

Altered myocardial perfusion during dobutamine stress testing in silent versus symptomatic myocardial ischaemia assessed by quantitative MIBI SPET imaging

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Abstract. The aim of the study was to compare the extent and severity of reversible underperfusion in silent versus painful myocardial ischaemia during the dobutamine stress test. A consecutive series of 85 patients with significant coronary artery disease and reversible perfusion defects on technetium-99m methoxyisobutylisonitrile single-photon emission tomography performed at rest and during high-dose dobutamine stress (up to 40 $\mu\text{g kg}^{-1} \text{min}^{-1}$) were studied. The left ventricle was divided into six segments. An ischaemic perfusion score was derived quantitatively by subtracting the rest from the stress defect score. Patients with multivessel disease had a higher ischaemic score (610 ± 762 vs 310 ± 411 , $P < 0.05$) and a higher number of reversible perfusion defects (2.1 ± 1.2 vs 1.1 ± 0.8 , $P < 0.01$) than patients with single-vessel disease. Typical angina occurred in 37 patients (44%) during the test. There was no significant difference between patients with and patients without angina with respect to age, gender, peak rate-pressure product, prevalence of previous myocardial infarction, diabetes mellitus, multivessel disease or number of stenotic coronary arteries. Stress, rest and ischaemic scores as well as the number and distribution of reversible defects were not different in patients with and patients without angina. Patients with angina more frequently had a history of typical angina before the test (43% vs 17%, $P < 0.01$) and ST-segment depression during the test (54% vs 25%, $P < 0.01$). It is concluded that in patients with coronary artery disease and ischaemia detected by dobutamine scintigraphy, the extent and severity of coronary artery disease and myocardial perfusion abnormalities are similar with or without angina during stress testing.

Key words: Silent ischaemia – Dobutamine stress test – Methoxyisobutylisonitrile single-photon emission tomography

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Introduction

Pharmacological stress testing with dobutamine is increasingly used for non-invasive diagnosis and evaluation of coronary artery disease in patients with suspected myocardial ischaemia and inadequate exercise capacity [1–8]. The induction of myocardial ischaemia with dobutamine infusion is mainly due to an increase in myocardial contractility and heart rate [9]. Dobutamine has also been reported to induce coronary blood flow heterogeneity [10]. Recent studies have shown that dobutamine stress testing in conjunction with technetium-99m methoxyisobutylisonitrile (MIBI) or thallium-201 single-photon emission tomographic (SPET) imaging is an accurate method for the diagnosis and localization of myocardial ischaemia and coronary artery disease based on the detection of reversible underperfusion [3–8]. The latter was shown to be more sensitive than angina and ST-segment depression [3–8]. However, the extent and severity of dobutamine-induced underperfusion have not been compared in the presence or absence of concomitant angina. Since recent studies have shown that the extent and severity of exercise-induced underperfusion have an impact on the prognosis [11, 12], identification of stress test variables associated with more severe perfusion abnormalities is a clinically relevant issue. Therefore, the aim of this study was to assess the extent and severity of dobutamine-induced perfusion abnormalities with or without angina during dobutamine stress testing in patients with coronary artery disease.

Materials and methods

Patient population. The study population was derived from a consecutive series of patients with limited exercise capacity referred to the nuclear imaging laboratory of our centre for diagnostic

evaluation of myocardial ischaemia. All patients underwent dobutamine stress testing in conjunction with ^{99m}Tc -MIBI SPET. Eighty-five patients were included according to the following criteria: (1) significant coronary artery disease defined as $\geq 50\%$ diameter stenosis of ≥ 1 major epicardial artery; (2) the occurrence of myocardial ischaemia during the test, defined as reversible perfusion defects on MIBI SPET in the distribution of ≥ 1 stenotic coronary artery; (3) absence of left ventricular hypertrophy or left bundle branch block. Mean age was 60 ± 10 years; 61 patients (72%) were males. A history and/or electrocardiographic evidence of a previous myocardial infarction were present in 47 patients (55%). A history of typical effort angina before the test was obtained in 24 patients (28%). On the day of the test, 65 patients (76%) were receiving anti-anginal medication, including beta blocker therapy in 44 cases (52%).

The patients were selected from among 125 patients with significant coronary artery disease with or without ischaemia on dobutamine MIBI study. Thus, the prevalence of a positive dobutamine MIBI study was 68% in our series of patients. Among the 40 patients with significant coronary artery disease and without ischaemia detected by dobutamine MIBI SPET, angina occurred in 14 (35%) during the test.

Dobutamine stress test. Dobutamine was infused through an antecubital vein starting at a dose of $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 3 min, then at $10 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 3 min, and increasing by $10 \mu\text{g kg}^{-1} \text{min}^{-1}$ every 3 min to a maximum of $40 \mu\text{g kg}^{-1} \text{min}^{-1}$. Atropine (up to 1 mg) was given in patients not achieving 85% of their age-predicted maximal heart rate [5]. The electrocardiogram was monitored throughout dobutamine infusion and recorded each minute. Cuff blood pressure was measured every 3 min. Significant ST-segment depression was defined as ≥ 1 mm horizontal or down-sloping depression 80 ms after the J point, below the resting baseline level. The test was interrupted if severe chest pain, ST-segment depression > 2 mm, ST-segment elevation > 2 mm in patients without previous myocardial infarction [13], significant ventricular or supraventricular tachyarrhythmia or a fall in systolic blood pressure of > 40 mmHg occurred during the test.

MIBI SPET imaging. Approximately 1 min before the termination of the stress test, an intravenous dose of 370 MBq of MIBI was administered. The acquisition of stress SPET images was started 1 h after MIBI injection. For the resting MIBI studies, 370 MBq was injected at least 24 h after the first study. Image acquisition and interpretation were performed according to a previously described protocol [5]. The left ventricular images were divided into six segments: anterior, septal (subdivided into the anterior and posterior septum), lateral, inferoposterior and apical. A persistent perfusion defect on both stress and rest imaging was classified as a fixed defect. A reversible defect was defined as a perfusion defect on stress images that partially or completely resolved at rest imaging. This was considered diagnostic of ischaemia. An experienced observer, unaware of patients' clinical and angiographic data, reviewed the images. The interpretation was semiquantitatively performed by visual analysis assisted by circumferential profile analysis. Each of the six left ventricular segments was scored on a four-grade classification where 0 = normal and 3 = severely reduced or absent uptake. The visual perfusion defect score was derived by the summation of the score of the six myocardial segments for both rest and stress imaging. The difference between the stress and rest scores (ischaemic score) was considered representative of the total amount of stress-induced underperfusion. The perfusion defect score was quantitatively calculated at rest and at stress imaging by measuring the area between the lower limit of

normal values (± 2 SD) and the actual circumferential profile in six short-axis slices.

Quantitative coronary angiography. All patients underwent coronary angiography within 3 months of dobutamine stress testing. Coronary lesions were quantified using a previously described method from our centre [14].

Statistical analysis. Unless specified, data are presented as mean values \pm SD. The chi square test and Fisher exact test were used to compare differences between proportions. Student's *t* test was used for analysis of continuous data. A *P* value < 0.05 was considered statistically significant.

Results

Haemodynamic response

Heart rate increased from 68 ± 13 to 132 ± 17 beats/min at peak stress ($P < 0.0001$) and systolic blood pressure from 133 ± 21 to 146 ± 31 mmHg ($P < 0.01$). Atropine was administered in 37 (44%) patients (mean dose = 0.6 mg). In 16 patients, the test was interrupted prematurely before reaching the maximal dose or the target heart rate. Reasons for premature termination of the test were angina in ten patients, ST-segment depression in three patients, hypotension in one patient and tachyarrhythmia in two patients. ST-segment depression occurred in 32 (38%). Thirty-seven patients (44%) developed typical angina during the test (symptomatic ischaemia group). The remaining 48 patients (56%) without angina during the test constituted the silent ischaemia group.

Demographic, haemodynamic and angiographic characteristics (Table 1)

There was no significant difference between patients with and patients without angina with respect to age, gender, prevalence of previous myocardial infarction, diabetes mellitus, hypertension or smoking. A history of typical effort angina was encountered more frequently in patients with angina during the test. Peak heart rate was significantly lower in patients with angina, whereas peak rate pressure product was not significantly different in the two groups. ST-segment depression occurred in 20 of 37 patients with and in 12 of 48 patients without angina (54% vs 25%, $P < 0.01$). Prevalence of multivessel disease, number of coronary arteries with significant stenosis, percentage diameter of the most severe stenosis and distribution of individual coronary artery stenoses were not significantly different between the two groups.

MIBI SPET results (Table 2)

There was no significant difference between patients with and patients without angina with respect to the number of myocardial segments with reversible defects, segments with perfusion defects on rest imaging, stress

Table 1. Clinical and angiographic data of patients with coronary artery disease and reversible perfusion defects with and without angina during dobutamine stress testing

	Angina (n=37)	Silent (n=48)
Age (years)	60±10	59±11
Male gender	26 (70%)	35 (73%)
Beta blocker therapy	22 (59%)	22 (46%)
History of angina pectoris	16 (43%)	8 (17%)*
Previous myocardial infarction	19 (51%)	28 (58%)
Diabetes mellitus	4 (11%)	6 (13%)
Multivessel disease	18 (49%)	22 (46%)
Number of stenotic arteries	1.7±0.8	1.7±0.9
% diameter of most severe stenosis	85%±16%	90±11%
>90% diameter stenosis in ≥1 artery	28 (75%)	39 (84%)
Peak heart rate (beats/min)	126±17	137±19*
Peak systolic blood pressure (mmHg)	156±32	138±31*
Peak rate pressure product	19,633±4,287	19,003±4,845
Peak dobutamine dose (µg kg ⁻¹ min ⁻¹)	40±0	39±4

* $P<0.01$ **Table 2.** Scintigraphic data of patients with coronary artery disease and reversible perfusion defects with and without angina during dobutamine stress testing

	Angina (n=37)	Silent (n=48)
Stress score	7.1±3.1	7.8±3.2
Rest score	3.5±2.0	4.0±2.3
Ischaemic score	3.2±1.6	3.9±2.3
Number of reversible defects	1.6±0.8	1.9±0.9
Number of fixed defects on rest imaging	1.2±1.0	1.2±1.1
Quantitative stress defect	1,426±1737	1,251±1354
Quantitative rest defect	1,063±1498	825±965
Quantitative ischaemic defect	472±630	458±671

Table 3. Distribution of reversible perfusion defects in the six major left ventricular segments in patients with and patients without angina during dobutamine stress testing

	Angina (n=37)	Silent (n=48)
Anterior	10 (27%)	15 (31%)
Septal anterior	8 (22%)	13 (27%)
Septal posterior	8 (22%)	11 (23%)
Inferoposterior	22 (59%)	28 (58%)
Lateral	5 (14%)	8 (17%)
Apex	6 (16%)	15 (31%)

Values are expressed as number and percentage (%) of patients with reversible perfusion defects in the specified region

perfusion defect score, rest score or ischaemic score by both visual and quantitative analysis. Exclusion of patients in whom the test was interrupted prematurely did not alter the comparable extent and severity of underperfusion with or without angina. The regional distribution of reversible defects was not different in the two groups (Table 3).

The perfusion scan of a patient with left anterior descending and right coronary artery stenosis and a reversible perfusion defect on dobutamine MIBI scintigraphy without angina or ST-segment depression during the test is shown in Fig. 1.

Patients with ST-segment depression

There was no significant difference between patients with and patients without ST-segment depression with respect to total number of reversible defects (1.8±1.0 vs 1.7±0.9) or quantitative ischaemic score (Table 4). Reversible perfusion defects without angina or ST-segment depression occurred in 36 patients (42%), whereas a combination of angina and ST-segment depression occurred in 20 patients (23%). The quantitative ischaemic score was not different in the groups with various combinations of angina and ST-segment depression (Table 4).

Extent and severity of ischaemia in single-vessel versus multivessel disease

Patients with multivessel disease (n=40) had a significantly higher number of reversible perfusion defects (2.1±1.2 vs 1.1±0.8, $P<0.01$), a significantly higher visual ischaemic score (4.7±2.5 vs 2.6±1.9, $P<0.01$) and a significantly higher quantitative ischaemic score (610±762 vs 310±411, $P<0.05$) than the 45 patients with single-vessel disease (Fig. 2).

Discussion

Evaluation of the extent and severity of reversible perfusion defects during stress testing is important for prognostic stratification of patients with coronary artery dis-

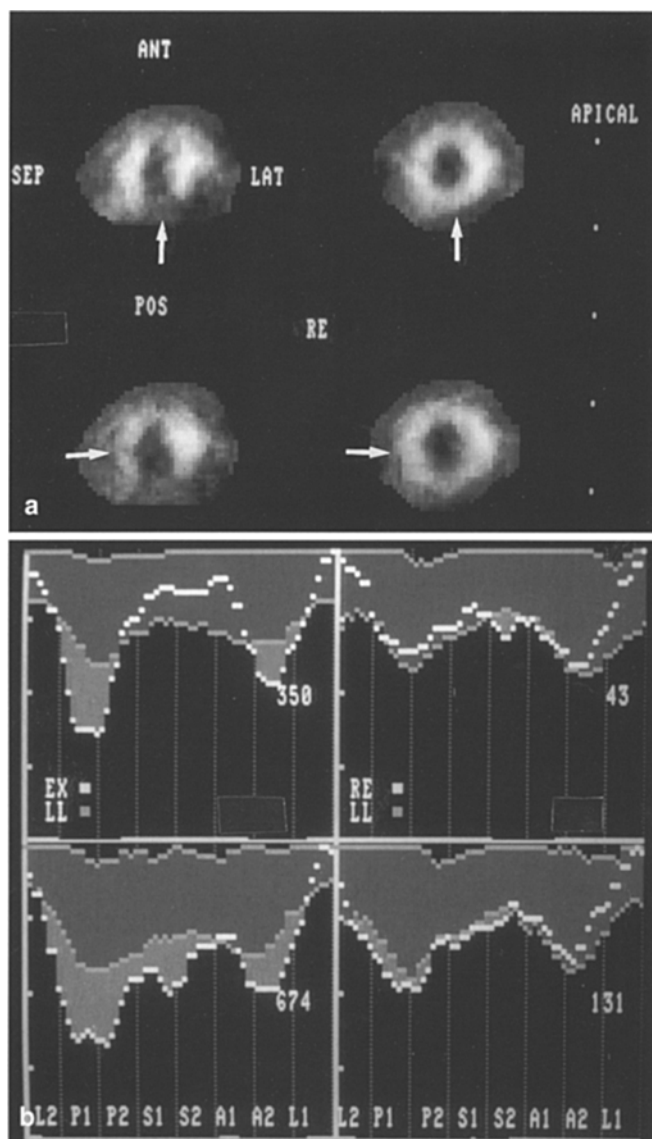


Fig. 1. **a** Dobutamine stress (left) and rest (right) MIBI perfusion scintigraphic images of a 55-year-old male with significant stenosis of the left anterior descending and right coronary arteries, from the apical short-axis level (the uppermost images are more apical). On the dobutamine stress images a large perfusion defect is observed in the posteroinferior wall (vertical arrows), and a small defect in the septum (horizontal arrows); these defects were shown to be reversible on the rest images. **b** Corresponding circumferential profile analysis. The patient had no symptoms or electrocardiographic changes during the test. *ANT/A*, Anterior; *SEP/S*, septum; *POS/P*, posterior; *LAT/L*, lateral. 1–2 is a clockwise division of the segments in the short-axis slices. *EX*, Stress; *RE*, rest; *LL*, lower limit

ease [11, 12]. In our study, the additional value of angina and/or ST-segment depression in patients with coronary artery disease and dobutamine-induced ischaemia manifested as reversible perfusion defects on MIBI SPET was evaluated. Our finding of a higher number of reversible perfusion defects and a higher ischaemic score in patients with multivessel versus single-vessel disease vali-

Table 4. Quantitative ischaemic perfusion defect score in patients with different combinations of angina and ST-segment depression during dobutamine stress testing

	Yes	No
ST depression	508±680 (32 pts)	430±479 (53 pts)
Combined ST depression and angina	441±614 (20 pts)	465±679 (65 pts)
ST depression and/or angina	534±699 (49 pts)	402±571 (36 pts)

pts, Patients

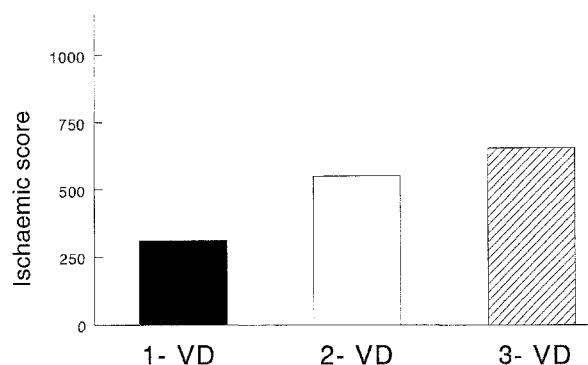


Fig. 2. Ischaemic perfusion defect score derived by quantitative analysis of the circumferential profile in patients with single-, two- and three-vessel disease (VD), showing a positive correlation between the defect extent and severity and number of stenotic coronary arteries

dates the use of perfusion scintigraphy in the assessment of the extent of myocardial ischaemia.

Our results show that in patients with significant coronary artery disease and myocardial ischaemia detected by dobutamine perfusion scintigraphy, the extent and severity of coronary artery disease and reversible underperfusion do not differ according to whether angina is or is not present during the test. Parameters of reversible underperfusion were also similar in patients who had both angina and ST-segment depression and in patients without this combination. Apart from a higher prevalence of a history of typical angina in symptomatic patients during the test, clinical characteristics were not different in patients with and patients without angina during the dobutamine stress test.

Comparison with previous studies

To our knowledge, this is the first study in which the extent and severity of underperfusion in silent and symptomatic ischaemia during dobutamine stress testing have been evaluated. Discordant results have been published on the functional significance of silent versus symptomatic ischaemia during exercise stress testing [15–20]. Re-

versible exercise-thallium defects were reported to be more extensive and severe in patients with compared to those without angina in the studies of Klein et al. [15] and Travin et al. [16], while others failed to demonstrate such a difference [17–20]. Klein et al. [15] concluded that the induction of pain is associated with substantially more functional abnormalities when patients with a broad spectrum of coronary artery disease are evaluated. They indicated that chest pain tends to lose its apparent value when its analysis is restricted to a coronary artery disease population with a greater pre-test likelihood of manifesting ischaemia.

Studies of left ventricular function

Various studies have compared the amount of abnormally contracting myocardium in silent and painful ischaemia during exercise stress testing using radionuclide ventriculography [21–23] or echocardiography [24–26]. Iskandrian and Hakki [21] and recently Nihoyannopoulos et al. [26] reported that angina correlated with more severe deterioration of regional function. Other studies have demonstrated a comparable segmental and global exercise-induced left ventricular dysfunction in silent and symptomatic ischaemia evaluated by exercise radionuclide ventriculography [22, 23] or echocardiography [24, 25]. We have recently shown that in patients with coronary artery disease, the extent and severity of dobutamine-induced left ventricular dysfunction assessed by echocardiography do not differ in patients with and patients without angina [27]. The results of this scintigraphic study confirm our previous findings. Although stress-induced wall motion abnormalities are highly specific for myocardial ischaemia, this study offers the following complementary advantages: (1) the quantitative assessment of perfusion compared to the visual semi-quantitative echocardiographic assessment of wall motion; (2) the ability of perfusion scintigraphy to detect ischaemia in akinetic segments; (3) the less operator-dependent characteristics of the perfusion imaging technique; (4) the higher sensitivity of perfusion scintigraphy as compared with echocardiography at submaximal stress [28].

Haemodynamic and electrical response

Our results demonstrate a slightly lower peak heart rate in patients with angina and a comparable peak rate-pressure product. This may be attributed to early interruption of the test in 18 patients because of angina. However, exclusion of patients in whom the test was terminated prematurely did not alter the comparable parameters of underperfusion in patients with and patients without angina. The lower peak heart rate in patients with angina is consistent with previous reports on exercise [15, 20] and dobutamine stress testing [27]. ST-segment depression

occurred more frequently in the symptomatic group. A higher prevalence of electrically silent ischaemia in asymptomatic patients has been reported during dobutamine [27] and exercise stress testing as well [17, 20, 25], which may suggest a common pathway for both the electrocardiographic and the pain response to ischaemic stimulus [20].

ST-segment depression and the amount of ischaemia

In this study, the extent and severity of reversible underperfusion during dobutamine stress testing did not differ in patients with and patients without ST-segment depression. We have previously reported a similar ischaemic wall motion score with or without ST-segment depression during dobutamine stress testing, and a higher number of ischaemic segments with normal baseline contraction in patients with ST-segment depression. However, in the present study we failed to identify a corresponding difference in number of segments with a completely reversible defect in patients with and patients without ST-segment depression. This contradiction may be explained by the fact that a partially reversible defect may represent ischaemia in the absence of baseline wall motion abnormalities. Additionally, in patients with myocardial infarction and stress-induced ST-segment elevation, concomitant ST-segment depression may represent reciprocal changes without true ischaemia. Hecht et al. [20] and Mahmarian et al. [19] reported that in patients with coronary artery disease, positive and negative exercise electrocardiographic findings were associated with a similar amount of ischaemia on exercise thallium scintigraphy. Conversely, Hecht et al. [25] concluded that exercise-induced ST-segment depression is the single most significant variable in relation to the amount of ischaemic myocardium assessed by exercise echocardiography.

Limitations of the study

We assessed myocardial ischaemia on basis of reversible perfusion defects, which may represent flow malperfusion as well as true ischaemia. The detection of reversible perfusion defects in dyssynergic segments may represent a clinical challenge. Another limitation of the study is that most of the patients were receiving anti-anginal medication which may modify symptoms and signs of ischaemia. We have previously shown that the administration of atropine enhances the detection of myocardial ischaemia during dobutamine stress testing, especially in patients receiving beta blockers [29]. Furthermore, the percentage of patients receiving medications was not different in the two groups. Finally, ST-segment depression in patients with myocardial infarction may represent reciprocal changes without ischaemia. Despite this limitation, exercise-induced ST-segment depression after myocardial infarction has general-

ly been considered as a marker of a positive test associated with an adverse outcome [30].

Conclusions

In patients with coronary artery disease and ischaemia manifested as transient perfusion defects on dobutamine MIBI SPET imaging, the extent and severity of coronary artery disease and reversible underperfusion were comparable in patients with and patients without angina during the test. Patients with symptomatic ischaemia had a higher prevalence of typical effort angina before the test and a higher prevalence of ST-segment depression during the test. The amount of ischaemic myocardium was similar in patients with and patients without ST-segment depression. The absence of angina and/or ST-segment depression during stress testing of patients with anatomically and functionally significant coronary artery disease was not an indicator of less severe ischaemia.

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