Dobutamine- vs exercise-induced ST segment elevation early after Q wave myocardial infarction

Prediction of functional recovery after revascularization

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Aims The association between stress-induced ST elevation and functional recovery following revascularization after myocardial infarction remains unclear. We assessed the relative accuracy of dobutamine- and exercise-induced ST elevation in Q wave leads in predicting functional recovery following revascularization, and we investigated the relationship of ST elevation to different wall motion responses to dobutamine.

Methods and Results Thirty-nine patients underwent dobutamine stress echo and exercise test 8 ± 2 days after Q wave myocardial infarction. All patients underwent angio-

Key Words: Acute myocardial infarction, dobutamine stress echo, exercise treadmill test, ST segment elevation.

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exercise- and dobutamine-induced ST segment elevation on infarct-related electrocardiographic leads in predicting functional recovery after revascularization early after Q wave myocardial infarction, and (b) to investigate the relationship of dobutamine- and exercise-induced ST segment elevation to contractile reserve and to different wall motion responses to dobutamine. For this purpose, we studied a series of patients with a first Q wave myocardial infarction who underwent both dobutamine stress echo and exercise treadmill test pre-discharge and underwent complete revascularization.

Methods

Patients

Between January and October 1998, 68 patients were enrolled in a research protocol to assess the value of pre-discharge dobutamine stress echo and exercise treadmill test in functional evaluation and risk stratification after Q wave myocardial infarction. These patients fulfilled the following inclusion criteria: (a) first episode of myocardial infarction diagnosed on the basis of typical chest pain lasting >30 min, ST elevation ≥0.1 mV in at least two leads and an increase in plasma creatine kinase and isoenzyme MB to at least twice the maximum normal limit; (b) absence of clinical history suggesting prior myocardial infarction and absence of Q waves or left bundle branch block in the electrocardiogram; (c) intravenous thrombolysis within 6 h of onset of chest pain; (d) absence of life-threatening arrhythmias and significant left ventricular dysfunction (rales, elevated jugular venous pressure, cardiomegaly and S₃ gallop) during the in-hospital course. From the initial cohort, 43 patients underwent revascularization by means of percutaneous transluminal coronary angioplasty or coronary artery bypass surgery. Four patients were excluded during the in-hospital period because of contraindications to the administration of dobutamine and/or inadequate echocardiographic study. The final study group, therefore, consisted of 39 patients (33 men, 6 women, with a mean age of 60 ± 8 years, range 45–76) who underwent revascularization and follow-up echocardiographic study. The myocardial infarctions were located electrocardiographically as anterior (leads V₁ to V₄) and inferolateral (leads II, III, aVF, I, aVL, V₅ and V₆). Standard antianginal medications, including short- and long-acting preparations, were not withheld prior to the examinations, except for beta-blocking agents, which were withdrawn 48 h before the stress echo study. The protocol was approved by the Ethics Committee of the Hospital.

Dobutamine–atropine infusion protocol and follow-up echocardiographic study

All patients underwent pre-discharge dobutamine stress echo at a mean of 8 ± 2 days after admission. Dobutamine was administered intravenously by an infusion pump, starting at a rate of 5 µg · kg⁻¹ · min⁻¹ and increasing every 3 min to 10, 15, 20, 30, up to a maximum of 40 µg · kg⁻¹ · min⁻¹ under continuous electrocardiographic and echocardiographic monitoring. Blood pressure was measured at baseline and at the end of each stage. When no end-point was reached, atropine (up to 1 mg) was coadministered[7]. Echocardiographic end-points, which were considered as criteria for test positivity, were defined as follows: (a) new abnormality of wall motion or myocardial thickening in a region with normal resting function (i.e. normokinesia becoming hypokinesia, akinesia or dyskinesia); (b) worsening of rest dyssynergy (i.e. hypokinesia becoming akinesia or dyskinesia). However, an akinetic segment at rest becoming dyskinetic was not considered as a positive response because it could be due to mechanical phenomena, such as passive stretching[8]. Other end-points requiring termination of the test were the following: peak dobutamine and atropine dose; achievement of 85% of target heart rate; severe angina and/or diagnostic ST segment changes; intolerable symptoms; hypertension (systolic blood pressure >220 mmHg, diastolic blood pressure >120 mmHg); hypotension (relative or absolute <30 mmHg decrease in blood pressure); ventricular arrhythmias (ventricular tachycardia; frequent polymorphous premature ventricular beats)[9]. ST segment elevation in infarct-related leads was not considered as a reason for termination of the stress echo study[5,6].

A 12-lead electrocardiogram was monitored throughout the study and recorded at a paper speed of 25 mm . s⁻¹ every 2 min. For the accurate comparison of the electrocardiogram during dobutamine stress echo and exercise stress test in the same individual, we carefully avoided displacement of the precordial leads to a higher or lower intercostal space. For this purpose, the exact locations in the chest were marked and the electrodes interfering with the transducer at the time of image acquisition (V₆, V₅ or V₄ in most cases) were removed and repositioned when necessary.

Follow-up echocardiograms were obtained in all patients at 7 ± 4 weeks after coronary angioplasty or bypass surgery. Segmental functional recovery was defined as an improvement of ≥ 1 grade in wall motion score from baseline to follow-up. Changes in global left ventricular function from pre-discharge baseline echo were assessed using the wall motion score index. For purposes of individual patient analysis, functional recovery was defined as an improvement of ≥ 1 grade in ≥ 2 segments. Resting echo images were analysed and compared by an observer blinded to all other data.

Exercise testing

All patients underwent a submaximal or symptom-limited exercise test, using a computer-assisted system (MAX-1, Marquette Electronics) according to the Bruce protocol was approved by the Ethics Committee of the Hospital.
protocol. The test was performed 24 h after the stress echo study. Beta-adrenergic blocking agents were discontinued 72 h before the test. Twelve-lead electrocardiogram and blood pressure were recorded at rest and at the end of each stage, at peak exercise and every 2 min into recovery. The test was terminated in the presence of one of the following criteria: (a) achievement of 85% of maximum target heart rate (calculated as 220 minus age), (b) ST segment depression ≥1 mm, (c) ST segment elevation in non-infarct-related leads ≥1 mm, and (d) significant arrhythmias, hypotension, chest pain, dyspnoea, or fatigue. ST segment elevation in infarct-related leads was not considered in itself as a reason for termination of the test[2].

Echocardiographic analysis

Two-dimensional echocardiographic images were recorded at baseline, at the end of low and peak dobutamine dose and during recovery (four-stage protocol), using a Hewlett-Packard Sonos 2500 ultrasound machine equipped with pharmacological protocol software and quad-screen display format. The studies were compared off-line in a cine-loop mode, side by side, by two independent investigators (N.E.M. and F.I.P.) blinded to all clinical, exercise and angiographic data. Differences in grading were resolved by consensus. Segmental wall motion was assessed using the 16-segment model[10]. Each segment was semi-quantitatively graded as follows: 1=normal; 2=hypokinetic, marked reduction of endocardial motion and thickening; 3=akinetie, absence of inward motion and thickening and 4=dyskinetic, paradoxical wall motion in the left ventricular centre in systole. Wall motion score index at baseline was obtained by dividing the sum of individual segmental scores by the total number of interpretable segments. Infarct zones were defined according to the theoretical maximal risk area[11,12]. The response of left ventricular segments with abnormal resting function to dobutamine was classified into five types: (1) biphasic response (improvement at low dose — up to 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) — with worsening at a higher dose); (2) sustained improvement (improvement in wall motion at low dose that persisted at maximum dose); (3) worsening (deterioration of resting function during dobutamine infusion without previous improvement); (4) no change in wall motion at any stage, and (5) dyskinesis (hypokinetic or akinetic segment becoming dyskinetic). The latter was added to the four classical types of responses in order to examine the relationship between ST segment elevation and dobutamine-induced dyskinesis. Myocardial viability in the infarct zone was defined as an improvement in regional function of ≥1 grade at low dose dobutamine (up to 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \)) i.e. a hypokinetic segment becoming normal or an akinetic segment becoming hypokinetic. Remote ischaemia was defined as the development of new dyssynergy in a segment not directly adjacent to the infarct area.

Electrocardiographic analysis

ST segment elevation during dobutamine stress echo or exercise test was measured manually and was defined as a shift of ≥1 mm, 80 ms after the J point in more than two contiguous infarct-related leads compared to baseline. Abnormal Q waves were defined as ≥0.04 s in duration and ≥25% of the R wave in depth. In order to assess the relationship between the amount of ST elevation and the number of myocardial segments showing functional recovery, we used both dobutamine stress echo and exercise test to calculate the total number of infarct-related leads with ST segment elevation. All electrocardiograms were analysed by two observers blinded to clinical, echocardiographic or angiographic data (M.K.K. and M.E.M.).

Angiography and revascularization procedures

The decision to perform revascularization was taken by the cardiologist in charge of the patient. ST segment elevation on either dobutamine stress echo or exercise test was not used as a criterion for intervention. Selective coronary angiography and left ventriculography were performed at a mean of 15 ± 5 days after admission, using the Judkins technique. Coronary artery stenosis was considered significant if the lumen diameter was less than 50%. The TIMI flow grade of the infarct-related artery was also evaluated[13]. Revascularization was performed at 4 ± 2 weeks after the episode of myocardial infarction. None of the revascularized patients had recurrent angina at follow-up.

Statistical analysis

Data are expressed as mean ± SD. The agreement between dobutamine stress echo and exercise stress test
was assessed by calculating the kappa value. The chi-square test was applied to compare proportions between the different groups. Correlation between numeric data was calculated by Pearson’s correlation coefficient. To assess the diagnostic accuracy of ST elevation and contractile response to dobutamine in predicting functional recovery, we calculated sensitivity, specificity, accuracy and predictive value according to the standard definitions. A P value <0.05 was considered significant.

Results

Dobutamine–atropine stress echo and exercise treadmill test data

The peak rate–pressure product during dobutamine stress echo increased from 8790 ± 1030 to 18 900 ± 3702 (P<0.001). No major side effects occurred during the infusion of dobutamine and atropine. In one patient the test was terminated prematurely owing to sudden development of junctional rhythm. This patient was included in the final analysis. The most frequent reason for termination of the test was the development of new wall motion abnormalities (biphasic response in 12 patients (31%), worsening in three patients (8%) and dyskinesis in one patient (3%)). Viability within the infarcted area was seen in 28 patients (72%), whereas remote ischaemia was seen in 10 patients (26%). The peak rate–pressure product was higher with exercise than with dobutamine (19 140 ± 4027 vs 18 900 ± 3701), although the difference was not statistically significant (P=ns). Thirty-two patients (82%) had a positive exercise treadmill test. ST segment depression occurred in 23 patients (59%), typical chest pain in 17 (44%), dyspnoea in five (13%) and hypotension in two (5%).

Nineteen patients (49%) developed ST segment elevation in the infarct-related leads during dobutamine infusion, in a total of 58 infarct-related leads (there was a deterioration of ≥1 mm compared to baseline in seven of these patients). ST segment elevation also occurred in 19 patients (49%) during exercise, in a total of 68 infarct-related leads. There was a significant agreement between the two tests regarding the occurrence of ST segment elevation, which is illustrated in Fig. 1. Concordant findings regarding the presence or absence of ST elevation were encountered in 31 patients. There were no significant differences in the peak heart rate achieved by dobutamine stress echo and exercise stress test between patients with concordant and discordant findings (129 ± 10 vs 132 ± 12 on dobutamine and 134 ± 11 vs 130 ± 8 on exercise, P=ns).

Table 1 shows the clinical characteristics of the patients, divided into four groups: those with (n=19) and without (n=20) ST segment elevation during dobutamine stress echo and those with (n=19) and without (n=20) ST segment elevation during exercise. There were no significant differences in age, sex, peak creatine kinase level, the site of myocardial infarction, the incidence of baseline ST elevation and the peak

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*P<0.001, **P<0.006, §P<0.007.
rate–pressure product. Baseline wall motion score index was lower in patients with ST segment elevation, although the difference was not significant.

**Angiographic findings**

Single-vessel disease was found in 20 patients (51%), two-vessel disease in 14 (36%) and three-vessel disease in five (13%). The TIMI flow grade of the infarct-related artery was nil in nine patients (23%), one in 10 patients (26%), two in three patients (8%) and three in 17 patients (43%). Angioplasty was performed in 32 patients and bypass surgery in seven. None of the patients required repeat intervention during the follow-up period. There were no significant differences between patients with and without ST segment elevation with respect to the incidence of multivessel disease, total occlusion or the TIMI flow grade of the infarct-related artery (Table 1).

**Correlation of ST segment elevation with different responses to dobutamine**

A biphasic response was more frequently observed in patients with ST segment elevation (11/19 vs 1/20, \(P<0.001\)) with dobutamine and 10/19 vs 2/20, \(P<0.006\) with exercise). The other wall motion responses to dobutamine were observed with similar frequency in patients with and without ST segment elevation. The incidence of remote ischaemia was also similar in the two groups (Table 1).

**Functional recovery following revascularization**

The baseline asynergy score was higher in those patients with, compared to those without, ST segment elevation during exercise (1·68 ± 0·2 vs 1·31 ± 0·3, \(P<0.007\)). Functional recovery at follow-up was detected in 22 patients (56%). Patients with dobutamine-induced ST segment elevation demonstrated a significant improvement in the asynergy score from baseline (1·25 ± 0·2 from 1·56 ± 0·2, \(P<0.001\)). Similar improvement was also observed in patients with exercise-induced ST segment elevation (1·25 ± 0·2 from 1·68 ± 0·2, \(P<0.004\)). In contrast, there was no significant improvement in the wall motion score index in patients without dobutamine- and exercise-induced ST segment elevation (1·25 ± 0·3 from 1·34 ± 0·3, \(P=ns\) and 1·2 ± 0·3 from 1·31 ± 0·3, \(P=ns\), respectively). Figures 2 and 3 illustrate the difference in the wall motion score index between patients with and without ST segment elevation during dobutamine stress echo and exercise stress test, respectively.

We also investigated the relationship between the number of leads showing ST segment elevation and the amount of myocardium demonstrating functional recovery, as represented by the difference between the baseline and follow-up asynergy score. There was a very good correlation between the number of leads with dobutamine-induced ST segment elevation and the difference in asynergy score \((r=0·45, P<0·005)\). A more significant correlation was found between the number of leads with exercise-induced ST segment elevation and the difference in asynergy score \((r=0·7, P<0·001)\) (Fig. 4). The sensitivity, specificity, accuracy and predictive value of the various parameters in predicting functional recovery are shown in Table 2. We found that a biphasic response during dobutamine stress echo carried a higher predictive value than ST elevation alone (100% vs 89%). When ST segment elevation occurred in both tests, or in more than three leads during the exercise test alone, its predictive value was similar to that of a biphasic response.

Finally, we investigated the diagnostic accuracy of ST segment elevation in predicting functional recovery in
anterior vs inferolateral infarctions (Table 3). The sensitivity of ST elevation in the anterior leads was higher compared with the overall population (90% vs 77%). Similarly, ST elevation in the anterior leads was more accurate in predicting functional recovery compared with the inferolateral leads (92% vs 68%), whereas their positive predictive values were comparable.

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sensitivity of ST elevation in the anterior leads was higher compared with the overall population (90% vs 77%). Similarly, ST elevation in the anterior leads was more accurate in predicting functional recovery compared with the inferolateral leads (92% vs 68%), whereas their positive predictive values were comparable.

Discussion

To our knowledge, this is the first study to compare the accuracy of ST segment elevation during pre-discharge dobutamine stress echo and exercise treadmill testing in predicting functional recovery early after acute myocardial infarction. The main findings are that
dobutamine- and exercise-induced ST segment elevation are strongly associated with functional recovery following revascularization, and that there is a significant correlation between the extent of electrocardiographic changes and the amount of functional recovery. Furthermore, the biphasic response during dobutamine stress echo, the development of ST elevation in both tests and the development of ST elevation in more than three leads during exercise stress test, are the most accurate methods of predicting functional recovery following revascularization (100%).

**Stress-induced ST elevation and myocardial viability**

The classical link between exercise-induced ST elevation in leads with Q waves and abnormal left ventricular wall motion and/or left ventricular aneurysm was supported by a number of investigators in the pre-thrombolytic era[14-16]. Dunn et al.[17], found evidence of peri-infarction ischaemia and/or abnormal ventricular wall motion in patients with exercise-induced ST elevation. These findings have been challenged in recent years by a number of studies, which extended the role of electrocardiography in the assessment of myocardial viability following myocardial infarction. Margonato et al.[2] reported an association between exercise-induced ST elevation and residual viability within the infarcted myocardium. This finding is in line with a recent experimental study[18], which suggests that stress-induced ST elevation in infarct-related leads, is related to acute ischaemia adjacent to a transmural necrosis. Therefore, ST elevation over the infarct scar may be triggered by critical ischaemia of subendocardial cells, a mechanism that could explain the relationship between ST elevation and the biphasic response. Studies performed early after acute myocardial infarction suggest that dobutamine-induced ST elevation identifies patients with a higher frequency of late functional improvement[5,6]. The mechanism of late functional improvement, however, may be different in patients with and without revascularization, whereas restoration of flow in persistently hypokinetic segments may lead to greater functional improvement. Therefore, the significance of stress-induced ST elevation in patients undergoing complete revascularization may be different.

**Incidence of ST elevation and comparison with previous studies**

Our results show that there is a significant agreement between the two tests as regards the inducibility of ST elevation ($k = 0.589$, $P<0.001$). The prevalence of ST elevation was the same for both modalities (48%). This value is slightly lower compared with previous studies which reported figures between 53% and 68%[3,6]. This discrepancy has already been reported[9], and may be due to the fact that all of our patients received intravenous thrombolysis, which can reduce the extent of wall motion abnormalities and possibly the incidence of ST elevation[20,21]. In our study, the incidence of exercise-induced ST elevation was higher in patients with greater baseline left ventricular dysfunction. Interestingly, patients with dobutamine-induced ST elevation did not have a higher baseline wall motion score index than those without. This finding is in line with the results of Elhendy et al.[22], who reported comparable baseline left ventricular function in patients with and without dobutamine-induced ST elevation early after myocardial infarction and prior to bypass surgery. It is possible that, in patients with a high baseline asynergy score, ST segment elevation may be preceded by echocardiographic end-points such as worsening of wall motion abnormalities, a mechanism which could explain the better correlation between exercise-induced ST segment elevation and functional recovery compared with dobutamine-induced ST elevation in our study. With regard to the baseline angiographic parameters, we found no relationship between ST segment elevation and TIMI flow grade, total occlusion of the infarct-related artery or the number of stenosed vessels.

**Correlation between stress-induced ST elevation and functional recovery**

We found a significant correlation between dobutamine- and exercise-induced ST elevation and functional recovery following revascularization. A similar observation has been reported by other investigators[3,5,6] in a number of studies including patients with and without revascularization. This similarity of findings may appear surprising, because the extent of functional improvement following revascularization may be greater than in the case of spontaneous recovery and may, therefore, have a different association with stress-induced ST elevation. However, possible explanations for this agreement could be the existence of myocardial stunning in our patients following bypass surgery, or stunning due to silent ischaemia, which could not be excluded since no repeat coronary angiogram was performed.

In an attempt to quantify the extent of ST elevation, we also assessed the relationship between the number of leads showing dobutamine- and exercise-induced ST elevation, with the degree of functional recovery as represented by the difference in wall motion score index. There was a significant correlation between the latter and the extent of dobutamine-induced ST elevation ($r=0.45$, $P<0.005$), and a more significant correlation with the extent of exercise-induced ST elevation ($r=0.7$, $P<0.001$). The relationship between the extent of ST elevation induced by stress and myocardial function has been previously reported[10], but it was defined as the difference in voltage from the J point rather than the number of affected leads. We elected to investigate the relationship between the ‘horizontal’ extent of ST...
elevation, as represented by the number of affected leads, and the functional improvement following revascularization. We arbitrarily set our cut-off point at three leads, as this number usually represents the minimum number of affected leads for inferior infarcts. We found that the occurrence of ST elevation in both tests or in more than three leads during exercise stress test alone, accurately predicts functional recovery (positive predictive value of 100%), whereas dobutamine-induced ST elevation in more than three leads carries a predictive value of 75%. Bearing in mind that a biphasic response in our study carried a higher predictive value than ST elevation alone, the previous result was not really surprising. In a high proportion of our patients, dobutamine stress echo was terminated as echocardiographic end-points were reached before the development of ST elevation. Our findings by no means reduce the value of electrocardiographic monitoring during dobutamine stress echo.

The overall sensitivity of ST elevation in predicting functional recovery in our study was slightly higher than that reported by Piéard et al.[5] (77% vs 69%) and by Ellhendy et al.[6] (77% vs 74%). Minor differences were also observed with regard to the accuracy and predictive values. These findings could be explained by the fact that previous studies included revascularized and non-revascularized patients. The difference in the study populations could also account for the higher predictive value of the biphasic response in our report. Finally, the diagnostic accuracy of ST elevation was higher in the anterior than the inferior leads, a finding which is in line with a previous report[8]. ST elevation in the inferolateral leads was as specific as in the anterior leads; however, the higher rate of false-negative results in this myocardial territory may account for the low sensitivity.

**Limitations of the study**

Our study has several limitations. We excluded patients with significant left ventricular dysfunction during the in-hospital course. In such a population, studies of myocardial viability are very important; however, the clinical management of these patients was initially more aggressive, therefore, their inclusion in our study was not justified on ethical grounds. The decision to perform revascularization procedures was taken by the individual cardiologist and not in a randomized fashion. However, there are several ethical considerations in performing randomized studies in such a group of patients, since a number of clinical factors can influence decision making and the mode of treatment. The time of follow-up may not be sufficient to detect full recovery of function, owing to the existence of stunning in the reperfused region for up to 6 months[23]. Left ventricular function was evaluated by a semiquantitative method using the wall motion score index, and not by radionuclide or quantitative angiographic measurements of ejection fraction. However, the usefulness of ejection fraction as an end-point in thrombolytic therapy has been challenged[34], and is not as sensitive a method of assessment as regional wall motion abnormalities induced by the infusion of dobutamine.

**References**


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