The incremental prognostic value of pharmacological stress echo over exercise electrocardiography in women with chest pain of unknown origin

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Aims The value of exercise electrocardiography in evaluating women with suspected coronary artery disease is limited. Conversely, stress echocardiography is effective for both diagnostic and prognostic purposes in females. The purpose of the study was to determine the relative prognostic value of exercise electrocardiography and pharmacological stress echocardiography in a cohort of women with chest pain of unknown origin, in order to verify whether criteria could be established for the daily non-invasive evaluation of such a low-risk profile population.

Methods and Results Exercise electrocardiography and pharmacological stress echocardiography (171 diprydiamole, 73 dobutamine) were performed in 244 women (age 60 ± 10 years) with chest pain and known coronary artery disease. A positive result of exercise electrocardiography (ST-segment shift ≥1 mm at 80 ms after the J point) was detected in 95 patients; a positive result of stress echocardiography (new regional wall motion abnormalities) was observed in 33 patients. During follow-up (36 ± 18 months), two deaths, five infarctions, seven unstable anginas, and 11 coronary revascularizations occurred. Using Cox analysis, the positive result of stress echocardiography (odds ratio=40·1) alone, was independently related to hard cardiac events (death, infarction). With spontaneous cardiac events (death, infarction, and unstable angina) as end-points, the multivariate prognostic predictors were a positive result of stress echocardiography (odds ratio=37·0), a family history of coronary artery disease (odds ratio=4·1), typical chest pain (odds ratio=3·7), and a positive exercise electrocardiography result with a rate-pressure product ≤20 000 (odds ratio=3·5). By adopting an interactive stepwise procedure, the prognostic value of stress echocardiography was incremental to that of clinical and exercise electrocardiography data. Nevertheless, the negative result of exercise electrocardiography and pharmacological stress predicted a very high and comparable (P=ns) 24-month survival rate when both hard and spontaneous cardiac events were taken as end-points.

Conclusions In women with chest pain, stress echocardiography is a strong and independent prognostic indicator, incremental to that shown by exercise electrocardiography. However, the two tests have a similar high negative predictive value in this population. Therefore, exercise electrocardiography has to be considered the initial approach and the only test when the result is negative, whereas stress echocardiography is warranted in selected conditions, including those in women with uninterpretable electrocardiograms, those unable to exercise maximally, and those with an ambiguous or ischaemic response to exercise electrocardiography.

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a requirement for a superior level of technology and specific expertise[9].

In the present study we sought to investigate whether criteria for the clinical use of exercise ECG and pharmacological stress echocardiography in women complaining of chest pain of unknown origin could be established on the basis of the prognostic information provided by the two tests.

Methods

Patients

The study group consisted of 244 women (mean [± SD] age 60±10 years) referred for evaluation of chest pain to two different institutions from November 1990 to October 1996. According to sex, age, and the characteristic of the chest pain[9]—typical in 89 (36%) patients and atypical in 155 (63%)—a mean 56±27 pre-test likelihood of coronary artery disease was attributed to the study group. The pre-test likelihood was <70 in 146 (60%) patients and ≥70 in 98 (40%) patients.

No patient had known coronary artery disease, as defined by a history of myocardial infarction, unstable angina, coronary revascularization and/or angiographically documented stenosis (>50%) of any of the three coronary arteries (eight patients had previously [6 months] undergone coronary angiography). In addition, no patient had significant valvular disease, dilated or hypertrophic obstructive cardiomyopathy, left bundle branch block on the baseline electrocardiogram, a poor acoustic window, an inability to exercise, a resting blood pressure ≥180/110, or was taking digitalis or antiarrhythmic medications. Left ventricular systolic function was normal or nearly so in all cases, as evidenced by the value of the resting wall motion score index (1.0 in 238 patients and 1.21±0.17 in the remaining six).

Patients underwent exercise ECG and pharmacological stress echocardiography with either dipyridamole (n=171) or dobutamine (n=73), in random order and on different days within 3 weeks of each other. All tests were performed after washout of antiangular medication (beta-blockers were discontinued for at least 48 h, and long-acting nitrates and calcium channel blockers for at least 24 h before the test). Patients undergoing dipyridamole stress were not to take phylline-containing drugs (i.e. theophylline, aminophylline) or beverages (i.e. coffee, tea, chocolate) for at least 24 h before the test.

Exercise electrocardiography

Exercise ECG was performed using an upright bicycle ergometer with an initial workload of 25 W, followed by increments of 25 W every 2 min. Heart rate and blood pressure were measured and a 12-lead electrocardiogram was recorded at rest and every minute during each stage of exercise and the recovery phase.

The development of horizontal or downsloping ST-segment depression or elevation ≥1 mm at 80 ms after the J point in at least two contiguous leads was taken as a criterion for myocardial ischaemia and test positivity. Indications to terminate the test were: achievement of 85% of the maximal predicted heart rate (maximal predicted heart rate=220–Age), severe ischaemia (ST-segment depression >2 mm or elevation >1 mm), severe symptoms (fatigue, grade III/IV chest pain, or dyspnoea), ventricular or supraventricular tachyarrhythmias, exaggerated blood pressure elevation (≥250 mmHg systolic, ≥120 mmHg diastolic), and a ≥10 mmHg decrease in systolic blood pressure.

The maximum rate-pressure product (heart rate × systolic blood pressure) was determined at peak of exercise in negative tests and at onset of ischaemic electrocardiographic changes in positive tests.

Stress echocardiography

Stress protocols

Dipyridamole was given intravenously according to the high dose protocol (up to 0.84 mg.kg⁻¹ over 10 min)[10]. Dobutamine was administered using an infusion pump in steps of 3 min each, with an initial dose of 5 μg.kg⁻¹ min⁻¹ up to a maximum of 40 μg.kg⁻¹ min⁻¹[11]. Starting in April 1993, the two stress protocols were modified with the co-administration of atropine (0.25 mg every minute up to a maximum dose of 1 mg), if no signs of ischaemia were detected and the heart rate was less than 85% of the age-predicted maximum at the end of the drug infusion[12,13]. A two-dimensional echocardiogram and 12-lead electrocardiogram were continuously monitored during drug administration and until the heart rate had returned to baseline values ±10% during the recovery phase. During the procedure, cuff blood pressure and the electrocardiogram were recorded every minute.

Criteria for test interruption were: peak dipyridamole or dobutamine plus atropine dose, achievement of 85% of the maximal predicted heart rate, onset of obvious new wall motion abnormalities, severe chest pain, horizontal or downsloping ST-segment depression >2 mm, ST-segment elevation >1 mm, systolic blood pressure >220 mmHg, diastolic blood pressure >120 mmHg, reduction in systolic blood pressure ≥30 mmHg, supraventricular or ventricular tachyarrhythmias, and intolerable symptoms.

Intravenous aminophylline (up to 240 mg) and metoprolol (up to 5 mg) were available to reverse the effects of dipyridamole and dobutamine, respectively.

Echocardiographic analysis

Images were obtained continuously from the standard apical and parasternal views using commercially available instruments (Sonos 2000, Hewlett Packard; Ultramark-7, ATL; SSH 140, Toshiba). Images, continuously recorded using 5-VHS videotape recorders (Panasonic MD 830; Panasonic 7330; Panasonic 6200),
were visually evaluated off-line by two independent observers. In case of disagreement, a third observer evaluated the images, and that judgement was binding. The regional wall motion was semiquantitatively assessed using a 16-segment model of the left ventricle\textsuperscript{14}. A four-point scale was assigned to each segment as follows: 1=normal; 2=hypokinesia; 3=akinesia; and 4=dyskinesia. A wall motion score index, obtained by dividing the sum of individual segment scores by the number of considered segments, was calculated both at baseline and at the peak of drug infusion.

The test was considered positive for myocardial ischaemia when any new regional wall motion abnormalities were detected.

**Electrocardiographic analysis**

Electrocardiographic changes were considered significant if an ST-segment shift $\geq 0.1$ mV from baseline at 80 ms after the J point occurred in at least two contiguous leads. In the case of right bundle branch block, the ST-segment shift was considered significant when it also occurred in leads V\textsubscript{1} and V\textsubscript{6}\textsuperscript{15}. Significant electrocardiographic changes were not taken as criteria for test positivity in the absence of induced new wall motion abnormalities; however, the development of ST-segment depression $>2$ mm or ST-segment elevation $>1$ mm was considered a criterion for interruption of the test.

**Follow-up data**

Follow-up data were collected following a review of the patient’s hospital chart, contact with the patient’s physician, telephone interview with the patient, and periodic visits to our outpatient clinic. The clinical events recorded during the follow-up were all causes of death (cardiac and non-cardiac), non-fatal myocardial infarction, unstable angina, and coronary revascularization procedures (surgery or PTCA). Follow-up data were available for all patients.

The cause of death was taken from hospital or physician records. Death was attributed to a cardiac origin in the case of documented 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 a change in the pattern of pre-existing angina requiring hospitalization.

**Statistical analysis**

Values were expressed as mean $\pm$ SD for continuous variables and as frequency and percentage for categorical variables. Continuous variables were compared using the Student’s unpaired t-test, while differences of categorical variables were assessed by the chi-square test. The Kaplan–Meier method was used for infarction-free and event-free survival analysis. For survival analysis, only one cardiac event was considered in each patient. Furthermore, patients were censored at the time of coronary revascularization (11 patients) or non-cardiac death (one patient). Differences in the survival curves were analysed using 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 procedures (SPSS for Windows 1995, Chicago, Illinois, U.S.A.). In addition, in order to investigate the prognostic value of stress echocardiography incremental to clinical and exercise ECG data, an interactive stepwise procedure was performed, where variables were included into the model in the same order as in clinical practice. Therefore, clinical data were first analysed and the global chi-square calculated. Subsequently, a second step was created after adding exercise ECG results to the independent predictors in the first step. Finally, a third analysis was conducted by adding stress echocardiography data to the multivariate predictors in the second step. The incremental prognostic value of the added variables was determined by comparison of the global chi-square calculated at each step. At each step, a $P$ value $\leq 0.1$ was taken as the required level of significance for entering a variable into the model.

The differences in risk were expressed as odds ratio with a corresponding 95% confidence interval (CI).

The analysis included the following covariates: age ($<\text{ or } \geq 65\text{ years}$), typical chest pain, coronary risk factors (family history of coronary artery disease, hypertension, hypercholesterolaemia, cigarette smoking, and diabetes), exercise ECG results (electrocardiographic positive result, positive result at rate-pressure product $\leq 20\,000$), and stress echocardiography results (echocardiographic positive result, wall motion score index at peak of drug infusion, and electrocardiographic changes during the test). A value of $P < 0.05$ was considered statistically significant.

**Results**

There was no major complication as a result of either exercise ECG or stress echocardiography.

**Exercise ECG results**

A positive result of exercise ECG was detected in 95 (37%) patients, of whom 30 (12%) had a rate-pressure product $\leq 20\,000$ (mean 17 654 $\pm$ 2279). Of the remaining 149 patients with an unchanged electrocardiogram, 33 (22%) exercised submaximally ($< 85\%$ of the maximal heart rate) with a mean rate-pressure product of 18 997 $\pm$ 1109.
As shown in Table 1, patients with ischaemia at ECG more often had a history of hypertension ($P<0.013$); there was no difference in the other clinical variables.

**Stress echocardiography results**

Four (1.6%) patients in whom the studies were prematurely terminated were not considered as a separate group. The results were included in the analysis as testing negative for ischaemia.

The echocardiogram was positive for ischaemia in 33 (14%) patients (22 had been investigated by dipyridamole and 11 by dobutamine). Of these 33 patients, 20 (61%) had concomitant significant electrocardiographic changes. In the ischaemic population the wall motion score index rose from $1.00 \pm 0.03$ in the resting condition to $1.26 \pm 0.13$ at peak of ischaemia.

Of the remaining 211 patients with a negative test result, 48 (23%) developed an isolated ischaemic electrocardiographic response.

Patients with echo positive results were older ($P=0.003$), and had a higher frequency of typical chest pain ($P=0.0005$), hypercholesterolaemia ($P=0.018$), and hypertension ($P=0.024$) than those with an unchanged echocardiogram (Table 2).

Table 1  Clinical characteristics for patients with positive and negative results of exercise electrocardiography

<table>
<thead>
<tr>
<th></th>
<th>ExECCG+ (n=95)</th>
<th>ExECCG− (n=149)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$60.0 \pm 8.6$</td>
<td>$58.8 \pm 9.1$</td>
<td>ns</td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>$36(38%)$</td>
<td>$35(36%)$</td>
<td>ns</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>$33(35%)$</td>
<td>$51(34%)$</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>$29(31%)$</td>
<td>$40(27%)$</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$47(49%)$</td>
<td>$50(34%)$</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$4(4%)$</td>
<td>$5(3%)$</td>
<td>ns</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>$20(21%)$</td>
<td>$20(13%)$</td>
<td>ns</td>
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</tbody>
</table>

Data presented are mean value ± SD or number (%) of patients. ExECCG +/− = positive/negative result of exercise electrocardiography; CAD=coronary artery disease.

Table 2  Clinical characteristics for patients with positive and negative results of stress echocardiography

<table>
<thead>
<tr>
<th></th>
<th>SE+ (n=35)</th>
<th>SE− (n=211)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$63.6 \pm 9.0$</td>
<td>$58.6 \pm 8.7$</td>
<td>0.003</td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>$21(64%)$</td>
<td>$68(32%)$</td>
<td>0.0005</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>$15(45%)$</td>
<td>$69(33%)$</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>$15(45%)$</td>
<td>$54(26%)$</td>
<td>0.018</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$19(58%)$</td>
<td>$78(37%)$</td>
<td>0.024</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$2(6%)$</td>
<td>$7(3%)$</td>
<td>ns</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>$7(21%)$</td>
<td>$33(16%)$</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or number (%) of patients. SE +/− = positive/negative result of stress echocardiography; other abbreviations as in Table 1.

**Outcome**

During a mean follow-up of 36 ± 18 months, 14 patients had a cardiac event: two deaths, five myocardial infarctions and seven unstable anginas. In addition, one patient died from a non-cardiac cause (cancer). There were $10(10\%)$ events among 95 patients with a positive result at the exercise ECG, and $11(33\%)$ events among 33 patients with a positive result at stress echocardiography ($P=0.002$). Eleven patients underwent coronary revascularization, of whom $8(95\%)$ (8%) had signs of ischaemia during the exercise ECG and $9(33\%)$ (27%) during stress echocardiography ($P=0.006$).

Patients with a pre-test likelihood ≥70 had a greater incidence of both cardiac events ($10(2\%) v 2-7\%; P=0.014$) and revascularization procedures ($10(2\%) v 0-7\%; P=0.0004$) than patients with a pre-test likelihood <70.

Of the population with a negative exercise ECG result, two (1.7%) events occurred among 118 patients who exercised maximally and two (6.1%) among 33 patients who exercised submaximally. In the subset of 211 patients with negative stress echo results, three (1.4%) events occurred. Finally, two (1.8%) events were experienced by 109 patients with negative exercise ECG and pharmacological stress test.

**Survival analysis**

The univariate predictors of hard cardiac events (death and myocardial infarction) are listed in Table 3. With a multivariate procedure, the positive result of stress echocardiography was the only covariate independently associated with hard cardiac events (odds ratio=40; 95% confidence interval [CI]=4.3–377.5; $P=0.0012$).

Stress echocardiography identified patients with a significantly different 24-month infarction-free survival rate, on the basis of the presence or absence of inducible ischaemia ($75.3\% v 99.5\%$; log rank=43; $P=0.0000$), while exercise ECG could not ($94(1\%) v 98.6\%$; log rank=3.7; $P=0.055$) (Fig. 1). Nevertheless, negative responses to the exercise ECG and pharmacological stress were comparable in predicting survival rates ($P=ns$) (Fig. 1).

The univariate predictors of spontaneous cardiac events (death, myocardial infarction, and unstable angina) are reported in Table 4. Using Cox analysis, spontaneous cardiac events correlated independently with positive results of stress echocardiography (odds ratio=37; 95% CI=9.3–146.2; $P=0.0000$), family history of coronary artery disease (odds ratio=4.1; 95% CI=1.2–14.2; $P=0.0237$), typical chest pain (odds ratio=3.7; 95% CI=1.1–11.9; $P=0.0312$), and positive results of exercise ECG at rate-pressure product ≤20 000 (odds ratio=3.5; 95% CI=1.1–11.0; $P=0.0342$).

Stress echocardiography was better able to identify subgroups of patients with different 24-month event-free
survival rates on the basis of the presence or absence of inducible ischaemia than exercise ECG (53·8% vs 99·0%; log rank = 83·9; P = 0·0000, 87·8% vs 97·9%; log rank = 7·9; P = 0·0049, respectively) (Fig. 2). However, no difference in survival rate was observed between patients with negative exercise ECG or stress echocardiography results (P = ns) (Fig. 2).

**Incremental value of stress echocardiography to clinical and exercise ECG data**

By using an interactive stepwise procedure, typical chest pain (odds ratio = 4·2; 95% CI = 0·8–22·2; P = 0·0927) was the only predictor of hard cardiac events among clinical data. This first statistical model showed a global chi-square of 11·2 (P = 0·0107) (Fig. 3). After the addition of exercise ECG covariates, the positive result of exercise testing at rate-pressure product ≤ 20 000 (odds ratio = 6·2; 95% CI = 1·4–27·8; P = 0·0172) and typical chest pain (odds ratio = 4·5; 95% CI = 0·9–23·5; P = 0·0705) correlated independently with prognosis. The global chi-square was 12·3 (P = 0·0021) (Fig. 3). Finally, when stress echocardiography data were included into the model, the positive result of stress echocardiography (odds ratio = 34·5; 95% CI = 3·9–302·9; P = 0·0014) was the only prognostic predictor. The final statistical model had a global chi-square of 47·7 (P = 0·0000) (Fig. 3).

In considering the spontaneous cardiac events as end-points, typical chest pain (odds ratio = 4·1; 95%
CI=1.3–13.4; \( P=0.0177 \) and family history of coronary artery disease (odds ratio=3.4; 95% CI=1.1–10.2; \( P=0.0324 \) were associated with outcome among clinical variables. In this case the global chi-square was 14.9 (\( P=0.0006 \)) (Fig. 3). At the second step, created after the inclusion of exercise variables, typical chest pain (odds ratio=3.5; 95% CI=1.0–11.9; \( P=0.0418 \) and the positive result of exercise ECG at a rate-pressure product \( \leq 20000 \) (odds ratio=3.4; 95% CI=1.8–15.9; \( P=0.0024 \) were independent prognostic predictors. The global chi-square at this step was 30.9 (\( P=0.0000 \)) (Fig. 3). After the addition of stress echocardiography variables, the positive result of stress echocardiography (odds ratio=37.0; 95% CI=9.4–146.2; \( P=0.0000 \) and family history of coronary artery disease (odds ratio=4.1; 95% CI=1.2–14.2; \( P=0.0237 \) were of independent prognostic importance; the global chi-square increased to 101.1 (\( P=0.0000 \)) (Fig. 3).

**Discussion**

**Clinical implications**

Our results show that in women referred for chest pain with an intermediate likelihood of coronary artery disease, pharmacological stress echocardiography provides incremental prognostic information to those of the

<table>
<thead>
<tr>
<th>Table 4 Univariate predictors of spontaneous cardiac events (death, myocardial infarction, unstable angina)</th>
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<tr>
<td><strong>OR (95% CI)</strong></td>
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<tr>
<td>Positive result of stress echo</td>
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<tr>
<td>Peak stress wall motion score index</td>
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<tr>
<td>Positive result of ExECG with rate-pressure product ( \leq 20000 )</td>
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<tr>
<td>Electrocardiographic changes during stress echo</td>
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<tr>
<td>Typical chest pain</td>
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<tr>
<td>Family history of CAD</td>
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<tr>
<td>Positive result of ExECG</td>
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<tr>
<td>Age ( \geq 65 )</td>
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<td>Hypertension</td>
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<td>Hypercholesterolaemia</td>
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<td>Diabetes</td>
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</table>

Abbreviations as in Tables 1, 2 and 3.
exercise ECG. This fact is not surprising, since stress echocardiography has a significantly higher specificity than exercise ECG in identifying organic coronary artery disease in women\[^5,6\]. However, the purpose of our study was not to demonstrate the superiority of one technique over the other in the risk stratification of women but, rather, to verify whether criteria could be established for the daily non-invasive evaluation of a low-risk profile population. With regard to this fact, data provided by our study have potential clinical implications. First, patients with a negative exercise ECG result had a benign prognosis, comparable to that found in patients with a negative pharmacological stress test and, importantly, comparable to that previously reported in patients with chest pain and normal coronary arteries\[^16,17\]. Second, two of the four events in patients with negative exercise ECG occurred among those who exercised submaximally, despite being representative of only 22% of the whole negative population. Third, although the positive result of the exercise ECG at the rate-pressure product $\leq 20000$ was an independent predictor of spontaneous cardiac events, it had an odds ratio 10 times lower than that shown by stress echocardiography (3.5 vs 37).

Based on these data, the exercise ECG has to be considered the initial approach, and the only test when the result is negative maximal in women with chest pain. In the remaining patients, such as those with a resting uninterpretable electrocardiogram, or those unable to exercise maximally, and those with an ambiguous or ischaemic response to the exercise ECG, pharmacological stress echocardiography is warranted. This strategy seems to be appropriate, when technological and human resources are available, in the management of women referred for chest pain.

**Comparison with previous studies**

The prognostic importance of exercise echocardiography in women with chest pain syndrome has been investigated by Heupler et al\[^19\]. In this study, echocardiographic evidence of ischaemia provided incremental prognostic power to clinical and exercise data when primary end-points were defined as cardiac death, myocardial infarction and late revascularization. Our results, obtained by using a different stress modality (i.e. pharmacological), reinforce those reported by Heupler et al., since they have been used to evaluate hard events (death, myocardial infarction) as end-points.

**Study limitations**

Since this was an observational study, coronary revascularization could be performed on the basis of the integration of test results with clinical, demographic and epidemiological data in the single patient. Consequently, revascularization procedures were more frequent in patients with inducible ischaemia during testing. The exclusion, by the analysis, of these patients may have lowered the positive predictive value of the two tests, particularly of stress echocardiography, since the dropout process involved a significantly higher percentage of patients with ischaemia at stress echocardiography than of patients with ischaemia at exercise ECG.

The severity of the exercise ECG response was assessed through the evaluation of a few parameters (ST-segment shift, rate-pressure product at ischaemia or at peak of stress). However, this simple analysis provided very useful prognostic information, capable of identifying patients at very low risk (those with an unchanged ECG during exercise) from patients with increased risk (those with signs of ischaemia at a rate-pressure product $\leq 20000$).

We pooled the results obtained with dipyridamole and dobutamine stress, although dipyridamole and dobutamine induce ischaemia by different mechanisms\[^19\]. Nevertheless, the two tests have virtually identical diagnostic accuracy, as has been made clear by a recent meta-analysis of $>800$ patients from 12 studies\[^20\]. 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 ischaemia in patients with intermediate to high pretest probability of coronary artery disease\[^21\]. Moreover, it has been demonstrated that the prognostic stratification capabilities of dobutamine and dipyridamole stress echocardiography are virtually identical\[^22–24\], further justifying the pooling of the data from the two tests.

The pharmacological stress protocol was not performed with co-administration of atropine in all patients, since atropine was introduced into clinical practice\[^12,19\] after the study was started. Although this fact could have reduced the rate of positive echocardiographic results, its impact on prognosis seems to have been irrelevant, given the excellent prognosis of patients with echocardiographic negativity.
References


