Identifying patients without favourable long-term outcome among those with medically stabilized unstable angina and a negative dipyridamole stress echocardiogram

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Received 1 September 2003; received in revised form 21 November 2003; accepted 28 November 2003

Abstract Aims Patients with medically stabilized unstable angina and a negative stress echocardiogram have a favourable outcome as a whole. This study sought to identify which subsets of patients are associated with serious events at long-term within this population.

Methods and results We studied and followed-up 128 patients (mean 2.2±1.3 years) with medically stabilized unstable angina and a negative dipyridamole stress echocardiogram. Cumulative survival rates were 98.2±1.3%, 96.0±2.2% and 93.2±3.2%, at 1, 2 and 4 years, respectively. Freedom from events (death, myocardial infarction, and revascularization) were 98.2±1.3%, 96.0±2.2% and 86.3±6.0%, at 1, 2, and 4 years, respectively. Cumulative mortality rate was higher in men (3.6±2.5%, 8.5±4.1%, and 12.2±5.4% at 1, 2, and 4 years, vs. 0% at the end of the follow-up in women; p = 0.034), and in those with previous myocardial infarction (4.3±4.3%, 9.1±6.2%, and 18.2±2.3% at 1, 2 and 4 years, vs. 1.1±1.1%, 2.9±2.1%, and 2.9±2.1% in those without previous myocardial infarction, respectively; p = 0.047).

Conclusion Among patients with medically stabilized unstable angina and a negative dipyridamole stress echocardiogram, male gender and previous myocardial infarction are associated with a non-favourable outcome.

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KEYWORDS
Unstable angina; Stress echocardiogram; Outcome.

ABBREVIATIONS
DSE, Dipyridamole stress echocardiogram; ECG, Electrocardiography; UA, Unstable angina.

Introduction

Patients with unstable angina (UA) comprise a heterogeneous group, having a variable prognosis.1,2
Although some studies have shown a beneficial effect of invasive management in patients with UA and ST-segment depression during chest pain, an electrocardiogram during chest pain is not available in most cases. In these patients with suspected UA, the initial goal is usually to get a clinical stabilization with medical treatment, and subsequently to perform risk stratification using non-invasive techniques.3

Although an exercise treadmill test is the recommended non-invasive technique for stratifying most patients with medically stabilized UA, the use of other imaging techniques has been increased over the last years, since a considerable proportion of patients are not able to perform an exercise treadmill test, and some studies have suggested an incremental prognostic value of stress echocardiogram and myocardial scintigraphy in patients with medically stabilized UA.4–9 Stress echocardiogram has demonstrated to be of indoubtable prognostic value in these patients, those with a negative test having a more favourable outcome in comparison with those with a positive test.5,7,9 However, some patients with medically stabilized UA experience major adverse events at mid- and long-term despite having performed a negative stress echocardiogram. The aim of the present study was to identify which subgroups of patients with medically stabilized UA and a negative Dipyridamole Stress Echocardiogram (DSE) are associated with serious events at long-term.

Patients and methods

Study population

We studied patients at our institution fulfilling the following criteria: (1) Hospital admission due to suspected UA. (2) Referral to the Laboratory of Echocardiography after having been stabilized under medical treatment, in order to perform risk stratification by DSE; patients were referred to stress echocardiogram due to different reasons, such as having performed a non-conclusive exercise treadmill test, being unable to perform an adequate exercise test or repolarization abnormalities at the basal ECG. (3) A negative result of the DSE. We identified 128 patients fulfilling these criteria, and they comprise the study population. Patients were followed for a mean of 2.2 ± 1.3 years.

Dipyridamole stress echocardiogram

DSE was performed using commercially available equipment (Sonos 5500, Phillips) using harmonic imaging.10 Transducer position and gain settings were optimised to obtain an uncluttered left ventricular cavity image with maximal endocardial definition. Stress echocardiogram was performed with dipyridamole infused intravenously (0.84 mg/kg body weight over 6 min). If the test was negative, additional atropine was given intravenously 4 min after the dipyridamole infusion was stopped (2 steps separately by 3 min up to a maximal dosage of 1.0 mg). Aminophyline (240 mg), which promptly reverses the effect of dipyridamole, was always available. Blood pressure and 12-lead electrocardiograms were recorded at baseline, every 3 min and at the end of dipyridamole protocol or before the premature cessation of the test. The presence of horizontal or down sloping ST-segment depression of at least 0.1 mV, 0.08 s after the J point vs. baseline recordings was considered a positive electrocardiographic finding but not a positive stress echo finding. Dipyridamole infusion was stopped for any of the following reasons: maximal pharmacological stress, a heart rate of 85% of age-predicted maximum heart rate, development of new wall motion abnormalities, progressive and severe angina, development of hypotension (decreased in systolic blood pressure ≥ 20 mmHg over the baseline), significant hypertension (systolic blood pressure > 240 mmHg), severe ventricular arrhythmias or atrioventricular blocks, dyspnea or development of bronchospasm.

Image acquisition was performed with the patient in the left lateral decubitus position before, during and after dipyridamole infusion. Images were obtained at para-sternal long-axis and short-axis as well as at the apical 4- and 2-chamber views. All views obtained at baseline were acquired at the end of each DSE level and when new wall motion abnormalities or worsening of pre-existing wall motion abnormalities occurred. These images were recorded on videotape and digitised on-line into quad-screen cine loop format.

For wall motion analysis, the left ventricle was divided into 16 segments according to the recommendations of the American Society of Echocardiography and each segment was scored using a 4-point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The only criterion of test positivity was defined as the occurrence of new or worsening pre-existing dysynchrony (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.
Follow-up

After having performed a negative DSE, all patients were discharged under medical treatment. Patients were followed-up by clinical interview with telephone contact. The following were considered as end-points: death, acute myocardial infarction, and coronary revascularization (either percutaneous coronary intervention or coronary artery bypass grafting).

Statistical analysis

Discrete variables are expressed as proportions, and continuous variables as mean ± standard deviation. Proportions were compared using the Chi-square test (Fisher’s test and continuous correction when necessary), and 2-tailed Student’s t-test was used to compare continuous variables. Kaplan–Meier curves were used to calculate the actuarial survival, and Log-Rank and Breslow tests were used to compare the outcome of different subgroups of patients. Associations were considered statistically significant in presence of a p value < 0.05, although all p values are provided.

Results

Baseline characteristics and results of the DSE

Table 1 shows baseline characteristics of the patients. Of note, the proportion of women was high, and rather similar to the proportion of men. This is probably due to the fact that women more frequently have repolarization abnormalities on the baseline ECG or have inability to perform adequately on an exercise treadmill test, thus being referred to DSE more frequently than men. Mean age was 69 ± 10 years, that can be also considered relatively high. Other baseline characteristics are also shown in Table 1.

ST-segment depression non-associated with new segmental abnormalities in left ventricular wall motion occurred in 3 patients (2.3%), and angina in 4 (3.1%). Following dipyridamole administration, heart rate increased from 73 ± 11 to 97 ± 17 beats per minute (p < 0.001). Major secondary effects during DSE were non-sustained ventricular tachycardia (n = 1), transient complete atrioventricular blockade (n = 1), and severe bradycardia (n = 1), that successfully reversed with propranolol (atrioventricular blockade and severe bradycardia). Minor secondary effects consisted of headache (21.1%), blush (13.3%), and non-specific chest pain (7.8%).

Follow-up and long-term outcome

Out of the 128 patients, 110 (86%) could be followed-up for a mean of 2.2 ± 1.3 years. The number of patients completing follow-up at 1, 2, and 4 years were 84, 60, and 13, respectively. During follow-up, there were 5 deaths, due to intracranial bleeding, sepsis, acute myocardial infarction, stroke, and in the post-operative period after coronary artery bypass grafting, at 1, 2, 15, 19, and 33 months of follow-up, respectively. Thus, out of the 5 deaths 4 were of cardiovascular origin, and 2 were cardiac deaths. Cumulative survival rates were 98.2 ± 1.3%, 96.0 ± 2.2% and 93.2 ± 3.2%, at 1, 2 and 4 years, respectively.

Although no patient was diagnosed with non-fatal myocardial infarction, coronary revascularization procedures were indicated in 3 cases:
2 percutaneous coronary interventions (at 46 and 56 months of follow-up), and 1 coronary bypass grafting (at 33 months of follow-up, dying in the post-operative period). Probabilities of being alive and free from cardiac events (acute myocardial infarction and coronary revascularization procedures) were 98.2 ± 1.3%, 96.0 ± 2.2% and 86.3 ± 6.0%, at 1, 2, and 4 years of follow-up, respectively.

Identification of patients at risk

Table 2 shows the outcome in different subgroups of patients. The outcome was significantly worse in male than in female patients, the latter having a 100% survival at the end of the follow-up (Fig. 1A), in comparison with a 3.6 ± 2.5%, 8.5 ± 4.1%, and 12.2 ± 5.4% mortality rates at 1, 2, and 4 years, respectively (90.9 ± 6.2% vs. 97.1 ± 2.1% at 2-year; Log-Rank: p = 0.034; Breslow: p = 0.038). Similarly, women had a higher probability of being free from events during follow-up in comparison with men (Fig. 1B).

Mortality rates in patients with previous myocardial infarction were 4.3 ± 4.3%, 9.1 ± 6.2%, and 18.2 ± 2.3%, in comparison with 1.1 ± 1.1%, 2.9 ± 2.1%, and 2.9 ± 2.1% in patients without previous myocardial infarction at 1, 2 and 4 years, respectively (90.9 ± 6.2% vs. 97.1 ± 2.1% at 2-year; Log-Rank: p = 0.047; Breslow: p = 0.085) (Fig. 2).

Thus, 2 characteristics were associated with higher mortality among patients with negative DSE: male gender and previous myocardial infarction. Fig. 3 shows the increased mortality rates at 1, 2, and 4 years in patients without any of these characteristics, in male gender patients, in patients with previous myocardial infarction and in those with both clinical features; mortality rates at 4 years were 0.0%, 12.2%, 18.2%, and 20.7%, respectively.

Discussion

Prognostic implications of a negative stress echocardiogram in UA

Exercise echocardiography offers superior prognostic information in patients with medically stabilized UA in comparison with exercise treadmill testing. The same occurs with dobutamine or dipyridamole echocardiography. Because of that, it has been postulated that exercise treadmill test would not be enough to achieve reliable risk stratification of patients with medically stabilized UA.

Patients with medically stabilized UA and a negative stress echocardiogram have a very low mid- and long-term mortality rate. In our study with patients with medically stabilized UA and a negative DSE, mortality rate was 1.8% at 1 year, 4.0% at 2 years, and 6.8% at 4 years, these data being in agreement with previous studies.

Identification of patients with negative DSE and a non-favourable outcome

There was a favourable outcome in our study population as a whole. However, events occurred especially in patients with 1 of these 2 characteristics: male gender, and previous myocardial infarction. Four-year mortality rates were 12.2%, 18.2%, and 20.7%, respectively, in male gender patients, in those with previous myocardial infarction, and in those with both characteristics, compared with 0% in those with any of these characteristics.

Studies evaluating the influence of gender on the outcome of patients with UA have yielded controversial results, but women have more favourable outcome than men in most studies. In the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Two-year probability of being alive and of being alive and free of events (death, myocardial infarction, and coronary revascularization)</th>
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<td></td>
<td><strong>Survival</strong></td>
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<tr>
<td>Present</td>
<td>Absent</td>
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<tr>
<td>Age over 70</td>
<td>98.3 ± 1.7</td>
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<tr>
<td>Female gender</td>
<td>100</td>
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<tr>
<td>Hypertension</td>
<td>95.0 ± 2.8</td>
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<tr>
<td>Diabetes mellitus</td>
<td>100</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>97.3 ± 2.7</td>
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<tr>
<td>Prior infarction</td>
<td>90.9 ± 6.2</td>
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<tr>
<td>Previous PCI</td>
<td>92.3 ± 7.4</td>
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<td>WMSI ≥ 1.5</td>
<td>90.0 ± 9.5</td>
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</tbody>
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p: Log-Rank/Breslow. PCI, percutaneous coronary intervention; WMSI, wall motion score index.
study by Lin et al., among patients with medically stabilized UA undergoing exercise echocardiography, men had higher incidence of events in comparison with women (18% vs. 10%, $p = 0.15$). Similar data have been found in patients with medically stabilized UA and a negative exercise test, as well as after dobutamine stress echocardiogram; among patients with acute myocardial infarction, however, only minor angiographic differences are attributable to gender. Women probably have a higher prevalence of microvascular angina and a lower probability of epicardial and multivessel coronary artery disease. Conversely, male gender is associated with a higher prevalence of epicardial coronary disease and multivessel disease. In a recent study by Cortiagiani et al. with UA patients undergoing DSE, women had worse prognosis than men when DSE showed an ischemic response, but not among patients with a negative DSE.

The presence of previous myocardial infarction is associated with a higher prevalence of multivessel disease and left ventricular dysfunction; these are both associated with a worse prognosis. Previous myocardial infarction has been repeatedly identified as a predictor of worse prognosis in patients with UA.

**Study limitations**

This study has some limitations. First, the relatively small number of events may have masked the effect of some clinical or echocardiographic variables on clinical outcome. Second, revascularization decisions may have been driven by some of the variables we have studied, such as previous infarction. Third, the number of patients completing

![Figure 1](image1.png)  
**Figure 1** Comparison between outcome of men and women at long-term. A: Cumulative survival rate. B: Probability of being free from events.

![Figure 2](image2.png)  
**Figure 2** Comparison between outcome of patients with and without previous myocardial infarction at long-term. A: Cumulative survival rate. B: Probability of being free from events.
4-year follow-up was small. Finally, dobutamine echocardiography instead of DSE would have permitted to evaluate the influence of myocardial viability on the outcome.17

Conclusions and practical implications

A negative DSE is associated with a favourable long-term outcome in patients with medically stabilized UA considered as a whole. However, some of these patients may still present major events during follow-up. In our series, these patients were especially male and had previous myocardial infarction. Thus, this subset of patients needs to be more strictly evaluated and closely followed-up, and even it could be speculated that DSE is not a good choice in men with previous infarction that present with unstable angina.

References


