Long term outcome in patients with silent versus symptomatic ischaemia during dobutamine stress echocardiography

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Objectives: To compare the long term prognosis of patients having silent versus symptomatic ischaemia during dobutamine stress echocardiography (DSE).

Design: Observational study.

Setting: Tertiary referral centre.

Patients: 931 patients who experienced stress induced myocardial ischaemia during DSE.

Results: Silent ischaemia was present in 643 of 931 patients (69%). The number of dysfunctional segments at rest (mean (SD) 9.6 (5.1) vs 8.8 (5.0), p = 0.1) and of ischaemic segments (3.5 (2.2) vs 3.8 (2.1), p = 0.2) was comparable in both groups. During a mean (SD) follow up of 5.5 (3.3) years, there were 169 (18%) cardiac deaths and 86 (9%) non-fatal infarctions. Multivariable Cox regression analysis showed age (hazard ratio (HR) 1.1, 95% confidence interval (CI) 1.02 to 1.05), previous myocardial infarction (HR 1.4, 95% CI 1.1 to 2.0), and number of ischaemic segments during the test (HR 2.0, 95% CI 1.0 to 3.7) as independent predictors of cardiac death and myocardial infarction. For every additional ischaemic segment there was a twofold increment in risk of late cardiac events. The annual cardiac death or myocardial infarction rate was 3.0% in patients with symptomatic ischaemia and 4.6% in patients with silent ischaemia (p < 0.01). Silent induced ischaemia was an independent predictor of cardiac death and myocardial infarction (HR 1.7, 95% CI 1.1 to 2.0). During follow up symptomatic patients were treated more often with cardioprotective therapy (p < 0.01) and coronary revascularisation (145 of 288 (50%) vs 174 of 643 (27%), p < 0.001).

Conclusions: Patients with silent ischaemia had a similar extent of myocardial ischaemia during DSE compared to patients with symptomatic ischaemia but received less cardioprotective treatment and coronary revascularisation and experienced a higher cardiac event rate.
segments were assigned to the regions with concomitant coronary artery and the right coronary artery. Overlapping and the apical inferior segment was considered to be an anterior descending coronary artery and the left circumflex, considered to be an overlapping segment between the left to the right coronary artery. The apical lateral segment was the left circumflex, and the inferior and basal septal segments descending coronary artery, the posterior and lateral wall to and anteroseptal walls were assigned to the left anterior
tion, as previously described. The anterior, apical, septal, myocardial segments based on echocardiographic localisa-
pnoea) during DSE. Coronary arteries were assigned to
equivalent symptoms (epigastric pain, jaw pain, and dys-
was defined as the presence of typical chest pain or anginal
rest became dyskinetic during stress. Symptomatic ischaemia
was not considered to be present when akinetic segments at
motion in wall motion score
dyskinesia). Ischaemia was defined as new or worsened wall
diagnosis during stress indicated by an increase of wall motion score ≥ 1 grade in ≥ 1 segments. Ischaemia was
not considered to be present when akinetic segments at rest became dyskinetic during stress. Symptomatic ischaemia was
defined as the presence of typical chest pain or anginal equivalent symptoms (epigastric pain, jaw pain, and dys-
pnea) during DSE. Coronary arteries were assigned to
tocardiographic localisation, as previously described. The anterior, apical, septal, and anteroseptal walls were assigned to the left anterior descending coronary artery, the posterior and lateral wall to the left circumflex, and the inferior and basal septal segments to the right coronary artery. The apical lateral segment was considered to be an overlapping segment between the left anterior descending coronary artery and the left circumflex, and the apical inferior segment was considered to be an overlapping segment between the left anterior descending coronary artery and the right coronary artery. Overlapping segments were assigned to the regions with concomitant abnormalities.

Follow up
Follow up data were collected by contacting the patient’s general practitioner and by review of hospital records. The date of the last review or consultation was used to calculate follow up time. Outcome events were overall death, cardiac death, and non-fatal myocardial infarction. Cardiac death was defined as death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was regarded as cardiac death. Non-fatal myocardial infarction was defined by two of the following symptoms: typical chest pain, increased cardiac enzyme concentrations, and typical changes on ECG.

### Statistical analysis
Continuous data were expressed as mean (SD). Student’s t-test was used to analyse continuous data. Differences between proportions were compared with the $\chi^2$ test. Univariate and multivariate Cox proportional hazard regression models (BMDP Statistical Software Inc, Los Angeles, California, USA) were used to identify independent predictors of late cardiac events. Variables were selected in a stepwise forward selection manner, including clinical and DSE data, with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The probability of survival was calculated by the Kaplan-Meier method and survival curves were compared by the log rank test. A probability value of $p < 0.05$ was considered significant.

### RESULTS
#### Patient characteristics and haemodynamic results
Silent myocardial ischaemia was present in 643 of 931 (69%) patients. Clinical risk factors were not significantly different between patients with and patients without angina during DSE, with the exception of history of angina, which was more often observed in patients with symptomatic ischaemia (table 1). Table 2 shows DSE characteristics of patients with silent and symptomatic myocardial ischaemia. There was no significant difference between patients with and patients without silent ischaemia with respect to the number of abnormal segments at rest and the number of ischaemic segments during DSE. No patient experienced a myocardial infarction during the test. Side effects among the 931 patients were non-sustained ventricular tachycardia ($< 10$ complexes) in 28 (3%), sustained ventricular tachycardia ($> 10$ complexes) in 13 (1%), severe hypotension (decrease in systolic blood pressure > 40 mm Hg compared with baseline) in seven (1%), atrial fibrillation in six (1%), and ventricular fibrillation in one (0.1%).

#### DSE and outcome
During a mean (SD) 5.5 (3.3) years follow up of the 931 patients, there were 265 (28%) deaths, of which 169 (18%) were attributed to cardiac causes. Non-fatal infarction

### Table 1 Clinical characteristics of patients with and without angina during dobutamine stress echocardiography (DSE)

<table>
<thead>
<tr>
<th>Silent ischaemia (n = 643)</th>
<th>Symptomatic ischaemia (n = 288)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>61 (13)</td>
<td>61 (11)</td>
</tr>
<tr>
<td>Men</td>
<td>465 (72%)</td>
<td>233 (81%)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>330 (51%)</td>
<td>161 (56%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>78 (12%)</td>
<td>29 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>195 (30%)</td>
<td>79 (27%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>163 (25%)</td>
<td>82 (28%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>122 (19%)</td>
<td>88 (30%)</td>
</tr>
<tr>
<td>History of angina</td>
<td>200 (31%)</td>
<td>196 (68%)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>107 (17%)</td>
<td>38 (13%)</td>
</tr>
<tr>
<td>Previous coronary angiography</td>
<td>219 (34%)</td>
<td>112 (39%)</td>
</tr>
<tr>
<td>Previous coronary bypass surgery</td>
<td>96 (15%)</td>
<td>43 (15%)</td>
</tr>
<tr>
<td>Previous coronary angioplasty</td>
<td>89 (14%)</td>
<td>56 (19%)</td>
</tr>
<tr>
<td>Ii blockers</td>
<td>243 (38%)</td>
<td>115 (40%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>177 (27%)</td>
<td>99 (34%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>180 (28%)</td>
<td>115 (40%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>302 (47%)</td>
<td>158 (55%)</td>
</tr>
<tr>
<td>Statins</td>
<td>174 (27%)</td>
<td>92 (32%)</td>
</tr>
<tr>
<td>Indication for DSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of CAD</td>
<td>350 (54%)</td>
<td>211 (73%)</td>
</tr>
<tr>
<td>Preoperative evaluation before non-cardiac surgery</td>
<td>186 (29%)</td>
<td>34 (12%)</td>
</tr>
<tr>
<td>Risk stratification after MI</td>
<td>107 (17%)</td>
<td>43 (15%)</td>
</tr>
</tbody>
</table>

*Mean (SD).

CAD, coronary artery disease; MI, myocardial infarction.
occurred in 86 (9%) patients and late revascularisation was performed in 319 (34%) patients. The annual cardiac death rate was 2.2% in the group of patients with symptomatic ischaemia during DSE and 3.8% in the group with silent ischaemia (p < 0.01). The annual myocardial infarction or cardiac death rate was 3.0% in patients with symptomatic ischaemia and 4.6% in patients with silent ischaemia (p < 0.01). Late revascularisation was more often performed in patients with symptomatic ischaemia (145 of 288 (50%) v 174 of 643 (27%), p < 0.001). Medical treatment was changed after detection of ischaemia by DSE in both groups but patients with angina during DSE were significantly more often treated with β blockers, aspirin, and statins (table 3).

On the other hand, the fact that fewer of these patients were treated with nitrates and calcium channel blockers at follow up is related to the higher incidence of coronary revascularisation in this group.

Figures 1 and 2 present Kaplan-Meier survival curves for the end point cardiac death and the combined end point cardiac death or non-fatal infarction, respectively. Patients with silent ischaemia had a significantly lower probability of survival during long term follow up than patients with symptomatic ischaemia. In particular, patients with silent ischaemia and multivessel disease had a poor long term prognosis (fig 3). This may be related to the fact that patients with symptomatic ischaemia and multivessel disease were more often referred for coronary revascularisation than patients with silent ischaemia and multivessel disease (111 of 220 (50%) v 141 of 509 (28%), p < 0.0001). Among patients with symptomatic ischaemia and multivessel disease, cardiac death occurred in 11 of 111 (11%) patients who were revascularised versus 22 of 109 (20%) patients who were treated medically (p = 0.05). Similarly, in patients with silent ischaemia and multivessel disease, cardiac death occurred in 18 of 141 (13%) patients who were revascularised versus 92 of 368 (25%) medically treated patients (p = 0.004).

No sex differences for cardiac death or hard cardiac events were present in the overall population, in the two groups of patients with symptomatic or silent ischaemia, or in the two groups of patients with single or multivessel disease.

**Incremental prognostic value**

Independent predictors of cardiac death in a multivariate analysis were age (HR 1.1, 95% CI 1.04 to 1.08), male sex (HR 1.8, 95% CI 1.2 to 2.7), smoking (HR 1.5, 95% CI 1.1 to 2.0), and the number of ischaemic segments during DSE (HR 2.1, 95% CI 1.1 to 4.1). Independent predictors of cardiac death or myocardial infarction were age (HR 1.1, 95% CI 1.02 to 1.05), previous myocardial infarction (HR 1.4, 95% CI 1.1 to 2.1), and the number of ischaemic segments during DSE (HR 2.0, 95% CI 1.0 to 3.7). For every ischaemic segment there was a twofold increment in risk of late cardiac events. Silent induced ischaemia was also an independent predictor of cardiac death or myocardial infarction (HR 1.7, 95% CI 1.1 to 2.0). An interaction term between silent induced ischaemia and the presence of ischaemia was not significant.

**DISCUSSION**

The current results show that patients with silent myocardial ischaemia during DSE have a higher incidence of long term cardiac death and myocardial infarction than do patients with symptomatic myocardial ischaemia. This association was observed irrespective of the presence and extent of resting or dobutamine stress induced new wall motion abnormalities.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>DSE data for patients with and without angina during DSE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Silent ischaemia (n = 643)</td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>127 (21)</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mm Hg)</td>
<td>135 (31)</td>
</tr>
<tr>
<td>Peak rate pressure product</td>
<td>16 573 (4290)</td>
</tr>
<tr>
<td>Peak dobutamine dose (µg)</td>
<td>37 (7)</td>
</tr>
<tr>
<td>Atropine use</td>
<td>230 (36%)</td>
</tr>
<tr>
<td>ST segment depression</td>
<td>248 (38%)</td>
</tr>
<tr>
<td>Number of dysfunctional segments at rest</td>
<td>9.6 (5.1)</td>
</tr>
<tr>
<td>Number of ischaemic segments</td>
<td>3.5 (2.2)</td>
</tr>
<tr>
<td>Arrhythmias and hypotension during the test</td>
<td>43 (7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for termination of the stress test</th>
</tr>
</thead>
<tbody>
<tr>
<td>85% of maximum heart rate</td>
</tr>
<tr>
<td>Maximum dose</td>
</tr>
<tr>
<td>Arrhythmias</td>
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<tr>
<td>Side effects</td>
</tr>
<tr>
<td>ST segment depression</td>
</tr>
<tr>
<td>Angina</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Medication at follow up of patients with and without angina during DSE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Silent ischaemia (n = 643)</td>
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Significant changes were observed in medical treatment of patients with and without angina during DSE. Patients with silent myocardial ischaemia during DSE were less often prescribed β blockers, aspirin, and statins than were patients with symptomatic ischaemia. In addition, late revascularisation was less often performed in patients with asymptomatic ischaemia during DSE. Moreover, in patients with multivessel disease and symptomatic or silent ischaemia during DSE, cardiac death occurred more often in medically treated patients than in patients who underwent myocardial revascularisation.

The worse long term prognosis of patients with asymptomatic myocardial ischaemia may be associated with less aggressive anti-ischaemic medical treatment and coronary revascularisation. β Blockers have been unequivocally shown in multiple studies to reduce angina and the incidence, frequency, and extension of episodes of silent ischaemia.26–28 The combination of β blockers with other anti-ischaemic medical treatment such as calcium channel antagonists has also been found to reduce the incidence of myocardial ischaemia more than either type of these medications alone.29 30 Also, statins have been shown to decrease transient myocardial ischaemia, probably due to improved endothelial function.31 Furthermore, myocardial revascularisation was previously shown in a prospective study to be associated with decreased asymptomatic ischaemia and improved clinical outcome compared with angina or ischaemia guided strategy.2 In the present study, the decision to perform coronary angiography was made on clinical grounds by the treating cardiologist. The prescription rate of β blockers or calcium antagonist was relatively low. It seems that in some patients symptoms of angina instead of signs of ischaemia on DSE were the reason to prescribe β blockers or calcium antagonists and to perform myocardial revascularisation.

Additionally, in this study absence of symptoms during dobutamine stress induced ischaemia was often observed (69%); this is in line with previous studies4 11 and is physiologically explained by the ischaemic cascade, since systolic dysfunction precedes the development of angina pectoris.

**Comparison with previous studies**

There are only a few studies on the long term prognostic implications of silent myocardial ischaemia during DSE. Bigi and colleagues35 studied 407 survivors from a first uncomplicated myocardial infarction who had myocardial ischaemia during DSE and were followed up for a 10 month period. Cardiac death and non-fatal myocardial re-infarction occurred, respectively, in six of 407 (1%) and 13 of 407 (3%) patients. No significant difference in spontaneous event-free survival was observed among patients with silent ischaemia. Bonou and colleagues33 studied 289 patients with...
Prognosis and silent ischaemia

Advanced age undergoing DSE. During a 35 (13) month follow up period, 15 (5%) cardiac deaths and 19 (7%) non-fatal myocardial infarctions occurred. There was no significant difference in prognosis between patients with silent ischaemia and patients with symptomatic myocardial ischaemia. In the present study the cardiac event rate was higher than in the previous studies; this may be related to the longer and nearly complete (99.5%) follow up. Previous data from 224 patients who underwent dobutamine stress myocardial perfusion imaging showed a similar outcome between patients with silent ischaemia and patients with symptomatic ischaemia.11–16 The different findings in that study may be related to differences in sensitivity between myocardial perfusion imaging and DSE, as well as a possible differences in management of patients after a positive study by these two techniques.

Some previous studies suggested a common pathway for both the electrical and pain response to ischaemic stimulus.16 These studies showed that during exercise stress testing patients with symptomatic ischaemia had a higher incidence of ST segment changes.16 However, the extent of ischaemia was comparable between patients with and patients without symptomatic ischaemia during DSE. The mechanism underlying the pathogenesis of silent or symptomatic ischaemia is complex and may include variations in pain threshold, a central nervous system alteration, or a particular biochemical pattern of inflammatory system activation.16–18 The relation between angina and extent of ischaemia is not clear. Several studies have assessed the extent of ischaemia in the presence and in the absence of symptomatic myocardial ischaemia during stress test with contradictory results. Some investigators have reported a greater extent and severity of ischaemia in symptomatic patients than in those with silent myocardial ischaemia,11–14 whereas other studies reported no difference in the amount of ischaemic myocardium between patients with and patients without symptomatic myocardial ischaemia during exercise or pharmacological stress testing.4,16 In the present study there are no significant differences between dysfunctional segments at rest and the number of ischaemic segments at peak in patients with and without symptomatic myocardial ischaemia. Moreover, the extent of ischaemia during DSE was an independent predictor of cardiac death and myocardial infarction, and the number of diseased vessels was related to an increased rate of cardiac events, particularly in patients with symptomatic ischaemia. This is in line with previous studies that show the total amount of ischaemic territory at risk is related more to the outcome than to the presence of symptoms.13,14,15,16,17

Study limitations

Data on coronary angiography were not available for all patients.

Conclusion

This study showed that patients with asymptomatic myocardial ischaemia during DSE had a worse long term cardiac event-free survival rate than did patients with symptomatic myocardial ischaemia. Patients with asymptomatic ischaemia should be treated with a complete medical therapy or revascularisation as patients with symptomatic myocardial ischaemia.

References


the following electronic only articles are published in conjunction with this issue of Heart.

Rheumatic involvement of all four cardiac valves
K Jai Shankar, P K Jaiswal, K M Cherian

Rheumatic involvement of all four heart valves is rare. A 35 year old woman presented with gradually progressive exertional dyspnoea for the preceding 10 years. On evaluation she was in atrial fibrillation with congestive heart failure. Clinical examination found evidence of stenosis of the mitral aortic and tricuspid valves with a history of rheumatic fever in childhood. Transthoracic echocardiography showed the involvement of all four cardiac valves. Few reports are available in the literature describing rheumatic quadrivalvar damage. Operator awareness of possible rheumatic involvement of all four valves is essential for appropriate diagnosis.

(Heart 2005; 91:e50) www.heartjnl.com/cgi/content/full/91/6/e50

Fatal infection after rapamycin eluting coronary stent implantation
F Alfonso, R Moreno, J Vergas

Septic complications after coronary stenting are extremely rare. The occurrence of cardiac related sepsis after rapamycin eluting stent deployment has not been previously reported. The potential role of drug eluting stents in locally blunting the innate response to bacterial agents is discussed.

(Heart 2005; 91:e51) www.heartjnl.com/cgi/content/full/91/6/e51