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Value of Pharmacologic Stress Echocardiography in Risk Stratification of Patients With Single-Vessel Disease: A Report from the Echo-Persantine and Echo-Dobutamine International Cooperative Studies

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Objectives. This study sought to verify the effectiveness of pharmacologic stress echocardiography in risk stratification of patients with single-vessel disease.

Background. Noninvasive prognostic assessment of single-vessel disease is an unresolved issue to date.

Methods. The study evaluated prospectively collected data from 754 patients with angiographic single-vessel disease who underwent either dipyridamole ($n = 576$) or dobutamine ($n = 178$) stress echocardiography. Invasive treatment (coronary revascularization within 3 months of stress testing) was performed in 260 patients and medical treatment in 494.

Results. Echocardiographic positivity was observed in 421 patients (56%). Patients treated invasively had a higher incidence of stress test positivity (69% vs. 49%, $p < 0.001$) and left anterior descending coronary artery involvement (60% vs. 46%, $p < 0.001$) than patients maintained with medical therapy. During a mean follow-up of 37 months, 54 hard cardiac events occurred (14 deaths, 40 nonfatal infarctions): 37 in medically and 17 in invasively treated patients (7.5% vs. 6.5%, $p = NS$). On Cox

analysis, a positive result on stress testing was the only independent prognostic predictor in medically treated patients (relative risk 2.92, 95% confidence interval 1.29 to 6.59). The 4-year infarction-free survival rate was higher for a negative than a positive stress test result in medically (93.9% vs. 87.3%, $p = 0.009$) but not invasively treated patients (92.7% vs. 97.1%, $p = 0.545$). Moreover, a significantly higher 4-year infarction-free survival rate was found in invasively versus medically treated patients with a positive ($p = 0.012$), but not in those with a negative, stress test result ($p = 0.853$).

Conclusions. Pharmacologic stress echocardiography is effective in risk stratification of single-vessel disease and can accurately discriminate patients in whom coronary revascularization can have the maximal beneficial effect. These findings have a potential favorable impact on the cost-effectiveness of invasive procedures.

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The natural history of single-vessel disease is generally benign (1-3). In the subset of patients with an angiographically proved low risk profile, several techniques have been proposed for risk stratification, including exercise stress testing (4,5) and stress nuclear cardiac techniques (6-10). To verify the effectiveness of pharmacologic stress echocardiography for identifying high risk patients with single-vessel disease, data from 754 patients prospectively enrolled in the Echo-Persantine International

Cooperative (EPIC) and Echo-Dobutamine International Cooperative (EDIC) studies were analyzed.

Methods

Patients. From the EPIC-EDIC data bank, 754 prospectively enrolled patients from eight centers (each contributing >50 patients) were selected. They met the following inclusion criteria: 1) pharmacologic stress echocardiography with either dipyridamole ($n = 576$) or dobutamine ($n = 178$); 2) technically acceptable echocardiographic study at baseline; 3) coronary angiography performed systematically after stress echocardiography (within 30 days) and showing a single-vessel disease, defined as $\geq 75\%$ visually assessed diameter reduction in a major coronary artery vessel (left anterior descending or large diagonal branch; left circumflex

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Abbreviations and Acronyms

ECG = electrocardiogram, electrocardiographic
 EDIC = Echo-Dobutamine International Cooperative Study
 EPIC = Echo-Persantine International Cooperative Study

or large marginal branch; and right coronary artery); 4) no significant left main disease ($\leq 50\%$ stenosis); 5) no history of previous coronary revascularization procedure (angioplasty or operation); 6) enrollment in a follow-up program. No patient meeting the inclusion criteria was excluded from the study for refusing follow-up.

Of 754 patients, 260 underwent invasive treatment consisting of coronary revascularization with either angioplasty ($n = 224$) or operation ($n = 36$) within 3 months of stress echocardiography. The remaining 494 patients were maintained with medical therapy, consisting of risk factor modification as well as antiplatelet therapy, nitrates and beta-adrenergic and calcium channel blocking agents individually or in combination at a dosage adequate for relieving angina without inducing intolerable side effects. The choice of invasive over medical treatment was made by the physician on the basis of symptoms, coronary anatomy, left ventricular function, stress echocardiographic result and general condition of the individual patient. The clinical and angiographic characteristics as well as baseline and stress echocardiography results are shown in Table 1.

Stress protocols. Two-dimensional echocardiography and 12-lead electrocardiographic (ECG) monitoring were performed in combination with either high dose dipyridamole (up to 0.84 mg over 10 min) or high dose dobutamine (up to 40 $\mu\text{g}/\text{kg}$ body weight per min, with coadministration of atropine up to 1 mg), according to the well established protocols (11,12). Starting in January 1992, the dipyridamole protocol was modified to include coadministration of atropine (up to 1 mg) (13). During the procedure, blood pressure and the ECG were recorded each minute.

Echocardiographic analysis. Two-dimensional echocardiograms were obtained with commercially available imaging systems. Echocardiographic images were recorded on VHS videotape for subsequent playback and analysis. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography with a 16-segment model (14). In all studies, *segmental wall motion* was semiquantitatively graded from 1 to 4 as follows: 1 = *normal* (normal motion at rest, with normal/increased wall motion [*hyperkinesia*] after dipyridamole or dobutamine); 2 = *hypokinetic* (marked reduction in endocardial motion and thickening); 3 = *akinetic* (virtual absence of inward motion and thickening); 4 = *dyskinetic* (paradoxical wall motion away from the center of the left ventricle in systole). The *wall motion score index* was derived by dividing the sum of individual segment scores by the number of interpretable segments. The only criterion of *test positivity* was defined as the occurrence of new or worsening preexisting dyssynergy (i.e., normokinesia becoming hypokinesia, akinesia or dyskinesia, or hypokinesia becoming akinesia

or dyskinesia). However, rest akinesia becoming dyskinesia was not considered a positive result because the change could be due to passive stretching phenomena rather than "active" ischemia. An ST segment shift ≥ 0.1 mV from baseline at 80 ms after the J point in at least two contiguous leads was also noted. Nonechocardiographic end points requiring test interruption without echocardiographic positivity were the following: peak dipyridamole or dobutamine plus atropine dose; achievement of 85% of target heart rate (i.e., Predicted target heart rate = $220 - \text{Age}$); achievement of conventional end points, such as severe chest pain or significant ST segment changes, or both. The test was also stopped, in the absence of diagnostic end points, for one of the following reasons of submaximal test results: 1) intolerable symptoms; and 2) limiting asymptomatic side effects, including hypertension (systolic blood pressure >220 mm Hg; diastolic blood pressure >120 mm Hg), hypotension (relative or absolute: >30 -mm Hg decrease in blood pressure), supraventricular arrhythmias (supraventricular tachycardia or atrial fibrillation), ventricular arrhythmias (ventricular tachycardia; frequent, polymorphous premature ventricular beats).

At each center, one observer (L.C., E.P., M.P., S.P., P.B., R.B., O.M., A.G.) who had passed the quality control procedures detailed elsewhere (15) reviewed the study; his or her reading was entered directly into the data bank. Investigators were unaware of the clinical outcome of the individual patient before they submitted their stress test interpretation.

Coronary angiography. Coronary angiography was performed in multiple projections using the standard Judkins or Sones technique. *Significant coronary artery disease* was defined as $\geq 75\%$ visually assessed reduction of the lumen diameter of any of the three coronary arteries or their primary branches. All angiograms were reviewed by two independent observers who were unaware of the stress test results.

Follow-up data. Follow-up data were obtained from at least one of four sources: 1) review of the patient's hospital record; 2) personal communication with the patient's physician and review of the patient's chart; 3) telephone interview with the patient conducted by trained personnel; or 4) patient visits to a staff physician at regular intervals in the outpatient clinic. By inclusion criteria, follow-up data were obtained for all patients.

Events were defined as cardiac-related death and nonfatal myocardial infarction. For patients who died in the hospital or at home, the cause of the death was elucidated from the medical record, the family and the local physician who signed the death certificate. *Cardiac-related death* required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. Death out of the hospital for which no autopsy was performed, was classified as *sudden unexpected death* and was attributed to a cardiac cause. *Myocardial infarction* was defined as a cardiac event requiring admission to the hospital, with development of new ECG changes and cardiac enzyme level increases.

Therefore, the *outcome events* were hard cardiac events

Table 1. Clinical, Angiographic, Baseline and Stress Echocardiographic Findings for Medically and Invasively Treated Patients

	Medically Treated Patients (n = 494)	Invasively Treated Patients (n = 260)	p Value
Age (yr)	54 ± 10	56 ± 9	NS
Men	430 (87%)	215 (83%)	NS
Recent (≤15 days) MI	267 (54%)	95 (36%)	< 0.001
Previous (>15 days) MI	125 (25%)	61 (23%)	NS
Diseased vessel			
LAD	230 (46%)	156 (60%)	< 0.001
RCA	166 (34%)	68 (26%)	< 0.05
LCx	98 (20%)	36 (14%)	< 0.05
75% diameter stenosis	127 (26%)	42 (16%)	< 0.005
90% diameter stenosis	148 (30%)	174 (67%)	< 0.001
100% diameter stenosis	219 (44%)	44 (17%)	< 0.001
WMSI at rest	1.30 ± 0.36	1.26 ± 0.32	NS
Abnormal ECG at rest	393 (79%)	179 (69%)	< 0.005
Positive stress test result	240 (49%)	181 (69%)	< 0.001
ECG changes during test	188 (38%)	168 (75%)	< 0.001
Chest pain during test	130 (26%)	157 (60%)	< 0.001
WMSI at peak of drug infusion	1.48 ± 0.39	1.46 ± 0.37	NS

Data presented are mean value ± SD or number (%) of patients. ECG = electrocardiogram/electrocardiographic; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery; WMSI = wall motion score index.

(i.e., cardiac-related death and nonfatal myocardial infarction) for infarction-free survival.

Statistical analysis. Results are expressed as mean value ± SD. Kaplan-Meier life-table estimates of infarction-free survival were used to summarize the follow-up experience in the study patients and to clarify presentation. For survival analysis only one event was considered for each patient. Patients who died of noncardiac death were censored at the time of death. Differences in survival curves were analyzed using the Mantel-Haenszel test. The individual effect of certain variables on infarction-free survival was evaluated with the use of the Cox regression model (BMDP 2L, Department of Biomathematics, University of California at Los Angeles, revised 1987). According to a stepwise selection process, variables were entered into, or removed from, the regression equation on the basis of a computed significance probability value (maximized partial likelihood ratio).

Variables selected for examination were age; gender; previous myocardial infarction; ECG changes at baseline; rest left ventricular function (evaluated through the wall motion score index at rest); stress test results (positive/negative result, wall motion score index at peak of drug infusion, rest-stress wall motion score index variation, ST-T wave changes during test, chest pain during test); and angiographic results defined both according to the vessel involved (left anterior descending, left circumflex or right coronary artery) and extent of stenosis (75%, 90% or 100%). Continuous variables were compared by means of the Student *t* test (two-tailed). Statistical analysis of discrete variables was performed with the chi-square test. A *p* value < 0.05 was considered statistically significant.

Results

Results of stress echocardiography. By inclusion criteria, echocardiograms in all patients were considered interpretable during testing and therefore suitable for analysis. In 31 patients, the test was submaximal for the occurrence of limiting side effects; these test results (4% of all studies) were included in the analysis. No major complications occurred during both dipyridamole and dobutamine stress echocardiography.

Echocardiographic positivity was induced in 421 (56%) of 754 patients. Patients treated invasively had an higher incidence of test positivity (69% vs. 49%, *p* < 0.001), left anterior descending coronary artery involvement (60% vs. 46%, *p* < 0.001) and 90% vessel stenosis (67% vs. 30%, *p* < 0.001) than patients maintained with medical therapy (Table 1). In contrast, medically treated patients had a higher incidence of recent myocardial infarction (54% vs. 36%, *p* < 0.001), right (34% vs. 26%, *p* < 0.05) or left circumflex coronary artery involvement (20% vs. 14%, *p* < 0.05) and 75% (26% vs. 16%, *p* < 0.005) or 100% vessel stenosis (44% vs. 17%, *p* < 0.001) than those treated invasively (Table 1). No difference between medically and invasively treated patients was seen for both wall motion score index at baseline (1.30 ± 0.36 vs. 1.26 ± 0.32, *p* = NS) and at peak drug infusion (1.48 ± 0.39 vs. 1.46 ± 0.37, *p* = NS) (Table 1).

Follow-up data. The mean duration of the follow-up was 37 months (range 2 to 140) and was <1 year in 155 medically treated patients (31%) and 96 invasively treated patients (37%). During the follow-up period, 14 patients died of cardiac-related and 15 of non-cardiac-related causes; further-

Table 2. Univariate Predictors of Prognosis in Medically Treated Patients (events considered: cardiac death, nonfatal myocardial infarction)

	Chi-Square	p Value
Positive stress test result	7.49	0.0062
ECG changes during test	6.24	0.0125
90% diameter stenosis	2.39	0.1223
Chest pain during test	2.35	0.1254
Age	2.02	0.1548
Rest-stress WMSI variation	1.76	0.1847
75% diameter stenosis	0.89	0.3442
Previous MI	0.72	0.3972
100% diameter stenosis	0.44	0.5076
LAD	0.30	0.5844
WMSI at peak of drug infusion	0.19	0.6623
WMSI at rest	0.13	0.7209
RCA	0.11	0.7409
LCx	0.05	0.8207
Gender	0.01	0.9251
Abnormal ECG at baseline	0.00	0.9992

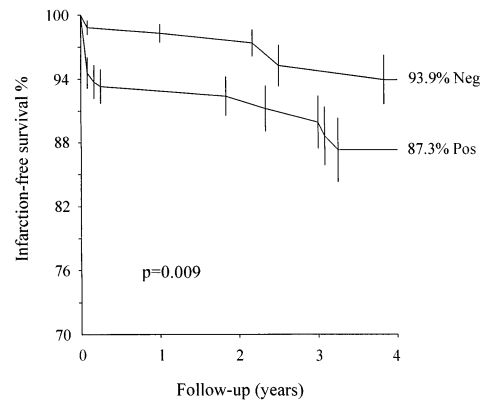
Abbreviations as in Table 1.

more, 40 patients had a nonfatal myocardial infarction. Of 54 hard cardiac events, 37 occurred in the subset of medically and 17 in the subset of invasively treated patients (7.5% vs. 6.5%, $p = \text{NS}$). Two of the 54 events (cardiac death) were procedure related.

After the first 3 months of follow-up, coronary revascularization was performed in 48 (9.7%) (31 angioplasty, 17 operation) of medically treated patients and in 7 (2.7%) (all operation) of the patients who underwent their first invasive treatment soon after stress echocardiography ($p < 0.001$ between the two groups).

When the end point of hard cardiac events was considered, univariate analysis identified two prognostic predictors for the medically treated patients: a positive stress test result and ischemic ECG changes during testing (Table 2). On multivariate analysis, only a positive stress test result was found to be an independent predictor of hard cardiac events (relative risk 2.92, 95% confidence interval 1.29 to 6.59, $p = 0.007$).

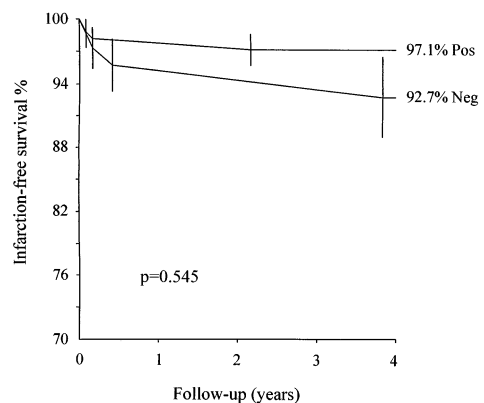
When only medically treated patients were considered, the 4-year infarction-free survival rate was significantly higher for those with a negative than for those with a positive result stress test (93.9% vs. 87.3%, $p = 0.009$) (Fig. 1). In contrast, when only invasively treated patients were considered, a nonsignificant higher 4-year infarction-free survival rate was found for those with a positive than for those with a negative stress test result before coronary revascularization (97.1% vs. 92.7%, $p = 0.545$) (Fig. 2). Of note, invasively treated patients had a significantly higher 4-year infarction-free survival rate than did medically treated patients when only the subgroup with a positive stress test result was considered ($p = 0.012$ vs. $p = 0.853$ for a negative stress test result).

**Figure 1.** Cumulative survival rates free of hard cardiac events (death and nonfatal infarction) in 494 medically treated patients with negative (Neg) or positive (Pos) stress testing results.

Discussion

Our results show that pharmacologic stress echocardiography is effective in risk stratification of patients with single-vessel disease, on the basis of the appearance of the induced wall motion abnormalities. These data confirm and expand previous experience with the strong prognostic power of pharmacologic stress echocardiography in various patient groups, ranging from those with chronic coronary artery disease (16-19) to patients evaluated after acute myocardial infarction (15,20,21), before major vascular surgery (22,23) and after coronary angioplasty (24).

Comparison with previous studies. In patients with single-vessel disease, the prognostic importance of inducible ischemia has been investigated with exercise ECG testing (4,5) and exercise radionuclide angiography (6-8), with disappointing results. Gibson et al. (9) found more valuable results with stress thallium scintigraphy when "soft" end points (unstable angina) were also considered. Parisi et al. (10) convincingly showed that the presence of exercise-induced reversible thallium perfusion defect was a valuable prognostic marker in

Figure 2. Cumulative survival rates free of hard cardiac events (death and nonfatal infarction) in 260 invasively treated patients with negative (Neg) or positive (Pos) stress testing results before coronary revascularization.

patients with angiographically documented single- and double-vessel disease and is superior to exercise electrocardiography in this regard.

Our study differs from previous studies for three reasons: 1) Stress echocardiography was used as the imaging technique; 2) dipyridamole or dobutamine was used as an exercise-independent stressor; and 3) the study cohort, prospectively enrolled on a multicenter basis, totaled 754 patients, allowing a statistically separate analysis for hard end points only.

Clinical implications. The results of our study confirm the benign prognosis of single-vessel disease and identified as a relatively higher risk subgroup those patients showing myocardial ischemia elicitable by pharmacologic stress echocardiography. Moreover, our data show that coronary revascularization is effective in improving infarction-free survival in patients with positive, but not in those with negative, stress echocardiography. These findings have relevant implications for the treatment of single-vessel disease: 1) Despite the fact that preprocedural demonstration of myocardial ischemia is considered necessary in the American College of Cardiology/American Heart Association Guidelines (25), to date there is no evidence that coronary revascularization is effective in reducing either mortality or subsequent myocardial infarction in patients with single-vessel disease (26-28). 2) The practice of performing coronary revascularization on the basis of coronary anatomic findings only, without preprocedural evaluation of the patient by noninvasive stress testing, is a frequent and particularly disturbing therapeutic option, overloading the health care system (29).

At present, careful stratification of patient risk by pharmacologic stress echocardiography seems to represent an effective strategy for selection of patients in whom coronary revascularization can have maximal beneficial effects in terms of prognosis, with the potential of improved cost-effectiveness for invasive procedures.

Limitations of the study. Our study was observational, not randomized, and the decision for medical treatment over coronary revascularization was made by the physician on the basis of clinical, anatomic and stress echocardiographic findings. It is possible that the intentional dropout process created a bias by exclusion of patients who would be expected to have a worse prognosis.

The angiographic evaluation was crude, with visual estimation of stenosis. No quantitative assessment was performed, and the analysis did not include assessment of plaque morphology, collateral circulation, site of stenosis or coronary dominance pattern. Nevertheless, simple visual assessment of coronary anatomy defines a readily identifiable angiographic subset.

We pooled the results obtained with dipyridamole and dobutamine stress, although dipyridamole and dobutamine induce ischemia by different physiologic mechanisms (30). Nevertheless, the two tests have virtually identical diagnostic accuracy, with the slightly higher sensitivity of dobutamine for single-vessel disease balanced by the higher specificity of dipyridamole, as has been made clear by the experience

obtained from directly comparing the two tests in >500 patients undergoing coronary angiography (31). The guidelines of the American College of Cardiology/American Heart Association explicitly state that "stress echocardiography by either exercise or pharmacological challenge (using vasodilators or dobutamine) is both sensitive and specific for detecting inducible myocardial ischemia in patients with intermediate to high pretest probability of coronary artery disease" (32). Moreover, it has been demonstrated that dobutamine and dipyridamole stress echocardiography has a virtually identical capability of prognostic stratification (33,34).

In our study there was no centralized reading of stress echocardiogram. Each echocardiogram (either at baseline or during stress) was interpreted at the peripheral center, and this reading was directly entered into the data bank. Results might have been affected by interinstitutional variability in readings of stress echocardiograms (35). However, this system allowed substantial sparing of human and technologic resources.

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