The grade of worsening of regional function during dobutamine stress echocardiography predicts the extent of myocardial perfusion abnormalities

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Abstract

Aim—To evaluate the angiographic, myocardial perfusion, and wall motion abnormalities in patients with severe compared with mild worsening of regional function during dobutamine stress echocardiography (DSE) for evaluation of myocardial ischaemia.

Methods—147 patients with significant coronary artery disease and new or worsening wall motion abnormalities during DSE were enrolled. Left ventricular function was evaluated using a 16 segment/4 grade score model where 1 = normal and 4 = dyskinesis. Simultaneous sestamibi SPECT myocardial perfusion imaging was performed in all patients.

Results—Severe worsening of regional function (an increase in wall motion score of two grades or more in $\geqslant 1$ segment) was detected in 37 patients, while 110 patients had mild worsening (an increase in wall motion score of no more than one grade in $\geqslant 1$ segment). Patients with severe worsening of regional function had more stenotic coronary arteries (2.31 (0.8) *v* 1.97 (0.8) (mean (SD)) ($p < 0.05$), a higher prevalence of left anterior descending coronary artery disease (95% *v* 73%) ($p < 0.05$), a higher resting wall motion score index (1.71 (0.42) *v* 1.51 (0.40) ($p = 0.01$), and more stress perfusion defects (3.8 (1.5) *v* 2.8 (1.5) ($p < 0.001$) compared with patients with mild worsening. Multivariate analysis identified the number of stress perfusion defects ($p < 0.005$, $\chi^2 = 8.8$) and the number of ischaemic segments on echocardiography ($p < 0.05$, $\chi^2 = 4.3$) as independent variables associated with severe worsening of regional function.

Conclusions—The grade of worsening of regional function during DSE predicts the underlying extent of myocardial perfusion abnormalities. The occurrence of severe worsening of regional function is associated with variables known to predict worse prognosis in patients with coronary artery disease.

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Keywords: coronary artery disease; myocardial perfusion; ventricular function; echocardiography

Stress induced left ventricular dysfunction is a specific echocardiographic sign of myocardial ischaemia.[1 2] Valuable data obtained from pharmacological stress testing are not restricted to the mere diagnosis of significant coronary artery disease. The extent of myocardial perfusion and wall motion abnormalities also identifies a subset of patients at a higher risk for cardiac events.[3–6] Therefore, the study of the correlation between stress test variables and known markers of poor prognosis is important in improving our understanding of the functional significance of any abnormalities detected. Worsening of regional function during dobutamine stress echocardiography (DSE) by one grade or more provides an accurate index for the diagnosis of coronary artery disease.[2] However, coronary angiographic and myocardial perfusion abnormalities in patients with worsening by two grades or more have not been evaluated. Although this pattern may theoretically represent severe ischaemia, such a correlation remains speculative. It is not known whether these patients have more severe coronary artery disease or more extensive myocardial perfusion abnormalities than those who develop worsening of regional function by only one grade. In this study we evaluated the clinical features and coronary angiographic, myocardial perfusion, and wall motion abnormalities in patients with severe compared with mild worsening of regional function during DSE.

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Methods

PATIENT SELECTION

The study population comprised 147 patients with suspected myocardial ischaemia and limited exercise capacity who underwent DSE with simultaneous sestamibi SPECT and fulfilled the following criteria:

- a positive DSE study defined as worsening of $\geqslant 1$ grade in $\geqslant 1$ left ventricular segment
- significant coronary artery disease detected by coronary angiography within three months of the dobutamine stress test
- absence of severe valvar heart disease, heart failure, or left bundle branch block.

Mean (SD) age was 59 (10) years. There were 108 men and 39 women. Ninety five patients (65%) had a previous Q wave myocardial infarct. Seventy nine patients (54%) had typical anginal complaints, whereas 35 (24%) had atypical or non-cardiac chest pain. Thirty

three patients (22%) were referred for routine functional evaluation after myocardial infarction.

DOBUTAMINE STRESS TEST

Dobutamine was infused through an antecubital vein starting at a dose of 5 followed by 10 μg/kg/min (three minute stages), increasing by 10 μg/kg/min every three minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given to patients not achieving 85% of age predicted maximum heart rate, and dobutamine infusion was continued. A three lead ECG (leads I, II, and III) was monitored continuously and a 12 lead ECG was recorded every minute. Cuff blood pressure was measured at rest and every three minutes during stress. The test was interrupted if severe chest pain, ST segment depression > 0.2 mV, significant ventricular or supraventricular arrhythmia, hypertension (blood pressure ⩾ 240/120), systolic blood pressure fall > 40 mm Hg, or any intolerable side effect regarded as being caused by dobutamine occurred during the test. Metoprolol (1–5 mg) was used intravenously to reverse the effects of dobutamine if they did not revert quickly.

STRESS ECHOCARDIOGRAPHY

Echocardiographic images were acquired from the standard views at rest and during stress and recovery. The left ventricular wall was divided into 16 segments and scored using a four point scale, where 1 = normal, 2 = hypokinesis, 3 = akinesis, and 4 = dyskinesis. Ischaemia was defined as new or worsening wall motion abnormality. As we have previously concluded, ischaemia was not considered if akinetic segments at rest became dyskinetic during stress without improvement at low dose dobutamine.[7] Wall motion score index was derived by dividing the sum of the scores of the 16 segments by 16. The echocardiograms were recorded on video tapes and digitised on optical disk. Images were compared side by side in quad screen format by two independent observers without the knowledge of the patients' clinical, scintigraphic, or angiographic data. In case of disagreement, a majority decision was achieved by a third investigator. The inter- and intraobserver agreement for DSE assessment in our laboratory are 91% and 92%, respectively.[8]

SPECT IMAGING

Approximately one minute before the termination of the stress test, an intravenous dose of 370 MBq of sestamibi was given. Stress images were acquired one hour after termination of the test. For resting studies 370 MBq of sestamibi were injected at least 24 hours after the stress study.[9] For each study we defined six oblique (short axis) slices from the apex to the base and three sagittal (vertical long axis) slices from the septum to the lateral wall. Each of the six short axis slices was divided into eight equal segments. The interpretation of the scan was performed semiquantitatively by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical, echocardiographic, or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in two or more contiguous segments or slices. This was considered diagnostic of ischaemia. A fixed perfusion defect was defined as a perfusion defect on stress images in two or more contiguous segments or slices that persisted on resting images.

SEGMENTAL MATCH OF SPECT AND ECHOCARDIOGRAPHIC IMAGES

Echocardiographic and scintigraphic images were matched into six major segments: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical. To assess the severity of perfusion abnormalities, each of the six major left ventricular segments was scored using a four grade score method (0 = normal, 1 = slightly reduced, 2 = moderately reduced, 3 = severely reduced or absent uptake). Perfusion score was derived by the summation of the score of the six myocardial segments for rest and stress images. Ischaemic score was obtained by subtracting rest from stress score. Rest (fixed perfusion defect) score was considered as infarction score.

CORONARY ANGIOGRAPHY

Coronary angiography was performed within three months from the dobutamine stress test. Lesions were quantified as previously described.[10] In brief, the 35 mm films were analysed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, Maastricht, Netherlands). For edge detection, a region of interest of 512 × 512 pixels was selected and digitised using a high fidelity charge coupled device video camera. The vessel diameter was determined by computing the shortest distance between the right and left contours. A computer derived estimation of the original arterial dimension was used to calculate the interpolated reference diameter. Significant coronary artery disease was defined as a diameter stenosis of ⩾ 50% in one or more major epicardial arteries.

STATISTICAL ANALYSIS

Unless specified, data are presented as mean (SD). The χ^2 test was used to compare differences between proportions. The Student *t* test was used for analysis of continuous data. Probability (p) values < 0.05 were considered statistically significant. Stepwise logistic regression models were fitted to identify independent predictors of severe worsening of regional function.

Results

DOBUTAMINE STRESS TEST

Dobutamine–atropine induced a significant increase of heart rate, systolic blood pressure, and rate–pressure product (table 1). Atropine was given to 70 patients (48%). Angina occurred in 85 patients (58%). One hundred and twelve patients (76%) reached the target

Table 1 Clinical features of patients with severe (group A) and mild (group B) worsening of regional function during dobutamine stress echocardiography

Clinical features	*Group A (n = 37)*	*Group B (n = 110)*	*p Value*
Age (years)	61 (9)	59 (10)	0.2
Male	29 (78)	79 (72)	0.6
Previous myocardial infarct	29 (78)	66 (60)	0.07
Anterior	17 (46)	31 (28)	0.07
Inferior	12 (32)	35 (32)	0.9
History of hypertension	14 (38)	39 (35)	0.2
Drugs			
β Blockers	11 (30)	43 (39)	0.4
Calcium channel blockers	18 (49)	59 (54)	0.7
Nitrates	24 (65)	66 (60)	0.7
ACE inhibitors	19 (51)	44 (40)	0.3
Peak stress heart rate (beats/min)	136 (14)	134 (15)	0.4
Peak stress SBP (mm Hg)	130 (25)	136 (28)	0.2
Peak rate–pressure product	17 550 (3589)	18 183 (4062)	0.4
Maximum dobutamine dose (μg/kg/min)	37.6 (6.0)	38.4 (5.0)	0.4
Angina during the test	21 (57)	64 (58)	0.9
ST segment depression	14 (38)	42 (38)	1
ST segment elevation	16 (43)	25 (23)	0.03

Values are mean (SD) or n (%).
ACE, angiotensin converting enzyme; SBP, systolic blood pressure.

Table 2 Perfusion abnormalities assessed by SPECT imaging in patients with severe (group A) and mild (group B) worsening of regional function during dobutamine stress echocardiography

Perfusion variables	*Group A (n = 37)*	*Group B (n = 110)*	*p Value*
Number of stress perfusion defects	3.8 (1.5)	2.8 (1.5)	0.0009
Number of rest perfusion defects	3.0 (2.0)	2.0 (1.6)	0.001
Number of reversible perfusion defects	1.4 (1.3)	1.5 (1.4)	0.8
Stress defect score	8.5 (4.6)	6.8 (4.1)	0.05
Rest defect score	5.5 (3.8)	3.9 (3.3)	0.01
Reversible defect score	3.0 (2.5)	2.9 (2.7)	0.9
Regional defect score (rest)*	1.40 (0.9)	1.01 (0.8)	0.04
Regional defect score (stress)*	2.41 (1.3)	2.03 (1.5)	0.03
Regional defect score (ischaemia)*	1.01 (0.8)	1.02 (0.7)	0.9

Values are mean (SD). Data are derived using a 6 segment/4 grade score model.
*Data derived on segmental basis in myocardial regions with ischaemia at echocardiography matched with the corresponding regions at SPECT using the 6 segment model.

Table 3 Coronary angiographic variables in patients with severe (group A) and mild (group B) worsening of regional function during dobutamine stress echocardiography

Angiographic variables	*Group A (n = 37)*	*Group B (n = 110)*	*p Value*
Single vessel CAD	7 (19%)	37 (34%)	0.1
2 vessel CAD	12 (32%)	39 (35%)	0.9
3 vessel CAD	18 (49%)	34 (31%)	0.08
Multivessel CAD	30 (81%)	73 (66%)	0.1
Number of stenotic arteries (mean (SD))	2.31 (0.8)	1.97 (0.8)	0.04
LAD CAD	35 (95%)	80 (73%)	0.01
LCx CAD	24 (65%)	61 (55%)	0.3
Right CAD	26 (70%)	76 (69%)	0.9
Occluded related artery	14 (38%)	32 (29%)	0.4

CAD, coronary artery disease; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery.

heart rate (85% of the maximum exercise heart rate predicted for age and sex). The test was interrupted before reaching the target heart rate because of angina (17 patients), ST segment depression (five patients), and hypotension (five patients). Eight patients (5%) failed to reach the target heart rate despite the use of the maximum dobutamine and atropine dose. The test was not interrupted because of new or worsening wall motion abnormalities in any patient.

STRESS ECHOCARDIOGRAPHY

Ischaemia (new or worsening wall motion abnormalities) was detected in all patients, by the inclusion criteria.

Worsening of two grades or more in ⩾ 1 segment occurred in 37 patients (25%) during stress. These patients were identified as the group with severe worsening of regional function (group A). In group A patients, 49 segments were normal at rest and became akinetic and 15 segments were hypokinetic at rest and became dyskinetic during stress. Among the 29 patients with previous Q wave infarction in group A, worsening of two grades or more occurred in the distribution of infarct related artery in 15 patients and in the remote regions in 14 patients.

Group B identified the remaining 110 patients with mild worsening of regional function (a maximum of one grade of worsening in ⩾ 1 segment). In group B patients, 169 segments were normal at rest and became hypokinetic and 175 segments were hypokinetic at rest and became akinetic during stress.

Clinical features and haemodynamic data from the dobutamine stress tests in both groups are given in table 1. Patients from group A had a higher wall motion score index than patients from group B at rest (1.71 (0.42) *v* 1.51 (0.40), $p = 0.01$) and at peak stress (2.07 (0.5) *v* 1.70 (0.44), $p < 0.0001$) and a greater number of ischaemic segments (4.3 (2.2) *v* 3.1 (2.2), $p < 0.01$).

MIBI SPECT

All patients of group A had abnormal scans. Ischaemia (partially or completely reversible defects) was detected in 29 patients (78%), whereas eight patients (22%) had a fixed perfusion defect. Ischaemia was detected in 83 patients in group B (75%) whereas 24 patients had a fixed defect and three had normal scans. Perfusion defect scores and number of perfusion defects during stress and rest are presented in table 2. Patients from group A had a larger number of perfusion defects and a higher defect score at rest and with stress images, whereas the ischaemic score and the number of reversible defects did not differ between the groups.

CORONARY ANGIOGRAPHY

Coronary angiographic findings are presented in table 3. Patients from group A had a larger mean number of stenotic coronary arteries and a higher prevalence of left anterior descending coronary artery disease than patients from group B. There was a trend to a higher prevalence of multivessel disease and total occlusion of the related coronary arteries in group A but the difference not statistically significant.

PREDICTORS OF SEVERE WORSENING OF REGIONAL FUNCTION

Multivariate analysis of clinical, angiographic, echocardiographic, and scintigraphic variables included age, sex, history of hypertension, previous myocardial infarction, treatment with β blockers, peak heart rate, resting wall motion score index, number of ischaemic segments on the 16 segment echocardiographic model, presence of multivessel coronary artery disease, number of stenotic coronary arteries, number of segments showing perfusion abnormalities and perfusion defect scores, and the number of ischaemic segments on echocardiography (by the 16 segment model). Independent predictors of severe worsening of function were the number of myocardial segments with

perfusion abnormalities on stress images (using the six segment model) ($p < 0.005$, $\chi^2 = 8.8$) and the number of ischaemic segments on echocardiography ($p < 0.05$, $\chi^2 = 4.3$).

Discussion

This study shows that severe worsening of regional function, defined as an increase of regional wall motion score of ≥ 2 grades, occurs in patients who have a profile of functional and anatomical abnormalities known to be associated with worse outcome compared with patients with mild worsening of regional function. Patients with severe worsening had a larger number of stenotic coronary arteries, a higher prevalence of left anterior descending coronary artery disease, more severe resting left ventricular dysfunction, a larger number of ischaemic segments by echocardiography, and more severe stress and rest myocardial perfusion abnormalities. These functional abnormalities have been reported to be associated with worse prognosis.[3–5 11 12] The association between severe worsening of regional function and more severe resting myocardial perfusion and wall motion abnormalities can be explained in many ways. In patients with more severe resting wall motion abnormalities, ischaemic myocardial segments with transient dysfunction during stress may lack structural support owing to the presence of necrotic segments at the borders of the ischaemic myocardium and therefore the ischaemic segments bulge more significantly. Another explanation is that in the presence of extensive resting left ventricular dysfunction, collateral flow to the ischaemic myocardium through the necrotic myocardial segments may be impaired owing to the disruption of microvascular integrity in these necrotic regions[13] and therefore ischaemic myocardium shows a severe deterioration in function. Although the pattern of severe worsening of regional function is assumed to represent more severe ischaemia, the severity of reversible perfusion abnormalities was similar to that in patients with mild worsening of function. It is possible that in presence of severe ischaemia, resting perfusion is impaired and accordingly, a part of the fixed defect is actually representing ischaemia rather than infarction. This view is supported by our finding that patients with severe worsening of regional function had in addition a greater number of ischaemic segments by echocardiography. Another explanation is that in the presence of more severe impairment of resting perfusion—as was the case in patients with severe worsening of regional function—additional impairment of perfusion during stress may be underestimated.[14 15] Nevertheless, the extent of stress perfusion abnormalities was reported to be the most powerful scintigraphic predictor of prognosis.[4] In our study, the extent of stress perfusion defects was an independent predictor of severe worsening of function during DSE using multivariate analysis of clinical, angiographic, echocardiographic, and scintigraphic variables. The number of ischaemic segments by echocardiography was also an independent predictor of the occurrence of severe worsening of regional function, denoting a greater extent and severity of ischaemia in these patients. This is not surprising as both the extent and severity of inducible wall motion abnormalities are expected to be related to the severity of the underlying coronary artery disease. The higher prevalence of dobutamine induced ST segment elevation in patients with severe as opposed to mild worsening of regional function can be explained by the known association between ST segment elevation and more severe myocardial perfusion and wall motion abnormalities.[16]

THE EXTENT OF CORONARY ARTERY DISEASE

The extent of coronary artery disease as assessed by the mean number of stenotic arteries was greater in patients with severe worsening of regional function. This can be explained by more severe reduction in coronary flow reserve with more extensive coronary artery disease. Additionally, the impairment of flow to the ischaemic regions may be more profound in the presence of more extensive coronary artery disease owing to diminished flow reserve of the collateral arteries from the adjacent perfusion bed. Porter *et al* reported that in dogs with experimental single vessel stenosis, the extent of myocardial perfusion defects measured by myocardial contrast was significantly lower in the zone of the original stenosis than in the perfusion defect in the same area when a second stenosis was made in the vessel supplying the adjacent perfusion bed.[17] They concluded that collateral flow limits the spatial extent of inducible ischaemia within the risk area of single vessel stenosis. Restoring blood flow to one perfusion bed reduces the extent of perfusion abnormalities that can be induced in an adjacent stenosed bed. In our study, patients with more severe worsening of regional function had a greater prevalence of left anterior descending coronary artery disease, which is likely to be associated with the more severe impairment of perfusion in these patients owing to the relatively large amount of myocardium perfused by that artery. It has been reported that the association between left anterior descending coronary artery disease and reduced left ventricular function—as was the case in patients with severe worsening of regional function in this study—predicts a worse prognosis.[11 12]

LIMITATIONS OF THE STUDY

The use of 99m technetium sestamibi for evaluation of myocardial perfusion during a dobutamine stress test may result in an underestimation of flow heterogeneity induced by dobutamine, as shown in recent experimental studies.[14 15] However, the impact of these findings on the clinical value of sestamibi in conjunction with dobutamine has not been studied. Fifty four of our patients (37%) were receiving β blockers, which may reduce the severity of ischaemia. However, the absence of β blocker treatment was not a predictive factor of severe regional ischaemia in our study. The assessment of the severity of worsening of regional function was based on semiquantitative

visual evaluation. The evolution of an accurate echocardiographic method for quantitative evaluation of wall motion would allow better evaluation and grading of the severity of inducible left ventricular regional dysfunction. Visual assessment, however, remains the most widely used technique for evaluation of stress echocardiographic images.[2] Finally, follow up was not performed to assess the prognostic value of wall motion changes. However, the study showed a strong relation between severe worsening of regional function and the established markers of worse prognosis.

CLINICAL IMPLICATIONS

The occurrence of severe worsening of regional function during dobutamine stress echocardiography is associated with functional abnormalities indicating a higher risk of cardiac events than in patients with only mild worsening of regional function. The prognostic significance of the grade of worsening of regional function requires further evaluation.

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