Prognostic Value of Pharmacological Stress Echocardiography Is Affected by Concomitant Antiischemic Therapy at the Time of Testing

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Background—The aim of this study was to determine whether antianginal medications affect the prognostic value of pharmacological stress echocardiography.

Methods and Results—From the EPIC–EDIC Data Bank, 7333 patients (5452 men; age; 59 ± 10 years) underwent pharmacological stress echocardiography with either high-dose dipyridamole (0.84 mg/kg over 10 minutes; n = 4984) or high-dose dobutamine (up to 40 μg·kg⁻¹·min⁻¹; n = 2349) (DET) for diagnostic purposes. At the time of testing, 1791 patients were on antiischemic therapy (nitrates and/or calcium antagonists and/or β-blockers). Patients were followed up for a mean of 2.6 years (range, 1 to 206 months). DET was positive for myocardial ischemia in 2854 patients (39%) and negative in 4479 (61%). Total mortality was 336 (4.5%). Death was attributed to cardiac causes in 161 patients (2.1%). Survival was highest in patients with negative DET off therapy and lowest in patients with positive DET studied on therapy (95% versus 81%; P = 0.0000). Survival was comparable in patients with a negative test on therapy and in patients with a positive test off therapy (88% versus 84%, P = NS).

Conclusions—Ongoing antiischemic therapy at the time of testing heavily modulates the prognostic value of pharmacological stress echo. In the presence of concomitant antiischemic therapy, a positive test is more prognostically malignant, and a negative test less prognostically benign. (Circulation. 2004;109:2428-2431.)

Key Words: ischemia ■ coronary disease ■ echocardiography ■ prognosis

Pharmacological stress echocardiography is an established cost-effective technique for the detection and prognostic stratification of coronary artery disease. Several echocardiographic parameters such as the extent of inducible wall motion abnormalities and pharmacological load have been related to coronary artery disease severity and outcome. A large body of evidence shows that medical therapy reduces sensitivity of pharmacological stress echocardiography, exerting a protective effect on ischemia. However, not all pharmacological stressors are equally affected because antiischemic therapy lowers the sensitivity of dipyridamole more than that of dobutamine. Additionally, not all antiischemic drugs are equally protective, with β-blockers more effective than calcium antagonists and long-acting nitrates in reducing test sensitivity. Prognostic stratification represents an important indication to pharmacological stress echocardiography. For this indication, the stress is frequently performed on therapy. Nonetheless, no prognostic data are available on the protective effect of medical therapy at the time of pharmacological stress testing on future outcome. Therefore, the aim of the present study was to assess the prognostic meaning of medical therapy in patients undergoing pharmacological stress echocardiography for diagnostic and/or prognostic purposes. This study represents a subanalysis of a previously reported multicenter prospective study using pharmacological stress echocardiography with either dipyridamole or dobutamine on 7333 patients. Results of the 2 pharmacological stressors were pooled for their comparable diagnostic and prognostic accuracy.

Methods

From the EPIC–EDIC and Institute of Clinical Physiology Data Bank between 1985 and 2000, 7599 prospectively enrolled consecutive patients (5452 men; mean age, 59 ± 10 years) with known or suspected coronary artery disease performed a pharmacological stress echocardiography test with either dipyridamole or dobutamine and entered a follow-up program. We lost 266 to follow-up (3%); therefore, the final population consisted of 7333 patients. The most common indication for testing was risk evaluation after infarction (29%); 2737 (37%) had a test performed for the evaluation of chest pain. Known coronary artery disease was present in 2696 (37%), reflecting prior myocardial infarction in 2696 (37%), reflecting prior myocardial infarction in 2696 (37%), reflecting prior myocardial infarction in 2696 (37%), reflecting prior myocardial infarction in 2696 (37%), reflecting prior myocardial infarction in 2696 (37%), reflecting prior myocardial infarction in 2696 (37%)
in 6%. Of the 2153 patients with previous myocardial infarction, 1681 were recent first uncomplicated myocardial infarctions (<15 days). Risk factors were highly prevalent, with 30% of the patients having hypertension and 40% having hypercholesterolemia. The pretest likelihood of coronary artery disease was estimated from age, sex, and symptoms; patients with known coronary artery disease were assigned a value of 100%. The estimated likelihood of coronary artery disease was <50% in 849 patients (11.5%), 50% to 80% in 2556 patients (34.8%), and >80% in 3928 patients (53.6%). According to individual needs and physician choices, 5542 patients were evaluated after antianginal drugs had been discontinued, and 1791 patients were evaluated during antiangiinal treatment (nitrates, calcium antagonists, and/or β-blockers). In our patient population, 1881 women (26% of the total population) were studied. Even though pharmacological stress echocardiography is the first-line examination in women because of the high percentage of false-positive tests with exercise electrocardiography, this was not the case at the beginning of stress echo life. This might explain the low percentage of women in the study population.

**Stress Protocols**

Two-dimensional echocardiography and 12-lead ECG monitoring were performed, in combination with either high-dose dipyridamole (up to 0.84 mg over 10 minutes) or high-dose dobutamine (up to 40 g/kg body weight per minute with coadministration of atropine up to 1 mg), in accordance with well-established protocols. During the procedures, blood pressure and ECG were recorded each minute. Quality control of stress echo performance and reading in enrolled centers was previously described in depth. Briefly, before a center could start recruiting patients, its reader was required to meet predefined criteria for stress echo reading; once that was achieved, the readings were directly entered into the data bank.

**Follow-Up Data**

Follow-up data were obtained in all patients by inclusion criteria. Cardiac mortality and total mortality were the primary end points. Hospital and physician records and death certificates were used to ascertain the cause of death, which was attributed to a cardiac cause if a cardiac illness provoked the final presentation or if death was sudden and unexpected. For the analysis of cardiac mortality, patients dying of other causes were censored from follow-up at the time of death. Coronary bypass surgery and coronary angioplasty were not identified as cardiac events, and patients were censored at the time of these procedures.

**Statistical Analysis**

Statistical analyses included descriptive statistics (frequency and percentage of categorical variables and mean and SD of continuous variables), Kaplan-Meier survival curves, and Cox proportional-hazards models. The following covariates were analyzed: age; sex; typical chest pain; hypertension; diabetes; hypercholesterolemia; left bundle-branch block; previous myocardial infarction; previous coronary revascularization; resting wall motion score index; positive echocardiographic result; wall motion score index at peak stress; change in wall motion score index (difference in wall motion score index from rest to peak stress); pharmacological dose; type of pharmacological stressor (dipyridamole or dobutamine); ECG modifications during pharmacological stress; presence of angina during pharmacological stress; presence of medical therapy at the time of testing; and different class of drugs at the time of testing (long-acting nitrates, calcium antagonists, β-blockers). Differences between survival curves were compared by use of the log-rank test. All analyses were performed with SPSS statistical software (SPSS Inc), and values of P<0.05 were considered statistically significant.

**Results**

The main clinical and echocardiographic data are reported in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Rest and Stress Findings in the Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, n</strong></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
</tr>
<tr>
<td><strong>Sex, M/F, n</strong></td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
</tr>
<tr>
<td><strong>Hypercholesterolemia, n (%)</strong></td>
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<tr>
<td><strong>History of angina, n (%)</strong></td>
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<tr>
<td><strong>Left bundle-branch block, n (%)</strong></td>
</tr>
<tr>
<td><strong>Previous myocardial infarction, n (%)</strong></td>
</tr>
<tr>
<td><strong>Previous coronary revascularization, n (%)</strong></td>
</tr>
<tr>
<td><strong>Dobutamine stress echo, n (%)</strong></td>
</tr>
<tr>
<td><strong>Dipyridamole stress echo, n (%)</strong></td>
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<tr>
<td><strong>Positive DET, n (%)</strong></td>
</tr>
</tbody>
</table>

DET indicates dipyridamole or dobutamine stress echocardiography.

**Stress Echocardiographic Findings**

Resting wall motion score index was 1.31±0.37. In total, 1368 patients (76%) were on calcium channel blocker therapy, 311 (17%) were on β-blocking agents, and 1415 (79%) were on long-acting nitrates or a combination of the 3 drugs. We found that 744 patients were positive on medical therapy and 2110 were positive off medical therapy (41% versus 38%; P<0.009). Patients with known coronary artery disease were more often on antiischemic therapy (30% versus 22%; P<0.000). Myocardial revascularization was performed in 2077 patients (28% of the total population) who were censored from follow-up at this time.

**Follow-Up Data**

Patients were followed up for a mean of 2.6±3 years. Total mortality was 336 individuals (4.5%); death was attributed to cardiac causes in 161 patients (2.1%).

**Total Mortality**

Kaplan-Meier survival estimates for total mortality showed a better outcome for those patients with negative pharmacological stress echocardiography test off therapy compared with those with a positive test (95% versus 81%, respectively; P=0.0000) on medical therapy (Figure), and mortality was comparable in patients with negative test on therapy and in patients with positive test off medical therapy (88% versus 84%; P=NS) (Figure). Univariate predictors of total mortality are reported in Table 2. With Cox’s proportional-hazard model, independent predictors of total mortality were age (relative risk [RR], 1.06; 95% CI, 1.04 to 1.07), male sex (RR, 1.34; 95% CI, 1.03 to 1.7), medical therapy at the time of testing (RR, 1.3; 95% CI, 1.0 to 1.6), previous non-Q-
Kaplan-Meier survival curves (considering total mortality as an end point) in patients stratified according to presence (DET +) or absence (DET −) of myocardial ischemia at pharmacological stress echocardiography on and off antianginal medical therapy. Best survival is observed in patients with no inducible ischemia off therapy; worst survival is seen in patients with inducible ischemia on therapy (positive DET vs negative DET off antianginal medical therapy, P<0.000; positive DET vs negative DET on antianginal medical therapy, P=0.074).

Discussion

In patients with known or suspected coronary artery disease, ongoing antischemic therapy at the time of testing heavily modulates the prognostic value of pharmacological stress echo. In the presence of concomitant antischemic therapy, a positive test is more prognostically malignant and a negative test is less prognostically benign. No prognostic difference was found among the various forms of antischemic drugs at the time of testing.

TABLE 2. Univariate Predictors of Total Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.05–1.07)</td>
<td>0.000</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.4 (1.13–1.8)</td>
<td>0.0030</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.2 (1.0–1.5)</td>
<td>0.0495</td>
</tr>
<tr>
<td>Previous non–Q-wave MI</td>
<td>1.6 (1.18–2.2)</td>
<td>0.0030</td>
</tr>
<tr>
<td>Antianginal therapy</td>
<td>1.8 (1.4–2.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>β-Blocking agents</td>
<td>1.9 (1.2–3.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>1.6 (1.2–2.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>1.5 (1.1–1.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>LBBB</td>
<td>1.68 (1.04–2.7)</td>
<td>0.0321</td>
</tr>
<tr>
<td>Previous Q-wave MI</td>
<td>1.6 (1.32–2.09)</td>
<td>0.000</td>
</tr>
<tr>
<td>Test positivity</td>
<td>2.09 (1.68–2.5)</td>
<td>0.000</td>
</tr>
<tr>
<td>Delta WMSI</td>
<td>3.8 (2.5–5.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>Rest WMSI</td>
<td>3.8 (3.01–4.9)</td>
<td>0.000</td>
</tr>
<tr>
<td>Peak WMSI</td>
<td>4.02 (3.2–5.0)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

MII indicates myocardial infarction; LBBB, left bundle-branch block; and WMSI, wall motion score index.

Comparison With Previous Studies

It has been demonstrated that antianginal therapy lowers the sensitivity of exercise echocardiography, as it does with vasodilator stress testing.6,13 The effects of antianginal therapy on dipyridamole time tend to parallel variations in exercise time tolerance.4 β-Blockers and monotherapy with a calcium antagonist and nitrates also protect the patient from dipyridamole-induced ischemia.4,7–8 The diagnostic sensitivity of dobutamine is heavily affected by concomitant β-blocker therapy but in a manner unrelated to changes induced in exercise tolerance.5 β-Blockers shift the doseresponse curve to dobutamine rightward and sharply lower test sensitivity unless atropine is used.9 Calcium antagonists and/or long-acting nitrates have only a mild effect on dobutamine stress sensitivity.5,6 Therefore, although dobutamine is often referred to as an “exercise-simulating agent,” the drug-induced changes in pharmacological stress echo response tend to mirror changes occurring during exercise stress with dipyridamole rather than with dobutamine.

To the best of our knowledge, no data are available on the prognostic impact of medical therapy on pharmacological stress echocardiography at the time of testing. Marwick et al16 have demonstrated a protective effect of β-blocker therapy on mortality in patients with a negative exercise echocardiography.

Study Limitations

In the present population, a very low percentage of patients were on β-blocking therapy. On one hand, this represents a clear lack of adherence to recommendations2; on the other, it is an observed pattern of prescription in our database, which simply reflected the clinical practice and the lack of a universally accepted policy of testing with regard to concomitant therapy.17–19 Nevertheless, the realistic information provided in this setting does not justify such a low use, which might have accounted for the poor prognosis of this subset of patients.

Clinical Implications

The present study has important clinical implications. Inducible myocardial ischemia during pharmacological stress testing in patients on medical therapy identifies the subset of patients at highest risk of death. For these patients, an aggressive approach has to be undertaken to change the natural history of coronary artery disease. On the opposite end, the incidence of death in patients with a negative pharmacological test off therapy is so low that no intervention could lower the spontaneous rate of death any further. At intermediate risk are those patients with a negative test on medical therapy or a positive test off medical therapy. Different clinical scenarios can be foreseen on the basis of the present results. First, a negative test on medical therapy might represent a false-negative result; therefore, repeating the test off therapy is advisable to assess the real ischemic burden through the conventional stress echocardiographic parameters,3,20 ie, number of ischemic segments, severity of induced dysfunction (both expressed by peak wall motion score index), pharmacological load, and time of onset of ischemia. This is in line with the recommendations of the American Heart Association in patients with stable angina.2 Second, in
the case of a positive test off medical therapy, the effect of therapy can be assessed with the advantage of using an objective, primary ischemic end point such as changes in stress.

Conclusions
Antiischemic medical therapy modulates the prognostic impact of pharmacological stress echocardiography unrelated to the class of drugs used. Test positivity on medical therapy can be considered a parameter of severity of ischemia. Remov-
ing a patient from antiischemic therapy is a decision the physician should make on an individual basis in view of the fact that pharmacological stress echocardiography is a versatile tool that can assess medical therapy efficacy in the long term prognosis.

Acknowledgment
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References
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