardiovascular risk factors. However, it represents an unresolved problem to date. In fact, traditional exercise-dependent techniques, such as electrocardiography and perfusion scintigraphy, have suboptimal diagnostic specificity in patients with systemic hypertension and therefore lack capability to adequately categorize patients into low- and high-risk subgroups. In recent years, echocardiography combined with physical or pharmacological stress has attracted growing interest for diagnostic purposes in hypertensive patients, having shown higher specificity without loss in sensitivity compared with both exercise electrocardiography and perfusion scintigraphy. Nevertheless, the prognostic value of stress echocardiography in hypertensives remains to be determined.

On the basis of these data, we sought to investigate the value of dipyridamole stress echocardiography in risk stratification of hypertensive patients referred for chest pain who had unknown coronary artery disease (CAD).

Methods

Patients

The study population was represented by 257 patients (110 men, 147 women; age, 63±9 years [mean±SD]) with mild to moderate hypertension who underwent dipyridamole stress echocardiography for evaluation of chest pain between October 1990 and April 1997. No patient had known CAD, as defined by history of myocardial infarction, unstable angina, coronary revascularization, and/or angiographically assessed stenosis >50% of any of the 3 coronary arteries or their major branches. Furthermore, no patient had significant valvular disease or dilated or hypertrophic cardiomyopathy. All patients had interpretable echocardiographic images both in the resting condition and during stress testing.

Hypertension was defined by systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg in ≥1 determination and/or treatment with antihypertensive therapy.

At the time of the test, all patients were receiving antihypertensive drugs, consisting of diuretics, ACE inhibitors, and α-blockers individually or in combination at the dosage adequate to obtain blood pressure control. In 245 patients (95%), stress testing was performed after washout of antianginal drugs, discontinuing β-blockers for ≥48 hours and long-acting nitrates and calcium channel blockers for ≥24 hours before the test. In the remaining 12 patients (5%), the test was performed under therapy with β-blockers (n=5), calcium channel...
Prognostic Value of Dipyridamole Stress

Dipyridamole was administered intravenously according to the high-dosage protocol (up to 0.84 mg/kg over 10 minutes). Starting in April 1993, the stress protocol was modified with the coadministration of atropine (up to 1 mg over 4 minutes).

A 2-dimensional echocardiogram and 12-lead ECG were continuously monitored during the test and until the heart rate had returned to baseline value ± 10% during the recovery phase. Cuff blood pressure and the ECG were recorded every minute.

Criteria for test interruption were onset of obvious new wall motion abnormalities, severe chest pain, horizontal or downsloping ST-segment depression ≥ 2 mm, ST-segment elevation ≥ 1.5 mm, symptomatic hypotension, supraventricular or ventricular tachyarrhythmias, and intolerable symptoms. Intravenous aminophylline (up to 240 mg) was immediately available to reverse the effects of dipyridamole.

Echocardiographic Analysis
Echocardiographic images were obtained continuously from the standard apical and parasternal views with commercially available instruments (Sonos 2000, Hewlett Packard; Sonotron 800, Vingmed; Ultramark-7, ATL). From 1990 to 1995, images were recorded continuously on S-VHS videocassette recorders (Panasonic MD 830; Panasonic 7330) for off-line visual analysis; starting in 1996, images were also recorded by use of a quad-screen cine-loop system. Images were evaluated by 2 independent observers. In case of disagreement, a third observer evaluated the images, and his or her judgment was binding.

Regional wall motion was semiquantitatively assessed in a 16-segment model of the left ventricle. A 4-point score was assigned to each segment as follows: 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. A wall motion score index (WMSI), obtained by dividing the sum of individual segment scores by the number of segments considered, was calculated both at baseline and at the peak of drug infusion.

The result of a test was considered positive when any new regional wall motion abnormalities or worsening of preexisting ones was detected.

The test was defined as positive at low or at high dose when new wall motion abnormalities appeared after ≥ 0.56 mg/kg or ≥ 0.56 mg/kg of dipyridamole, respectively, had been infused.

In our experience, the intraobserver and interobserver reproducibility in stress echo readings is 92% and 89%, respectively, as previously described.

ECG Analysis
ECG changes were considered to be ischemic if an ST-segment shift ≥ 0.1 mV from baseline at 80 ms after the J point occurred in at least 2 contiguous leads.

In the case of right bundle-branch block, the ST-segment shift was considered to be significant when it also occurred in lead V_{6} and/or V_{7}. ECG changes were not taken as criteria for positivity of the test in the absence of induced new wall motion abnormalities; however, the development of ST-segment depression ≥ 2 mm or ST-segment elevation ≥ 1.5 mm was considered to be significant enough for interruption of the test. In patients with left bundle-branch block, preexisting ST-segment depression ≥ 0.1 mV, or paced rhythm as well as in patients taking digitalis or antiarrhythmic medications, ECG changes were considered nondiagnostic.

Follow-Up Data
Follow-up data were obtained from review of the patient’s hospital chart, contact with the patient’s physician, telephone interview with the patient, and periodic visits in our outpatient clinic. The follow-up data were available for all patients. The clinical events recorded during the follow-up were cardiac and noncardiac deaths, myocardial infarction, unstable angina, and coronary revascularization procedures (surgery or angioplasty).

The cause of death was established from hospital or physician records; death was attributed to a cardiac origin in the case of documentation of significant arrhythmias and/or cardiac arrest, congestive heart failure, or myocardial infarction. Moreover, any death that occurred suddenly out of hospital was ascribed to a cardiac cause. The diagnosis of acute myocardial infarction was made on the basis of symptoms, ECG changes, and cardiac enzyme level increases. Unstable angina was defined by angina at rest or change in pattern of preexisting angina requiring hospitalization.

Statistical Analysis
Values were expressed as mean ± SD for continuous variables and as frequency and percentage for categorical variables. Continuous variables were compared by Student’s unpaired t test, and differences of categorical variables were assessed by the χ^2 test. The Kaplan-Meier method was used for estimation of infarction-free survival and of event-free survival. For survival analysis, only 1 event was considered in each patient. When patients underwent coronary revascularization, they were censored at the time of the procedure. Likewise, when patients died of noncardiac causes, they were censored at the time of death.

The differences of the survival curves were analyzed by the log-rank test.

The capability of certain variables to predict subsequent outcome was assessed by the Cox proportional hazard model using univariate and stepwise multivariate analysis (SPSS for Windows, 1995). The differences in risk were expressed as ORs with the corresponding 95% CIs. The analysis included the following variables: age (< 65 or ≥ 65 years), sex, family history of CAD, hypercholesterolemia, cigarette smoking, diabetes, dipyridamole stress echocardiographic result (positive/negative), dose of drug to induce echocardiographic positivity, WMSI at peak of drug infusion, rest-stress WMSI variation (representing an integrated estimation of the extent and severity of wall motion abnormalities), ECG changes during the test, and angina during the test.

A value of P < 0.05 was considered statistically significant.

Results
Feasibility and Side Effects
No major complications occurred during dipyridamole stress echocardiography. Of 257 tests, 4 were interrupted prematurely because of the appearance of limiting side effects, consisting of severe chest pain in the absence of new wall motion abnormalities (n = 2), symptomatic hypotension (n = 1), and atrial fibrillation (n = 1). Therefore, the overall feasibility of the test was 98.4%. All side effects were reversed by aminophylline administration. The results of these 4 patients who did not complete the stress protocol were included in the analysis, and the tests were considered negative for ischemia.

Stress Echocardiography Results
Atropine was added to dipyridamole in 100 patients (39%). The following changes in hemodynamic profile were documented at peak of stress: increment of heart rate from 70 ± 12 to 109 ± 17 bpm, reduction of systolic blood pressure from 142 ± 20 to 139 ± 23 mm Hg, reduction of diastolic blood pressure from 84 ± 10 to 77 ± 12 mm Hg, and increment of rate-pressure product from 10 568 ± 7181 to 15 225 ± 3744.

Echocardiographic positivity was identified in 72 patients (28%), 27 during the low and 45 during the high dose (11 patients during atropine administration). In the positive pop-
During a follow-up of 32.6 months, the WMSI increased from 1.05 ± 0.11 in resting conditions to 1.36 ± 0.19 at peak of drug infusion.

Of the remaining 185 patients with negative stress testing results, 38 (21%) developed an isolated ST-segment depression during dipyridamole infusion.

The clinical characteristics and the baseline and stress echocardiography results for the study population are illustrated in Table 1.

**Follow-Up Data**

During a follow-up of 32 ± 18 months, there were 27 cardiac events (3 deaths, 8 myocardial infarctions, and 16 cases of unstable angina) and 5 deaths of noncardiac causes (4 cancer and 1 stroke). Moreover, 27 patients underwent coronary revascularization with either surgery (n = 18) or angioplasty (n = 9), 22 within 3 months (mean, 1.4 ± 1.0 months) and 5 after 3 months (mean, 12.6 ± 17.6 months) from stress testing. Patients with positive echocardiographic results who underwent coronary revascularization were found to have a greater frequency of low-dose than high-dose positivity (52% versus 24%; P = 0.018) and higher rest-stress WMSI variation in comparison with patients treated conservatively (0.40 ± 0.17 versus 0.26 ± 0.10; P < 0.001). Table 2 summarizes the incidence of cardiac events and revascularization procedures in the positive and in the negative population.

The incidence of cardiac events in the negative population was similar for patients evaluated with (n = 89) and without (n = 96) atropine (6.7 versus 5.2%; P = NS).

Finally, no event occurred among 38 patients who developed ECG but not echocardiographic positive response during stress testing.

**Survival Analysis**

Considering hard cardiac events (death, myocardial infarction) as end points, the following variables showed a decremental prognostic power at univariate analysis: positive echocardiographic result (P = 0.0060), rest-stress WMSI variation (P = 0.0076), low-dose positive echocardiographic result (P = 0.0176), and peak-stress WMSI (P = 0.0235) (Table 3). At multivariate analysis, the positive echocardiographic result (OR, 5.5; 95% CI, 1.4 to 16.6; P = 0.0143) was the only variable independently correlated with prognosis.

When spontaneous cardiac events (death, myocardial infarction, and unstable angina) were considered as end points, the strongest univariate predictor of outcome was the positive echocardiographic result (P = 0.0000), followed by rest-stress WMSI variation (P = 0.0006), family history of CAD (P = 0.0009), peak-stress WMSI (P = 0.0084), low-dose positive echocardiographic result (P = 0.0148), and ECG changes during the test (P = 0.0073) (Table 4). At multivariate analysis, the prognostic importance of a positive echocardiographic result (OR, 4.2; 95% CI, 1.8 to 9.6; P = 0.0007) and family history of
CAD (OR, 4.2; 95% CI, 1.5 to 6.9; \(P=0.0034\)) was independent and additive.

The 3-year survival rates for the negative and the positive populations were 97% and 87%, respectively (\(P=0.0019\)) considering hard cardiac events (Figure 1) and 96% and 74% (\(P=0.0000\)) considering spontaneous cardiac events (Figure 2).

Discussion

The results of our study show that dipyridamole stress echocardiography is safe and highly feasible in hypertensive patients, because no complications and a very low incidence of limiting side effects were observed during the test, in keeping with the larger experiences reported by multicenter studies that collected data from thousands of unselected patients.\(^\text{18}\) Moreover, our results demonstrate first the effectiveness of dipyridamole stress echocardiography in risk stratification of hypertensive patients with chest pain, on the basis of presence/absence of the induced new wall motion abnormalities. In particular, a negative echocardiographic result was found to be associated with only 3% and 4% event rates over 3 years of follow-up when hard and spontaneous cardiac events, respectively, were considered as end points.

Stress-Test Technique

Recent studies have demonstrated that in hypertensive patients, pharmacological stress echocardiography shows an accuracy at least comparable to that of myocardial scintigraphy, with a superior specificity\(^\text{11}\) and a similar sensitivity.\(^\text{11,19}\) These data, coupled with the larger availability and lower cost in comparison with nuclear medicine, make pharmacological stress echocardiography an attractive option for evaluation of hypertensive patients complaining of chest pain.

Among pharmacological stressors, dipyridamole and dobutamine are the most popular, and it is now clearly established that they have similar accuracy\(^\text{20}\) as well as the capability of prognostic stratification.\(^\text{21,22}\) In the present study, the choice to use dipyridamole instead of dobutamine was suggested by superior safety,\(^\text{18,23,24}\) feasibility,\(^\text{25,26}\) and last but not least, the lower cost of dipyridamole in Italy.

Clinical Implications

Although the results of this study emphasize the prognostic importance of dipyridamole stress echocardiography in hypertensive patients, this imaging technique is not to be considered an alternative but rather complementary to exercise ECG testing, which remains the first choice in the screening phase, in that it is physiological, simpler, and very low cost and provides a high negative predictive value in patients with chest pain and unknown CAD, similar to that shown by dipyridamole stress echocardiography.\(^\text{27}\) The latter can be recommended in selected conditions, such as in patients with equivocal or ischemic ECG response during exercise\(^\text{2–4}\) and those unable to exercise or with an uninterpretable ECG. In our opinion, the application of this strategy can have a beneficial effect in the cost-effectiveness of management of CAD in patients with arterial hypertension.

Limitations of the Study

Because this was an observational study, coronary revascularization was performed on the basis of stress-test results and the individual clinical condition. Consequently, revascularization procedures were much more frequent in patients with inducible ischemia, particularly when it was identified as

\[\text{TABLE 4. Univariate Predictors of Spontaneous Cardiac Events (Death, Myocardial Infarction, Unstable Angina)}\]

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive echocardiographic result</td>
<td>5.2 (2.4–11.2)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Rest-stress WMSI variation</td>
<td>3.8 (1.8–8.1)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>3.7 (1.7–7.9)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Peak-stress WMSI</td>
<td>2.8 (1.3–6.0)</td>
<td>0.0084</td>
</tr>
<tr>
<td>Low-dose positive echocardiographic result</td>
<td>3.4 (1.3–9.1)</td>
<td>0.0148</td>
</tr>
<tr>
<td>ECG changes during test</td>
<td>2.3 (1.1–4.8)</td>
<td>0.0361</td>
</tr>
<tr>
<td>Angina during test</td>
<td>2.1 (0.9–4.8)</td>
<td>0.0637</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.1 (0.9–4.8)</td>
<td>0.0829</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.9 (0.9–9.6)</td>
<td>0.0883</td>
</tr>
<tr>
<td>Age (\geq) 65 years</td>
<td>1.6 (0.8–3.4)</td>
<td>0.2382</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.6 (0.7–3.3)</td>
<td>0.2452</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.3 (0.6–2.9)</td>
<td>0.4665</td>
</tr>
</tbody>
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Figure 1. Cumulative survival rates free of hard cardiac events (including cardiac death and nonfatal myocardial infarction) in patients with negative (Neg) and positive (Pos) result of dipyridamole stress echocardiography.

Figure 2. Cumulative survival rates free of spontaneous cardiac events (including cardiac death, nonfatal myocardial infarction, and unstable angina) in patients with negative (Neg) and positive (Pos) result of dipyridamole stress echocardiography.
severe in the time and space domain (ie, low-dose, high rest-stress WMSI variation). It is presumable that this dropout process may have lowered the positive predictive value of the test for hard end points, although the echocardiographic evidence of ischemia was found to be a very strong and independent predictor of outcome.

The stress protocol was not performed with coadministration of atropine in all patients, because atropine was introduced in the clinical practice when the study was started. Nevertheless, the prognosis in the negative population did not differ between patients evaluated with or without atropine. This is not surprising, because atropine administration induces a step-up in sensitivity of dipyridamole stress echocardiography, particularly in patients with single-vehicle disease.14,20 who represent a well-recognized low-risk population.28,29

The influence of left ventricular hypertrophy on the echocardiographic response to stress, as well as its prognostic implications, was not evaluated. However, it has been found that stress echocardiography has similar accuracy in hypertensive patients with and without left ventricular hypertrophy.10 Moreover, left ventricular hypertrophy is a strong prognostic predictor, independent of the presence of organic CAD in catheterized patients,30 as well as of inducible ischemia during dipyridamole stress echocardiography in patients with uncomplicated myocardial infarction and 1-vehicle disease.31

References

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