The Exercise Test That Indicates a Low Risk of Events

Differences in Prognostic Significance Between Patients With Chronic Stable Angina and Patients With Unstable Angina

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OBJECTIVES

The objective of this prospective study was to determine the differences in the prognostic significance of an exercise test (ET) that indicates a low risk of events (low-risk exercise test [LRET]) between patients with unstable angina (UA) and those with chronic stable angina (CSA).

BACKGROUND

It is not known whether the prognostic significance of an LRET is influenced by the disease that is the reason for performing exercise testing.

METHODS

All patients not presenting with high-risk criteria were submitted to a prognostic ET. The ET was performed by patients with CSA and patients with primary UA stabilized with medical therapy. Medical therapy was planned for all patients. A combined end point was defined as cardiac death, nonfatal acute myocardial infarction or hospital admission for UA. Multivariate analysis was performed to determine the independent predictors of events.

RESULTS

Low-risk criteria were fulfilled by 105 patients with UA and 86 patients with CSA. The mean follow-up time was 347 ± 229 days. The event rate was higher in the UA group than in the CSA group (28% vs. 9%, p < 0.001). The CSA group showed worse ET results. Performance of ET by patients with UA was the principal predictor of events (odds ratio 4.2, p < 0.0005).

CONCLUSIONS

Among patients who underwent an LRET, those with UA had a rate of events significantly higher than that of patients with CSA, despite the worse results of ET in patients with CSA. (J Am Coll Cardiol 2001;38:1974–9) © 2001 by the American College of Cardiology

One of the most important phases in attending to patients with coronary artery disease is risk stratification, as an appropriate management strategy will be derived from this. In patients with chronic stable angina (CSA), the exercise test (ET) is the noninvasive technique most frequently used for risk evaluation. In this group of patients, various prognostic markers of ET have been identified (e.g., occurrence of angina, degree of ST-segment depression, number of leads with ST-segment depression) (1–7), and prognostic indexes have been compiled for some of these (2,3).

In contrast, in patients with unstable angina (UA), the clinical and electrocardiographic (ECG) findings are determinants of risk stratification and the choice of the most appropriate therapy (8). High-risk patients (e.g., ST-segment depression, heart failure) with UA must undergo cardiac catheterization and revascularization therapy. Patients with low- or moderate-risk UA stabilized by medical therapy undergo a prognostic evaluation based on an ischemia-provoking test, usually ET, whose interpretation is based on criteria validated in the overall population of patients with stable coronary artery disease. However, in the light of our experience, an ET that indicates a low risk of events (low-risk exercise test [LRET]) does not necessarily imply a favorable prognosis (9). This is probably because after an acute coronary syndrome, the instability of the atherosclerotic lesion can persist despite clinical stabilization (10).

With these observations in mind, the objective of the present study was to determine, by means of a prospective study, the possible differences in the prognostic significance of an LRET between patients with UA and those with CSA.

METHODS

Study group. For the purposes of this prospective study, between January 1997 and March 1999, all patients who presented with CSA or primary UA stabilized with medical therapy and who did not present with high-risk criteria underwent a prognostic ET. We considered high-risk criteria to be any of the following: angina with pulmonary edema, angina with new or worsening mitral regurgitation murmurs, angina with S3 or rales, angina with hypotension or refractory angina. In accordance with the study protocol, the medical therapy employed was that considered appropriate by the physician responsible for each individual patient. Coronary arteriography was not performed.

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Given the absence of inducible ischemia, as well as patients with patients unable to complete stage II of the Bruce protocol in the absence of inducible ischemia, as well as patients with severe systolic dysfunction on the echocardiogram.

Exercise test. The exercise test was performed on a treadmill, according to the standard Bruce protocol (13), using a commercially available, computerized system for exercise electrocardiography. The prescribed pharmacologic therapy was maintained in all patients. Blood pressure was measured before starting the test and then at 2-min intervals, at the time of maximal effort and whenever clinically indicated. Twelve-lead electrocardiography was performed before starting the test and was repeated at 3-min intervals during exercise (at the end of each stage of the Bruce protocol), at the time of maximal effort, at 1-min intervals during at least the first 5 min of the recovery phase and whenever clinically indicated. Throughout the test, three ECG leads and the lead with the greatest deviation of the ST segment were monitored continuously.

Criteria for ending the test were: 1) physical exhaustion or achievement of the maximal heart rate permitted according to age (220 – age in years); 2) a decrease in systolic blood pressure below the baseline or hypertensive response (systolic blood pressure ≥230 mm Hg or diastolic blood pressure ≥130 mm Hg); 3) ataxia, syncope or presyncope; intense dyspnea; severe claudication; or evidence of peripheral hypoperfusion (cyanosis or pallor); 4) ventricular arrhythmia (frequent premature ventricular contractions, polymorphic premature ventricular contractions or three-beat runs); 5) technical difficulties in the monitoring of ECG or blood pressure; 6) severe angina pectoris; 7) ST-segment depression ≥1 mm or ST-segment elevation ≥1 mm in the pathologic non-Q-wave leads (not lead aVR), measured at 80 ms from the J point (positive ECG proof). The reading of ST-segment deviation effected by the computerized system of exercise electrocardiography was confirmed by a cardiologist experienced in the technique.

The Duke index was calculated from this formula: duration of exercise in minutes – (5 × maximal net deviation of the ST segment [in mm] during or after exercise) – (4 × angina index). The angina index was rated 0 if the patient did not experience angina during the test; 1 if the patient had angina, but this did not curtail his or her exercise; and 2 if angina was the reason for stopping the test (2).

The following were classified as high-risk criteria in the ET: 1) a positive clinical and/or ECG response at any time, with a heart rate <120 beats/min, or when the response occurred during the first two stages of the Bruce protocol; 2) ST-segment depression ≥1 mm, persisting ≥6 min in the recovery phase or present in five or more leads; 3) ST-segment depression ≥2 mm at any level of exercise; 4) ST-segment elevation (not in lead aVR) in the non-Q-wave leads; 5) a sustained decrease in systolic blood pressure during progressive exercise; 6) the presence of ventricular tachycardia; and 7) Duke index ≥10.

Patient management. All patients admitted to the hospital with the diagnosis of primary UA routinely underwent 12-lead electrocardiography and determination of cardiac enzymes (plasma CK and CK-MB isoenzyme). Exercise testing was performed in the hospital in all patients with UA, after ≥72 h of being symptom-free.

Patients with CSA underwent determination of hemoglobin, glucose, triglycerides and total cholesterol and its fractions. Rest electrocardiography and chest radiography were performed in patients with signs or symptoms of heart failure. Echocardiography was carried out in patients with a previous myocardial infarction, pathologic Q waves on the ECG, signs or symptoms of heart failure or a murmur suggestive of mitral regurgitation.

An appropriate management strategy was decided prospectively: patients with an ET that indicated a high risk of events (presence of one or more of the high-risk criteria) underwent coronary arteriography and evaluation of revascularization; and patients who completed an LRET (absence of high-risk criteria) were treated medically.

Follow-up. Patients who underwent an LRET were evaluated in the hospital’s Cardiology Unit as outpatients at three months after ET and subsequently every six months. For patients who failed to attend appointments, follow-up was achieved by means of a telephone interview conducted...
by medical personnel. In the follow-up, events were considered in descending order of seriousness: death of cardiac origin, nonfatal acute myocardial infarction and hospital admission for UA. Cardiac death was considered as death occurring in the absence of a clinical or pathologic diagnosis of an extracardiac cause. The presence of acute myocardial infarction or UA was confirmed in all patients by means of the corresponding hospital clinical reports. For patients with more than one event, only the most important was considered.

**Study variables.** The following variables were recorded prospectively: 1) clinical variables: age, gender, tobacco habit, arterial hypertension, hypercholesterolemia, diabetes mellitus, history of ischemic heart disease (hospital admission for UA or acute myocardial infarction), previous revascularization (coronary angioplasty and/or coronary artery bypass graft surgery), previous peripheral arterial disease (stroke or intermittent claudication) and motive for exercise testing (UA or CSA); 2) ECG variables: abnormal baseline ECG; and 3) ergometric variables: duration of ET (in minutes), maximal rate–pressure product (systolic blood pressure $\times$ heart rate), percentage achieved of predicted maximal heart rate, positive clinical response, positive ECG response, positive ET result (positive clinical and/or ECG response) and Duke index.

**Statistical analysis.** Quantitative variables are expressed as the mean value $\pm$ SD. Univariate comparisons between groups of continuous variables were performed by using the Student $t$ test for unrelated samples, and the Mann-Whitney $U$ test if the data were not distributed in a normal fashion. Qualitative variables are expressed as percentages, and univariate comparisons were performed by using the chi-square test and applying the Fisher correction when necessary. Kaplan-Meier life-table curves were used to illustrate the event-free time elapsed, using the log-rank test for comparisons. Cox regression was used for the multivariate analysis of event-free survival. We tested, in the Cox model, the candidate predictors, including those variables associated with the end points in the univariate analysis and those not associated with the end points in the univariate analysis, but with prognostic value in previous studies. These variables were age, gender, tobacco habit, arterial hypertension, diabetes mellitus, history of ischemic heart disease, previous revascularization, previous peripheral arterial disease, motive for exercise testing (UA or CSA), abnormal baseline ECG, duration of ET, positive clinical response, positive ECG response, positive ET result and Duke index. Variables were selected in a stepwise backward selection manner, with retention set at a significance level of 0.05. The results of these analyses are summarized as odds ratios with corresponding 95% confidence intervals. A $p$ value $<0.05$ was considered statistically significant. All calculations were performed using the SPSS statistical software package.

### Table 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With UA</td>
</tr>
<tr>
<td></td>
<td>(n = 105)</td>
</tr>
<tr>
<td>Male gender</td>
<td>88 (84%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>$60 \pm 9$</td>
</tr>
<tr>
<td>Smoking</td>
<td>54 (51%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>56 (53%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (41%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (21%)</td>
</tr>
<tr>
<td>History of CAD</td>
<td>31 (29%)</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>PVD</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Abnormal baseline ECG</td>
<td>44 (42%)</td>
</tr>
</tbody>
</table>

Data are presented as the number (%) of patients or mean value $\pm$ SD.  

**RESULTS**

During the study period, ET was performed in 206 patients with a diagnosis of primary UA that had been stabilized with medical therapy. Eleven patients (5%) were unable to complete stage II of the Bruce protocol and were consequently excluded from the study. Of the remaining 195 patients who underwent ET, in 87 (45%) it proved to be high risk and in 108 (55%) low risk. Three of the 108 patients (2%) with an LRET were lost to follow-up, and the size of this subgroup was 105.

The ET was performed by 148 patients with CSA. In 12 patients (8%), the ET was inconclusive because of their inability to complete stage II of the Bruce protocol without the onset of ischemia. Of the remaining 136 patients, the ET indicated low risk in 86 (63%). None of the patients with CSA was lost to follow-up.

**Clinical characteristics.** The baseline clinical characteristics are shown in Table 1. The patients with UA were more likely to be smokers and their baseline ECG was more likely to be abnormal. There were no statistically significant differences in the remaining clinical variables analyzed. In patients who had undergone revascularization, this procedure had taken place more than six months before their inclusion in the study.

The majority of patients in the CSA group (80%) were in functional class I or II of the Canadian Cardiovascular Society. Echocardiography was performed in 89 (85%) of the 105 patients with UA, and in 45 (52%) of the 86 patients with CSA. In the latter group, the presence of slight or moderate left ventricular dysfunction was seen more frequently (24% vs. 11%, $p = 0.1$), but the difference was not statistically significant. None of the patients in either group had severe systolic dysfunction.

Patients with UA received more nitrates (61% vs. 38%, $p = 0.0001$) and cholesterol-lowering drugs (39% vs. 16%, $p = 0.0001$), as compared with patients with CSA. There were no differences between patients with UA and patients with CSA with regard to therapy with beta-blockers (32% vs. 44%, $p = NS$), calcium antagonists (34% vs. 42%, $p =$
NS), angiotensin-converting enzyme inhibitors (5% vs. 3%, p = NS) and antiplatelet agents (75% vs. 78%, p = NS).

Exercise test results. The exercise test results are shown in Table 2. The variables measured showed less favorable results in the group of patients with CSA. In this group, both the duration of the test and the Duke index were lower, whereas the proportion of positive tests was higher. The median interval from hospital admission to ET in patients with UA was four days.

Events during follow-up. The mean duration of follow-up was 347 ± 229 days (range 30 to 960). Events occurred in 37 patients (19%). The rate of events was higher in the group with UA (28% vs. 9%, p = 0.001). The distribution of events in the two groups is shown in Table 3.

Predictors of events. Table 4 lists the clinical, ECG and ergometric variables that were independent predictors of events during follow-up. The ET performed by patients with UA was the principal predictor of events (odds ratio [OR] 4.2, 95% confidence interval [CI] 1.8 to 9.6; p = 0.0005). Figure 1 shows the event-free survival curves for patients with and without UA. Diabetes mellitus, previous peripheral vascular disease and arterial hypertension were also predictors of events. None of the variables derived from the ET had independent predictive power. However, in the separate analysis of the group of patients with UA, the presence of a positive clinical response during ET was the only independent predictor of events (OR 2.9, 95% CI 1.3 to 6.4; p = 0.008).

**DISCUSSION**

Exercise test and prognosis. Studies on the prognostic value of ET have been carried out in a wide range of patients: those with UA (14–17), acute myocardial infarction (18,19) and coronary artery disease known or suspected before coronary arteriography (2). The proportion of LRETs in these patients varied depending on the pathologic findings and criteria employed to define an ET (i.e., high or low risk). An LRET was performed in 34% (1,2) to 77% (3) of patients with CSA or suspected coronary disease, whereas 63% of the patients included in this study had an LRET, probably because we included patients who, in other studies, were classified as medium risk. The percentage of LRETs is not well established, and in one study, almost 30% of patients with UA presented with signs of ischemia during ET (20). Using our criteria, 55% of our patients with UA had an LRET. Regarding baseline characteristics, the tobacco habit and presence of an abnormal ECG were more frequent in patients with UA, but we do not believe that these differences influenced the results.

It has yet to be established whether the indications of ET performed by patients with UA or CSA have any influence on the prognostic value of an LRET. In the present study, we found that the principal independent predictor of events was the performance of ET by patients with UA. This finding is concordant with the fact that, at least in patients with UA stabilized with medical therapy, an LRET does not necessarily indicate a good prognosis. Although the mortality and nonfatal infarction rates in this group of patients is low (17,21–23), hospital re-admission for UA can reach 29% (22). Our results are in contrast to the low rate of events associated with an LRET in the overall

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**Table 2. Results of the Exercise Test**

<table>
<thead>
<tr>
<th></th>
<th>Patients With UA (n = 105)</th>
<th>Patients With CSA (n = 86)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (min)</td>
<td>9 ± 2</td>
<td>7 ± 4</td>
<td>0.0001</td>
</tr>
<tr>
<td>%TMHR</td>
<td>80 ± 13</td>
<td>77 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>21,481 ± 7,079</td>
<td>20,902 ± 5,835</td>
<td>NS</td>
</tr>
<tr>
<td>Positive clinical response</td>
<td>17 (16%)</td>
<td>40 (46%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive ECG response</td>
<td>34 (32%)</td>
<td>57 (66%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive result</td>
<td>41 (39%)</td>
<td>64 (74%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Duke index</td>
<td>5 ± 5</td>
<td>0 ± 6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number (%) of patients.

**Table 4. Independent Predictors of Events During Follow-Up**

<table>
<thead>
<tr>
<th>Reason for Exercise Test</th>
<th>Coefficient</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA</td>
<td>1.4</td>
<td>4.2</td>
<td>1.8–9.6</td>
<td>0.0005</td>
</tr>
<tr>
<td>PVD</td>
<td>0.8</td>
<td>2.4</td>
<td>1.0–5.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9</td>
<td>2.4</td>
<td>1.2–4.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.7</td>
<td>0.4</td>
<td>0.2–0.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

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**Figure 1.** Event-free survival curve (in days), according to the reason for exercise test (i.e., chronic stable angina or unstable angina). Ch. = chronic.
population of patients who undergo coronary arteriography (2,3). In the present study, although patients with an LRET had a low mortality rate, the group of patients with UA had a statistically significant higher incidence of nonfatal myocardial infarction (7% vs. 1%) and re-admission for UA (19% vs. 6%). This suggests that an LRET does not carry the same prognostic value when performed by a patient with UA as it does when performed by a patient with CSA. This worse prognostic significance of an LRET in our patients with UA is clear, despite the fact that patients with CSA had worse variables on the ET (Table 2). It is probable that the very pathophysiology of UA—derived from the rupture of atheromatous plaques incapable of provoking ischemia (24)—may account for the fact that our patients had a lower presence of flow-limiting lesions. This may explain the relatively low predictive power of ET in this group of patients. It is possible that coronary spasm, the spontaneous lysis of a coronary thrombus with or without distal embolisms, large plaques within the arterial wall and abnormalities of the microvascular circulation may play a considerable role in the “unstabilization” of our patients. Moreover, the survival curves show a continuous divergence, even at the end of the study period, at a time when one might expect a degree of stability to result from the therapy applied in patients with UA. It is probable that one episode of UA identifies a patient who will have plaques that are more vulnerable over long periods. In this respect, it would be useful to find out whether other tests to induce ischemia, such as stress echocardiography or scintigraphic techniques, could provide additional prognostic information (25,26). It would be interesting to determine whether imaging techniques could also alter the specificity in the group of patients with CSA.

In our study group, both diabetes and previous peripheral vascular disease were associated independently with a worse prognosis. These and other variables (previous myocardial infarction, male gender) have been described elsewhere (14,22) as predictors of cardiac events in patients with UA and an LRET. Despite the fact that the univariate analysis showed statistically significant differences between the groups with regard to the tobacco habit variable, the multivariate analysis did not find this to be an independent predictor of events. A possible explanation might be that patients with UA stop smoking after their first hospital admission. The present study suggests that certain other clinical variables should be taken into account when determining the prognosis of a patient with an LRET, especially the diagnosis of the patient before ET is performed. In addition, given that an LRET in patients with UA does not indicate a good prognosis, future studies should attempt to determine whether an aggressive management strategy might be indicated in this group of patients.

**Study limitations.** Our study group consisted of a highly selected group of patients: individuals at high risk because of clinical or ergometric variables were excluded from the study. Consequently, our results are not applicable to the overall population of patients with UA or CSA.

Hospital re-admission for UA may be problematic as an end point. Perhaps patients with UA manifest their symptoms more clearly than patients with CSA, or they are more frequently integrated into medical systems, with the result that such patients may be more easily re-admitted. However, hospital re-admission for UA is an end point accepted in several prognostic studies of patients with UA (4,20).

**Conclusions.** The result of ET carried out for a prognostic purpose is usually worse in patients with CSA than in those with UA stabilized with medical therapy. However, in patients with an LRET, those with UA have a significantly higher incidence of recurrent ischemic events than that of patients with CSA. This allows the deduction that the prognostic significance of ET is dissimilar between the two patient groups.

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**REFERENCES**


