DOBUTAMINE STRESS TEST: ITS ROLE IN THE DIAGNOSIS AND FUNCTIONAL EVALUATION OF CORONARY ARTERY DISEASE

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DE ROL VAN DE DOBUTAMINE STRESS TEST VOOR DIAGNOSE EN FUNCTIONELE EVALUATIE VAN CORONAIR LIJDEN

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To my parents

To Amany, Ahmed and Abdel-Hamead

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Contents

CHAPTER 1

INTRODUCTION

Dobutamine stress testing is increasingly used for the diagnosis and functional evaluation of coronary artery disease (1-10). High dose dobutamine in conjunction with echocardiography or myocardial perfusion scintigraphy was shown to have a good accuracy for the diagnosis and localization of coronary artery disease (1-6). Low-dose dobutamine echocardiography is of potential value in the identification of myocardial viability and the prediction of functional improvement of dyssynergic myocardium spontaneously or after revascularization (11-13). However, the clinical utility and limitations of dobutamine stress testing in the diagnosis of myocardial viability and ischemia in some clinical settings have not been investigated. The role of dobutamine stress echocardiography and myocardial perfusion scintigraphy in the diagnosis of peri-infarction ischemia has not been established. The influence of fixed wall motion and perfusion abnormalities on the occurrence of ischemic response in peri-infarction area in patients with infarct-related artery stenosis was not studied. Additionally, it is not known if observation of various changes in contractility from low to high-dose dobutamine may be provide data regarding myocardial viability and ischemia additional to those obtained only at low or high dose.

Previous studies have focused mainly on the value of echocardiography and myocardial perfusion scintigraphy in conjunction with dobutamine stress testing and little attention was given to electrocardiographic changes during the test which may be of clinical value especially in presence of suboptimal echocardiographic or scintigraphic imaging. Furthermore, the significance of the presence of a combination of ischemic markers like angina, ST-segment depression, transient wall motion abnormalities and reversible perfusion defects has not been evaluated. It is not known if a combination of theses markers in a positive study would identify patients with more severe ischemia and may be of potential value in prognostic stratification of patients with known or suspected coronary artery disease.

In this work, we investigated the value of dobutamine stress testing in the assessment of myocardial ischemia and viability in some clinical settings that have not been previously investigated. Furthermore we assessed the value of symptoms and new observations on electrocardiographic and wall motion changes during the test for the assessment of myocardial ischemia and viability.

Part I

Part I deals with various topics related to the diagnosis of myocardial ischemia during dobutamine stress test in consideration of symptoms, electrocardiographic, scintigraphic and echocardiographic findings during stress.

Chapter 2: is a study of myocardial perfusion and wall motion abnormalities in patients with ST-segment elevation during dobutamine stress test in which the relationship between ST-segment elevation and myocardial ischemia was assessed in a large population with suspected myocardial ischemia.
Chapter 3: is a study of the relationship between dobutamine-induced T-wave normalization in the electrocardiogram and myocardial ischemia on simultaneous echocardiography and myocardial perfusion scintigraphy in patients with non Q-wave myocardial infarction.
Chapter 4 and 5 deal with the value of angina and ST-segment depression in patients with a positive dobutamine stress test as predictors of the severity of myocardial ischemia assessed by echocardiography and myocardial perfusion scintigraphy respectively.
Chapter 6: is a study of the theory that in patients with reversible perfusion defects on dobutamine perfusion scintigraphy, the absence of transient wall motion abnormalities on simultaneous echocardiography implies the presence of less severe ischemia.
Chapter 7: is a study of the value of dobutamine stress echocardiography for the detection of vascular compromise after coronary artery bypass surgery.
Chapter 8: deals with the value of dobutamine stress echocardiography for the diagnosis of peri-infarction and remote coronary artery stenosis in symptomatic patients late after acute myocardial infarction and studies the impact of the extent and severity of regional baseline wall motion abnormalities on the accuracy of the test for detecting infarct-related artery stenosis.
Chapter 9: is a parallel study using dobutamine 201 thallium SPECT imaging.
Chapter 10: is a study of the relationship between contractile response of akinetic segment to both low and high dose dobutamine and myocardial ischemia assessed by simultaneous 201 thallium SPECT.
Chapter 11: is a study of fixed and inducible wall motion abnormalities as predictors of systolic blood pressure response during dobutamine stress test in patients with left ventricular dysfunction after myocardial infarction.
Chapter 12 and 13: are reports of 2 patients with different congenital coronary artery anomalies in whom dobutamine stress testing was clinically useful in the functional assessment of the anatomical abnormalities.

Part II

Part II deals with the value of dobutamine stress echocardiography, thallium perfusion scintigraphy and electrocardiography for the diagnosis of myocardial viability and the prediction of functional improvement spontaneously or after revascularization.

Chapter 14: we assessed the value of low-dose dobutamine echocardiography in the prediction of improvement of ventricular function after first acute myocardial infarction in patients without cardiac medications. The study group

comprised patients with or without thrombolysis, which was not previously investigated.

Chapter 15: is a head to head comparison of low-dose dobutamine echocardiography and rest-redistribution thallium SPECT myocardial perfusion imaging for the diagnosis of myocardial viability and the prediction of spontaneous recovery of left ventricular function after a recent myocardial infarction.

Chapter 16 and 17: we assessed the value of T-wave normalization and ST-segment elevation respectively during dobutamine stress test in the diagnosis of myocardial viability and the prediction of late functional improvement in patients with recent Q wave myocardial infarction.

Chapter 18: is an editorial dealing with the published data in addition to our experience regarding the functional significance of stress-induced ST-segment elevation after a recent myocardial infarction.

Chapter 19: we evaluated the relationship between the echocardiographic phenomenon of akinesis becoming dyskinesis at high dose dobutamine stress and myocardial viability in patients with chronic ischemic left ventricular dysfunction undergoing surgical revascularization.

Chapter 20: is a study of the impact of the severity of coronary artery stenosis and the collateral circulation on the extent of myocardial viability and reversible dysfunction in patients with chronic left ventricular dysfunction undergoing dobutamine stress testing before elective coronary artery bypass graft surgery.

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Part I ASSESSMENT OF MYOCARDIAL ISCHEMIA

CHAPTER 2

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Evaluation By Quantitative 99m-Technetium MIBI SPECT and Echocardiography of Myocardial Perfusion and Wall Motion Abnormalities in Patients With Dobutamine-Induced ST-Segment Elevation

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ST-segment elevation during exercise testing has been attributed to myocardial ischemia and wall motion abnormalities (WMA). However, the functional significance of ST-segment elevation during dobutamine stress testing (DST) has not been evaluated in patients referred for diagnostic evaluation of myocardial ischemia. DST (up to 40 μg/kg/min) with simultaneous echocardiography and technetium-99m sestamibi single-photon emission computed tomography (SPECT) was performed in 229 consecutive patients with suspected myocardial ischemia who were unable to perform an adequate exercise test; 127 (55%) had a previous acute myocardial infarction (AMI). ST elevation was defined as ≥1 mm new or additional J point elevations with a horizontal or upsloping ST segment lasting 80 ms. Reversible perfusion defects on SPECT and new or worsening WMA during stress on echocardiography were considered diagnostic of ischemia. ST elevation occurred in 40 patients (17%) during the test; 34 of them (85%) had previous AMI. All patients with ST-segment elevation had abnormal scintigrams (fixed or reversible defects, or both) and abnormal wall motion (fixed or transient defects, or both) at peak stress. In patients who had ST elevation and no previous AMI (n = 6), ischemia was detected in all by echocardiography and in 5 (83%) by SPECT. In patients with previous AMI, the prevalence of ischemia was not different with or without ST elevation (53% vs 43% by echocardiography and 53% vs 48% by SPECT, respectively). Baseline regional wall motion score in the infarct zone was higher in patients with ST elevation. In conclusion, myocardial perfusion defects and WMA at peak stress are a hallmark in patients with ST-segment elevation during DST. However, ST-segment elevation is a specific marker of ischemia only in patients without previous AMI.

(Am J Cardiol 1995;76:441–448)

Exercise-induced ST-segment elevation in the electrocardiogram has been attributed to left ventricular dysfunction, myocardial aneurysm, or transmural myocardial ischemia due to severe coronary artery stenosis or coronary spasm.[1–11] Despite the known role of wall motion abnormalities (WMA) in patients with ST elevation during exercise,[4,6] previous studies have focused mainly on resting WMA, and little attention was paid to stress-induced WMA that may be associated with this electrocardiographic finding. It has been postulated that WMA due to either myocardial infarction or exercise-induced ischemia represent a common underlying mechanism of exercise-induced ST elevation. However, few data are available to support this contention.[8] In a few studies, ST elevation during dobutamine stress testing (DST) was attributed to myocardial ischemia in the absence of previous acute myocardial infarction (AMI)[12] and to stress-induced left ventricular asynergy in patients evaluated early after AMI.[13] However, the functional significance of this electrocardiographic finding has not been reported in patients referred for diagnostic evaluation of myocardial ischemia. Accordingly, the aim of this study was to evaluate the prevalence and functional significance of ST elevation during DST in patients with suspected myocardial ischemia undergoing DST with simultaneous echocardiography and technetium-99m sestamibi single-photon emission computed tomography (SPECT).

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METHODS

Study population: The study population comprised 229 consecutive patients (137 men and 92 women, mean age 59 ± 11 years) with known or suspected coronary artery disease unable to exercise or to perform an adequate exercise test, referred to our imaging laboratory for evaluation of chest pain by dobutamine technetium-99m sestamibi SPECT. Simultaneous echocardiography was performed in all patients as a part of a research protocol in our center. All patients gave informed consent to undergo the study. Patients with bundle branch block or ventricular hypertrophy were excluded. One hundred twenty-seven patients (55%) had a previous AMI, which

TABLE I Clinical Characteristics and Hemodynamic Variables During Dobutamine Stress Testing in Patients With (group A) and Without (group B) ST-Segment Elevation

	Group A (n = 40)	Group B (n = 189)	p Value
Men/women	31/9	106/83	<0.05
Mean age (yr)	58 ± 10	59 ± 12	NS
Previous AMI	34 (85)	93 (49)	<0.0001
Resting HR (beats/min)	72 ± 13	69 ± 14	NS
Peak HR (beats/min)	132 ± 16	134 ± 16	NS
85% of target HR reached	34 (79)	158 (82)	NS
Resting systolic BP (mm Hg)	136 ± 31	135 ± 21	NS
Peak systolic BP (mm Hg)	139 ± 35	146 ± 30	NS
Resting diastolic BP (mm Hg)	77 ± 13	79 ± 12	NS
Peak diastolic BP (mm Hg)	74 ± 15	75 ± 14	NS
Chest pain	12 (30)	48 (25)	NS
ST-segment depression	14 (35)	33 (17)	<0.05

Values are expressed as mean ± SD or number of patients (%).
AMI = acute myocardial infarction; BP = blood pressure; HR = heart rate.

TABLE II Echocardiographic and Scintigraphic Findings in 102 Patients Without Previous Infarction With (group A) and Without (group B) ST-Segment Elevation

	Group A (n = 6)	Group B (n = 96)	p Value
Normal echocardiography	0	70 (73)	<0.005
WMA at rest	2 (33)	12 (13)	NS
WMA at peak stress	6 (100)	26 (27)	<0.005
New or worsened WMA	6 (100)	22 (23)	<0.0001
Normal scintigraphy	0	63 (66)	<0.005
RPD with or without FPD	5 (83)	27 (28)	<0.005

Values are expressed as number of patients (%).
FPD = fixed perfusion defects; RPD = reversible perfusion defects; WMA = wall motion abnormalities.

TABLE III Echocardiographic and Scintigraphic Findings in 127 Patients With Previous Infarction With (group A) and Without (group B) ST-Segment Elevation

	Group A (n = 34)	Group B (n = 93)	p Value
Normal echocardiogram	0	16 (17)	<0.01
WMA at rest	32 (94)	69 (74)	<0.05
WMA at peak stress	34 (100)	77 (83)	<0.01
New or worsened WMA	18 (53)	40 (43)	NS
WMS at rest	25.0 ± 6.4	21.1 ± 4.8	<0.005
WMS at peak stress	26.7 ± 6.4	22.2 ± 6.4	<0.0001
Ischemic WMS	1.9 ± 3.2	1.8 ± 3.2	NS
Akinetic + dyskinetic segments at rest	2.9 ± 3	1.1 ± 1.7	<0.001
Akinetic + dyskinetic segments at peak	3.7 ± 3.1	1.7 ± 2.1	<0.001
Normal scintigram	0	11 (12)	<0.01
RPD with or without FPD	18 (53)	45 (48)	NS
Perfusion defect score at rest	3,023 ± 2,955	1,589 ± 1,345	<0.05
Perfusion defect score at peak stress	2,978 ± 2,563	1,775 ± 2,281	<0.05
Ischemic perfusion score	401 ± 737	389 ± 1,322	NS

Values are expressed as mean ± SD or number of patients (%).
WMS = wall motion score; other abbreviations as in Table II.

was recent (<1 month) in 34 patients. The diagnosis of AMI relied upon a typical history of chest pain, a diagnostic increase in serum creatine kinase and evolutional electrocardiographic changes. On the day of the test, 154 patients (67%) were receiving antianginal therapy; 113 of them were receiving β blockers.

Dobutamine stress test: Dobutamine was infused through an antecubital vein starting at a dose of 10 μg/kg/min, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given to patients not achieving 85% of their age-predicted maximal heart rate.[14] A 12-lead electrocardiogram was recorded each minute. The level of ST segment was calculated after signal averaging by a computer-assisted system (Cardiovet CSG/12, Schiller, Baar, Switzerland). Cuff blood pressure was measured every 3 minutes. The electrocardiograms were revised by 2 experienced cardiologists unaware of clinical, echocardiographic, or scintigraphic data. Pathologic Q waves were defined according to established criteria.[15] ST elevation was defined as new or additional elevation ≥1 mm at the J point, with a horizontal or upsloping ST-segment lasting 80 ms during stress in ≥1 electrocardiographic lead (the PQ segment was considered the isoelectric line).[3] ST-segment depression was defined as ≥1 mm horizontal or downsloping depression 80 ms after the J point, and below the resting baseline level. The test was interrupted prematurely if severe chest pain, ST-segment depression >2 mm, ST elevation >2 mm in patients with normal baseline electrocardiogram, significant ventricular or supraventricular arrhythmia, or a systolic blood pressure decrease of >40 mm Hg occurred during the test.

Sestamibi single-photon emission computed tomography imaging: Approximately 1 minute before the termination of the stress test, an intravenous dose of 370 MBq of sestamibi was administered. Stress SPECT imaging was begun 1 hour after sestamibi injection. For the resting studies, 370 MBq of sestamibi was injected 24 hours after the first study. Left ventricular images were divided into 6 segments: anterior, lateral, inferoposterior, interventricular septum (subdivided in anterior and posterior septum), and apex. Image interpretation was performed by an experienced observer unaware of the patients' electrocardiographic or echocardiographic data. A persistent perfusion defect on both stress and resting 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 ischemia.[16] The interpretation of the scan was semiquantitatively performed by visual analysis, and assisted by the circumferential profiles analysis. To assess perfusion defect size, perfusion defect score was quantitatively calculated at rest and at stress images by measuring the area between the lower limit of normal values (±2 SD) and the actual circumferential

profile in 6 short-axis slices. Ischemic perfusion score was derived by subtracting rest from stress score in segments with reversible defects.

Stress echocardiography: Stress echocardiography was performed in all patients according to a previously described protocol.[16] For both rest and stress studies, the left ventricular wall was divided into 16 segments and scored using a 4-point scale: 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. Both inward endocardial motion and myocardial thickening were considered for analysis. Wall motion score was derived by the summation of the score of the 16 segments. The diagnosis of ischemia was based on the occurrence of new or worsening WMA during the test, compared with baseline, in ≥1 segment. As we have previously concluded,[17] ischemia was not considered when akinetic segments at rest became dyskinetic during stress. Ischemic wall motion score was defined as the difference between peak and rest regional wall motion score in ischemic segments. Assessment of images was performed by 2 experienced investigators without knowledge of scintigraphic or electrocardiographic data. In case of disagreement, a consensus was reached with a third investigator. In our center, the inter- and intraobserver variability for the interpretation of stress echocardiographic studies is 91% and 92%, respectively.[18]

Coronary angiography: Coronary angiography was performed, using the Judkins technique, within 3 months in 106 patients (46%). Significant coronary artery disease was defined as a diameter stenosis of ≥50% in ≥1 major epicardial artery.

Regional myocardial function and perfusion: In patients with myocardial infarction, the location of resting WMA was presumed to represent the infarction zone. To assess regional myocardial perfusion and function, 2 myocardial segments were identified: (1) the anterior segment, which included the anterior wall, the interventricular septum, and the apex (assigned to leads V_1 to V_4); and (2) the inferior segment, which included the inferior and posterior wall (assigned to leads II, III, and aVF). Because of the infrequent occurrence of resting WMA confined only to the lateral wall, this segment, together with leads I, aVL, V_5, and V_6, were added to either the anterior or the inferior segment in the presence of concomitant abnormalities in 1 of these segments. Myocardial segments at echocardiography and at SPECT were matched in these 2 locations.

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

RESULTS

Dobutamine stress test: Heart rate and systolic blood pressure increased significantly from rest to peak stress (70 ± 13 vs 134 ± 16 beats/min and 135 ± 25 vs 145 ± 32 mm Hg, respectively, p <0.0001 for both). In 30 patients, the test was interrupted prematurely before reaching the maximal dose or 85% of the target heart rate because of a limiting side effect (angina in 15 patients, ST-segment depression in 7 patients, hypotension in 6 patients, and significant tachyarrhythmias in 2 patients).

ST elevation of ≥1 mm occurred in 34 of 127 patients with (27%) and in 6 of 102 patients without (6%) previous AMI. These 40 patients formed group A. Group B comprised 189 patients without ST elevation; 93 of them (49%) had previous AMI. Patients in group A had a higher prevalence of previous AMI and male gender. In patients with previous AMI, pathologic Q waves were detected in 27 of 34 group A patients (79%) and in 59 of 93 group B patients (63%), p = NS. Clinical characteristics and hemodynamic data in both groups are listed in Table I. Echocardiographic and scintigraphic findings in both groups are listed in Tables II (patients without AMI) and III (patients with previous AMI).

Stress echocardiography: ST elevation was associated with a higher prevalence of myocardial ischemia in patients without (Figure 1) but not with (Figure 2) pre-

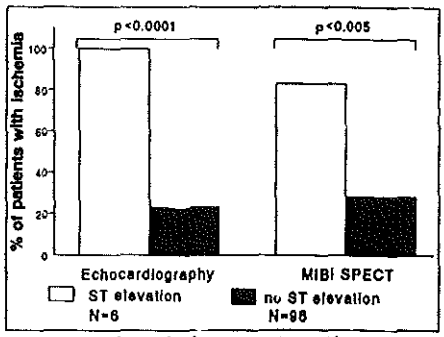

FIGURE 1. Prevalence of ischemia in patients without previous myocardial infarction with (n = 6) and without (n = 96) ST-segment elevation as diagnosed by echocardiography and technetium-99m sestamibi single-photon emission computed tomography (MIBI SPECT).

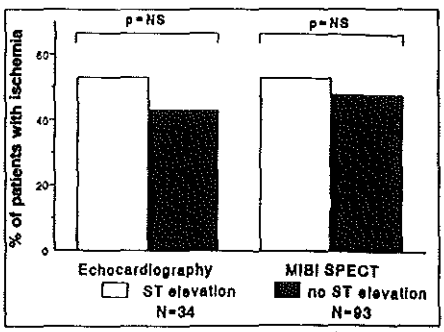

FIGURE 2. Prevalence of ischemia in patients with previous myocardial infarction with (n = 34) and without (n = 93) ST-segment elevation as diagnosed by echocardiography and technetium 99m sestamibi single-photon emission computed tomography (MIBI SPECT).

TABLE IV Regional Wall Motion and Myocardial Perfusion Defect Score in Anterior Myocardial Segments With Baseline Dyssynergy With and Without ST-Segment Elevation During Dobutamine Stress Testing in Patients With Previous Myocardial Infarction

	ST Elevation (25 segments)	No ST Elevation (42 segments)	p Value
Rest WMS	18.3 ± 5.7	15.5 ± 4.5	<0.05
Stress WMS	19.1 ± 5.9	16.0 ± 5.0	<0.001
Ischemic WMS	0.9 ± 2.3	0.7 ± 2.1	NS
New and/or worsened WMA	10 (40)	15 (36)	NS
Rest perfusion defect score	1,668 ± 1,531	1,067 ± 1,193	<0.05
Stress perfusion defect score	1,680 ± 1,437	1,180 ± 1,154	<0.05
Ischemic perfusion score	338 ± 628	301 ± 1,003	NS
Reversible perfusion defects	10 (40)	16 (38)	NS

Values are expressed as mean ± SD or number (%).
Abbreviations as in Tables II and III.

TABLE V Regional Wall Motion and Myocardial Perfusion Defect Score in Inferior Myocardial Segments With Baseline Dyssynergy With and Without ST-Segment Elevation During Dobutamine Stress Testing in Patients With Previous Myocardial Infarction

	ST Elevation (17 segments)	No ST Elevation (40 segments)	p Value
Rest WMS	9.0 ± 2.1	7.2 ± 2.6	<0.05
Stress WMS	9.5 ± 2.5	7.8 ± 3.1	<0.05
Ischemic WMS	0.6 ± 1.6	0.7 ± 2.0	NS
New and/or worsened WMA	6 (35)	13 (33)	NS
Rest perfusion defect score	1,284 ± 1,491	899 ± 923	<0.05
Stress perfusion defect score	1,327 ± 1,494	972 ± 1,031	<0.05
Ischemic perfusion score	142 ± 216	144 ± 405	NS
Reversible perfusion defects	7 (41)	14 (35)	NS

Values are expressed as mean ± SD or number (%).
Abbreviations as in Tables II and III.

vious AMI. In patients with previous AMI, ST elevation was associated with a higher prevalence of resting WMA, a higher wall motion score at rest and at peak stress, a similar ischemic wall motion score (Figure 3), and more myocardial segments with akinesia or dyskinesia at rest and at peak stress (Table III). In patients with previous AMI and ST elevation, the prevalence of ischemia did not differ in the presence or absence of Q waves: 15 of 27 (56%) versus 3 of 7 (43%), respectively (p = NS).

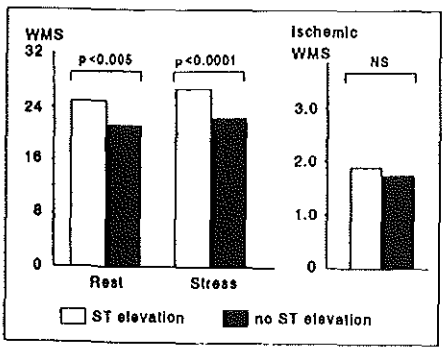

FIGURE 3. Rest, peak, and ischemic wall motion score (WMS) in patients with previous myocardial infarction with (n = 34) and without (n = 93) ST-segment elevation.

Results of sestamibi single-photon emission computed tomography: ST elevation was associated with a higher prevalence of ischemia in patients without (Figure 1) but not with (Figure 2) previous AMI. The electrocardiogram and perfusion scan of a patient without previous AMI, ST elevation during DST, and a completely reversible defect are shown in Figure 4. In patients with previous AMI, ST elevation was associated with a higher perfusion score at rest and at peak stress and a similar ischemic perfusion score compared with patients without ST elevation (Table III). In patients with previous AMI and ST elevation, the prevalence of ischemia did not differ in the presence or absence of Q waves: 16 of 27 (59%) versus 2 of 7 (29%), respectively (p = NS).

Regional myocardial perfusion and function: In patients with previous AMI, regional myocardial perfusion and function were compared in dyssynergic myocardial segments at rest with and without ST elevation during stress in the anterior (Table IV) and inferior (Table V) segments. In both locations, resting score was higher with ST elevation, whereas the ischemic score and prevalence of ischemia were not different with or without ST elevation.

The electrocardiograms and perfusion scans of 2 patients with previous anterior AMI, ST-segment elevation in Q leads during DST, and a perfusion defect on resting images with (Figure 5) and without (Figure 6) partial reversibility are presented.

Analysis of subgroups: PATIENTS WITHOUT PREVIOUS MYOCARDIAL INFARCTION: In patients with reversible perfusion defects and no previous AMI, the ischemic perfusion score was significantly higher in patients with (n = 5) than without (n = 27) ST elevation (994 ± 652 vs 271 ± 407, p <0.01). Similarly, in patients with stress-induced WMA who had no previous AMI, the ischemic wall motion score was significantly higher in patients with (n = 6) than without (n = 22) ST elevation (4.2 ± 3.2 vs 2.7 ± 3.1, p <0.05).

PATIENTS WITH RECENT MYOCARDIAL INFARCTION: ST elevation occurred in 16 of 34 patients (47%) with recent AMI. Prevalence of ischemia was not different with or without ST elevation: 9 of 16 (56%) versus 9 of 18 patients (50%) by echocardiography and 9 of 16 (56%) versus 11 of 18 (61%) by SPECT, respectively.

PATIENTS WITH ST-SEGMENT DEPRESSION: ST-segment depression occurred in 29 patients with and in 18 without previous AMI (14 in group A and 33 in group B). ST depression was associated with a higher prevalence of ischemia in patients without previous AMI (12 of 18 [67%] versus 16 of 84 [19%] [p <0.0001 by echocardiography] and 13 of 18 [72%] versus 19 of 84 [23%] [p <0.0001 by SPECT]) and with previous AMI (18 of 29

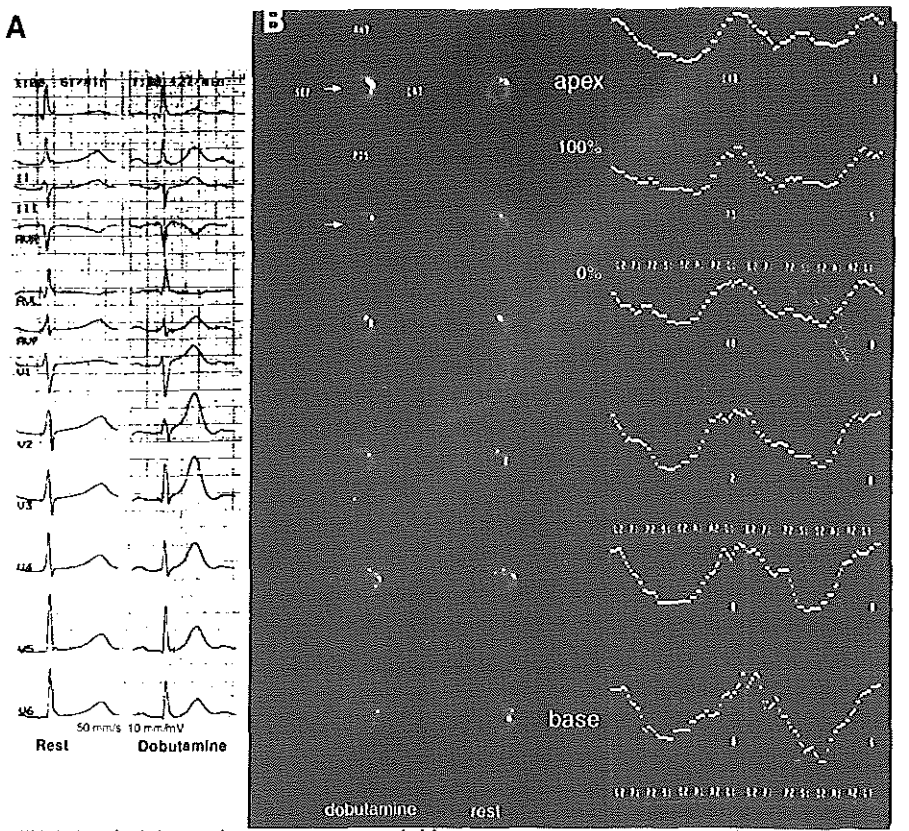

FIGURE 4. *A*, 12-lead electrocardiogram at rest and at peak dobutamine stress in a 53-year-old woman without a history or electrocardiographic evidence of previous myocardial infarction, showing ST-segment elevation in leads V_1 to V_3. *B*, dobutamine stress and rest sestamibi single-photon emission computed tomographic images in the 6 short-axis slices represented together with the corresponding circumferential profile analysis of the same patient, showing a completely reversible perfusion defect in the apical septum *(arrows)*. ANT = anterior; LAT = lateral; POS = posterior; SEP = septal.

[62%] versus 40 of 98 [41%] [p <0.05 by echocardiography], and 20 of 29 [69%] versus 43 of 98 [44%] [p <0.05 by SPECT]). In group A patients with previous AMI (n = 34), the prevalence of ischemia by both techniques was not different in patients with (n = 12) and without (n = 22) concomitant ST-segment depression.

Coronary angiography: Coronary angiography was performed in 19 group A patients (48%). Three of them had no previous AMI. All patients had significant coronary artery disease: 3-vessel (n = 7), 2-vessel (n = 3), and 1-vessel (n = 9) disease. The site of ST elevation was predictive of significant disease in the corresponding coronary artery in all patients.

Eighty-seven group B patients (46%) underwent coronary angiography. Significant coronary artery disease was detected in 59 patients; 3-vessel (n = 6), 2-vessel (n = 17), and 1-vessel (n = 36) disease. No significant disease was detected in 28 patients. In patients with previous AMI, ST elevation was associated with a higher prevalence of total occlusion of ≥1 major artery (50% vs 14%, p <0.005), whereas the prevalence of multivessel disease was 56% in patients with (9 of 16) and 29% in patients without (14 of 48) ST elevation (p = NS).

DISCUSSION

In the present study, the prevalence and functional significance of ST elevation during DST was evaluated in patients with known or suspected coronary artery disease in whom the test was performed with simultaneous echocardiography and technetium-99m sestamibi SPECT for diagnostic evaluation of myocardial ischemia. Our results show that dobutamine-induced ST elevation is a common occurrence in patients with previous AMI. In such patients, ST elevation is associated with more se-

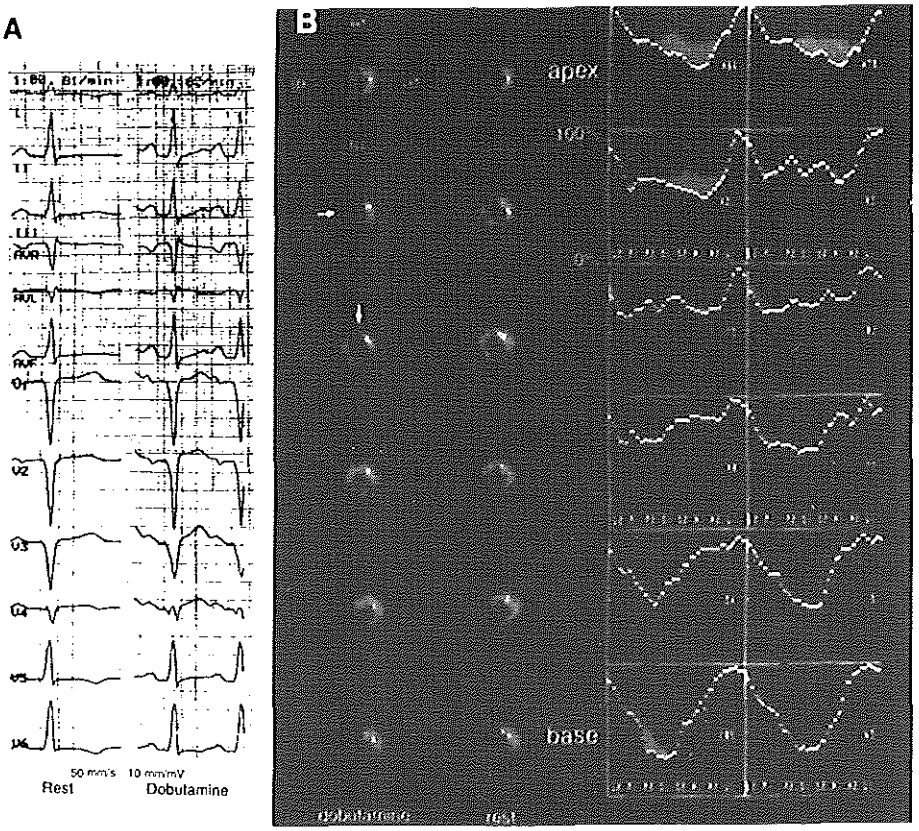

FIGURE 5. *A*, resting and peak dobutamine stress electrocardiogram of a 41-year-old man with a history of old anterior myocardial infarction and Q waves in leads V_1 to V_3, showing ST-segment elevation in V_2 to V_3 on the stress electrocardiogram. *B*, dobutamine stress and rest sestamibi single-photon emission computed tomographic images of the same patient, showing a partially reversible perfusion defect in the apical septum *(horizontal arrow)* and a completely reversible defect in the anterior wall *(vertical arrow)*. Abbreviations as in Figure 4B.

vere global and regional left ventricular dysfunction, and a higher prevalence of total occlusion of ≥1 coronary artery. Results also show that despite being compatible with ischemia, ST elevation in patients with recent or old myocardial infarction is not specific for stress-induced overall or peri-infarction ischemia assessed by echocardiography and SPECT. The low specificity for ischemia was also noted in patients without Q waves. This can be explained by the low sensitivity of Q waves for the detection of baseline WMA, especially in patients with old myocardial infarction.[19] In contrast, ST depression was associated with a higher prevalence of ischemia. However, patients with concomitant ST-segment depression and elevation did not have a higher prevalence of ischemia than patients with isolated ST elevation. This may be explained by the occurrence of reciprocal ST depression without true ischemia.[20] In patients without previous AMI, ST elevation was not a usual occurrence (6%) and was associated with ischemia in the corresponding myocardial segments. In patients without previous AMI who had ischemia on echocardiography or SPECT, ischemia was more severe in patients with than without ST elevation.

Comparison with previous studies: Coma-Canella[12] reported ST elevation during DST in 20 of 90 patients with angina and no previous AMI. All had severe coronary artery stenoses. The high prevalence of ST elevation in that study may be related to the selection of patients with a high prevalence of unstable angina. However, no imaging technique was applied for the detection of ischemia. Coma-Canella et al[13] reported that in patients with recent AMI who underwent DST with thal-

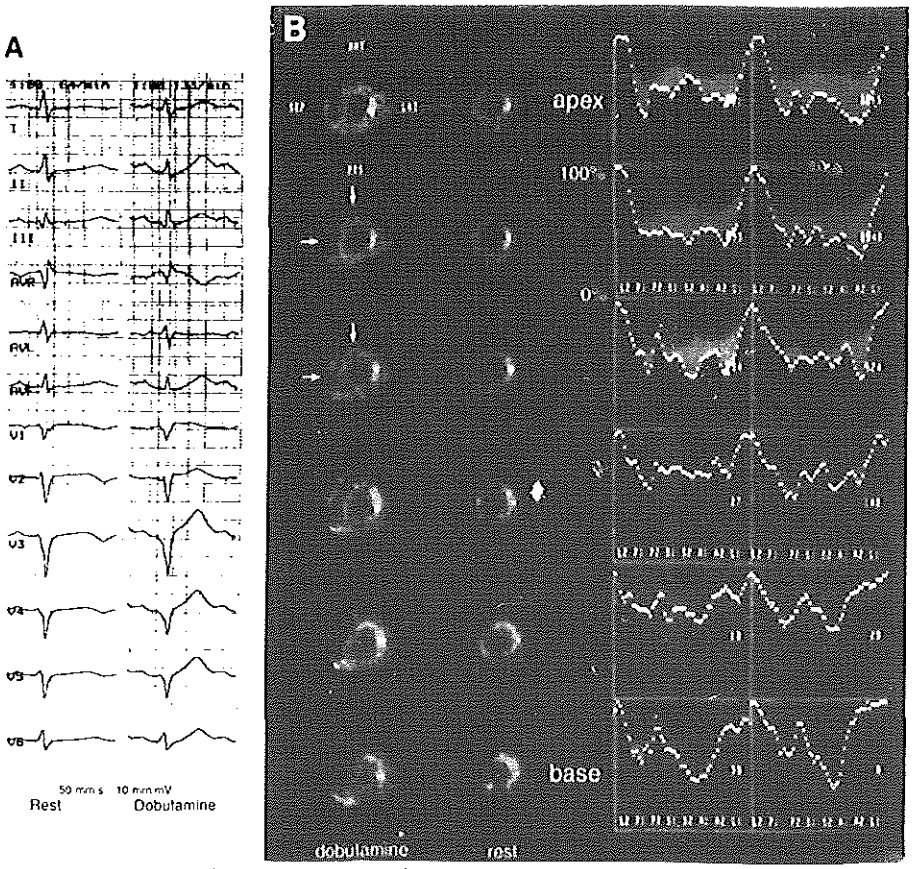

FIGURE 6. *A*, resting and peak dobutamine stress electrocardiogram of a 62-year-old man with a history of old anterior myocardial infarction and Q waves in leads V_1 to V_4, showing ST-segment elevation in V_1 to V_4. *B*, dobutamine stress and rest sestamibi single-photon emission computed tomographic images of the same patient, showing a large and severe fixed perfusion defect in the anterior wall *(vertical arrows)* and septum *(horizontal arrows)*. Abbreviations as in Figure 4B.

lium scintigraphy and radionuclide ventriculography. ST elevation was not related to ischemia but to stress-induced left ventricular asynergy. However, the inverse correlation between the change in regional ejection fraction and the level of ST elevation in their study may represent a poor contractile response in myocardial segments corresponding to ST elevation rather than stress-induced asynergy, which is a specific marker of ischemia. Previtali et al[21] reported a case of high-dose dobutamine-induced ST elevation and akinesia of the inferior wall in a patient with 2-vessel disease. Coronary angiography performed during ischemic episodes revealed patency of coronary arteries, excluding coronary spasm as an underlying mechanism. They concluded that dobutamine may induce transmural myocardial ischemia in the presence of severe coronary lesions by increasing myocardial oxygen demand and inducing myocardial blood flow maldistribution.

ST elevation during exercise has been attributed to left ventricular WMA, myocardial aneurysm, or transmural myocardial ischemia due to either severe coronary artery spasm or fixed coronary artery disease.[1-11] Gallik et al[7] reported that exercise-induced ST elevation is an ominous sign of severe reversible hypoperfusion in patients without previous AMI. In our study, ST elevation identified a population with more severe reversible hypoperfusion and stress-induced WMA than patients who had ischemia without ST elevation. The absence of a history or electrocardiographic finding of AMI appears to be the most common characteristic that separates patients in whom stress-induced ST elevation reflects severe ischemia from those with marked abnormality of

left ventricular function.[8] However, exercise-induced ST elevation in patients after acute AMI has been attributed in some studies to peri-infarction ischemia.[10–13] Margonato et al[10] reported that exercise-induced ST elevation after acute AMI correlated with reversible thallium-201 perfusion defects in the peri-infarction area. A limitation of that study is the absence of a control group with the same clinical characteristics without ST elevation or T-wave normalization.

Mechanism of ST-segment elevation: Chahine et al[8] postulated that WMA that are either permanent in patients with previous AMI or transient due to ischemia in the absence of AMI constitute a common mechanism underlying ST elevation during stress. The results of our study support this hypothesis, because we detected WMA in all patients with ST elevation at peak stress in corresponding myocardial segments in the presence or absence of previous AMI.

Clinical implications: With regard to an ischemic response to dobutamine infusion, ST-segment elevation in patients without previous AMI would help with diagnosis in the presence of suboptimal or equivocal echocardiographic or scintigraphic images, and would identify patients with more severe ischemia. Because ST elevation is not a specific marker of ischemia in patients with previous AMI, it should not be used as a criterion for termination of DST.

Study limitations: The diagnosis of ischemia in this study relied on stress echocardiography and SPECT without performing coronary angiography in all patients. However, these techniques were reported as accurate methods for the diagnosis of coronary artery disease.[16,22–25] Echocardiographic detection of ischemia may be difficult in severely dyssynergic segments. However, echocardiography accurately detects ischemia in the normal peri-infarction region represented in the same electrocardiographic segment. Furthermore, there was a double check on the occurrence of ischemia using 2 imaging techniques; with these 2 techniques, a similar prevalence of ischemia was encountered. The intake of medications may have reduced the prevalence of ischemia at echocardiography and SPECT. However, it is unlikely that ischemia was seen on the electrocardiogram in the absence of transient perfusion or WMA, or both, because perfusion and WMA occur earlier than electrocardiographic changes in the ischemic cascade.[26]

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CHAPTER 3

T WAVE NORMALIZATION DURING DOBUTAMINE STRESS TEST IN PATIENTS WITH NON-Q MYOCARDIAL INFARCTION: A MARKER OF MYOCARDIAL ISCHAEMIA?[1]

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ABSTRACT

Conflicting results in heterogenous patient population have been described on the functional significance of stress-induced T wave normalization (TWN) in the ECG. The aim of this study was to evaluate the relation between TWN during dobutamine stress test (DST) and stress-induced ischaemia evaluated by echocardiography and myocardial perfusion scintigraphy in patients with previous non-Q myocardial infarction. Among 520 patients who underwent DST in conjunction with simultaneous echocardiography and 201 thallium or sestamibi SPECT for evaluation of suspected myocardial ischemia, 36 were selected according to the following criteria: previous non-Q myocardial infarction, normal QRS, negative T waves in 2 or more ECG leads and no significant ST segment depression or elevation at rest or during stress. Diagnosis of ischaemia relied upon the occurrence of reversible perfusion defects by scintigraphy and stress-induced wall motion abnormalities by echocardiography. During the test TWN (defined as negative T wave becoming upright in one or more ECG lead) occurred in 20 patients (group 1), while in 16 patients T waves remained negative (group 2). The prevalence of ischaemia was higher in group 1 than in group 2 both by scintigraphy (85% vs 38%, p=0.004) and by echocardiography (70% vs 32%, p=0.02). The sensitivity, specificity and accuracy of TWN for the detection of ischaemia were 74%, 77% and 75% by SPECT and 74%, 65% and 69% by echocardiography respectively.

Conclusion: In patients with non-Q myocardial infarction and suspected myocardial ischaemia, TWN without concomitant ECG changes during DST is associated with a higher prevalence of ischaemia compared to patients with

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[1] *Eur Heart J; in press.*

persistent T wave inversion. This ECG finding should not be disregarded as a marker of ischaemia in that particular patient population.

Key Words: Dobutamine stress echocardiography, SPECT perfusion imaging, T wave normalization, Myocardial ischaemia.

INTRODUCTION

Conflicting results have been described on the functional significance of the normalization of inverted T waves in the electrocardiogram during exercise stress test (1-5). In particular, some studies have demonstrated that T wave normalization (TWN) has a low specificity for myocardial ischaemia (4,5). Therefore, some authors have proposed that in addition to myocardial ischaemia a direct "neurogenic" mechanism due to sympathetic stimulation may be responsible of TWN (6,7). Dobutamine is a sympathomimetic agent used for pharmacological stress testing (8-12). The observations on the electrocardiographic changes during dobutamine stress test have been confined to the classical ST segment depression and/or elevation (8,9) with no available data regarding the prevalence and the functional significance of TWN during dobutamine stress test in absence of concomitant ST segment changes. Patients with non-Q wave myocardial infarction frequently exhibit negative T waves on baseline electrocardiogram. The significance of normalization of negative T waves during stress in these patients has not been evaluated. Therefore, the aim of this study was to evaluate the relationship between TWN during dobutamine stress test and stress-induced ischaemia assessed by simultaneous dobutamine stress echocardiography and single photon emission computed tomographic 201 thallium or 99m MIBI imaging in patients with previous non-Q myocardial infarction undergoing dobutamine stress test for diagnostic evaluation of myocardial ischaemia.

METHODS

Patient selection

The study group comprises 36 out of 520 consecutive patients referred for the nuclear imaging laboratory of our institute for the diagnosis or the functional assessment of coronary artery disease who underwent dobutamine stress test in conjunction with echocardiography and 201 thallium or sestamibi SPECT. They fulfilled the following criteria: 1) a previous myocardial infarction based on the typical history of chest pain and a diagnostic rise (at least twice the normal values) of the serum creatine kinase. Infarction was recent (< 1 month) in 12 patient (33%). 2) normal QRS defined as absence of pathological Q waves, ventricular hypertrophy or bundle branch block. 3) normal ST segment both at rest and at peak stress defined as absence of ≥ 1 mm ST segment depression or elevation. 4) negative T waves at rest in ≥ 2 leads. Mean age was 59 $\pm$ 11 years. There were 25 men. At the time of the study 19

patients were treated with beta-blocking agents.

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 10 μg/kg/min, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age predicted maximal heart rate. The ECG (3 leads) was monitored throughout dobutamine infusion and a 12-lead ECG was recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted prematurely if severe chest pain, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test.

SPECT imaging

Approximately 1 minute before the termination of the stress test, an intravenous dose of 370 MBq of sestamibi (8 patients) or 74 MBq of thallium (28 patients) was administered. The acquisition of stress SPECT imaging was started immediately after thallium injection and one hour after sestamibi injection. For the resting studies, 370 MBq of MIBI were injected 24 hour after the first study. Resting thallium studies were acquired 4 hours after the test, 30 min after the reinjection of 37 MBq of thallium. Image acquisition and interpretation were performed according to a previously described protocol (11). Shortly, The left ventricular images were divided into 6 segments; anterior, lateral, infero-posterior and septal (subdivided in anterior and posterior septum) and apical. A persistent perfusion defect on both stress and resting imaging was classified as fixed. A reversible defect was defined as a perfusion defect on stress images that partially or completely resolved at resting imaging. This was considered diagnostic of ischaemia. The interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. To assess the extent and severity of hypoperfusion, each of the 6 major left ventricular segments was scored on a 4 grade score where 0 = normal and 3 = severely reduced or absent uptake. Perfusion score was derived by the summation of the individual score of the 6 myocardial segments for both rest and stress imaging. The difference between stress and rest score (ischemic score) was considered representative of the total amount of stress-induced hypoperfusion and presumably myocardial ischaemia.

Stress echocardiography

Stress echocardiography was performed in all patients according to a previously described protocol (11). For both rest and stress studies, left ventricular wall was divided into 16 segments and scored using a 4-point scale of wall motion and thickening, where 1=normal, 2=hypokinesis, 3=akinesis and 4=dyskinesis. The diagnosis of ischaemia was based on the occurrence of

new or worsening wall motion abnormalities during the test in one or more segments. Wall motion score was derived by the summation of individual scores of the 16 segments at rest and at peak stress. The difference (Δ) between peak and rest wall motion score was used as a global measure of stress-induce left ventricular dysfunction and presumably ischaemia. The overall outcome of stress with the 2 imaging modalities was expressed as normal, ischaemia (new wall motion abnormalities or transient perfusion defects), infarction (fixed wall motion abnormalities or fixed perfusion defects) or infarction+ischaemia (worsening of resting wall motion abnormalities or partially reversible defects).

Coronary angiography: Coronary angiography was performed, using the Judkins technique, within 3 months of the stress test, in 24 patients. Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$ in one or more major epicardial arteries.

Electrocardiographic localization of abnormalities: To correlate the location of electrocardiographic abnormalities with scintigraphic, echocardiogarphic and angiographic abnormalities, 2 electrocardiographic sites were considered: 1) anterior (leads V1-V4) which was assigned to the anterior wall, septum and apex and to the left anterior descending coronary artery . 2) infero-lateral (II,III,aVF,I,aVL,V5,V6) which was assigned to the lateral, and infero-posterior wall and to the left circumflex and the right coronary artery.

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. The Student *t* test was used for analysis of continuous data. A $p<0.05$ was considered statistically significant. Results were represented with the corresponding 95% confidence interval.

RESULTS

No serious complications occurred during the test. Heart rate increased from 65 $\pm$ 12 to 131 $\pm$ 13 beats/min at peak stress ($p<0.001$) and systolic blood pressure increased significantly from 127 $\pm$ 20 to 141 $\pm$ 25 mm Hg ($p<0.005$). Atropine was administered in 22 patients. Typical angina occurred during the test in 13 patient. Based on the changes of T waves during dobutamine stress test, patients were divided in 2 groups, group 1 (n=20) with TWN and group 2 (n=16) with persistent negative T waves. The demographic data, stress test results and coronary arteriography findings in 24 patients are summarized in Table I. Peak rate pressure product was similar with or without TWN (19,650 $\pm$ 4,960 vs 17,275 $\pm$ 4,168, p = NS). Age, gender, beta blocker therapy and proportion of patients with a recent myocardial infarction were not significantly different in the two groups.

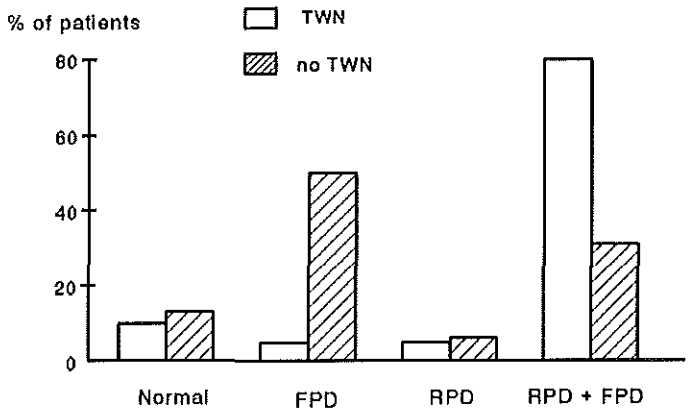

Figure 1. Distribution of the perfusion patterns in patients with (open bars) and without (dashed bars) T wave normalization. FPD = fixed perfusion defects; RPD = reversible perfusion defects.

SPECT results: The distribution of the scintigraphic patterns in patients with and without TWN is depicted in Figure 1a. Consistent with the history of previous myocardial infarction, few patients had a normal resting scan. The prevalence of an ischemic pattern on stress scintigraphy was higher in patients with than patients without TWN. Reversible perfusion defects occurred in 17 out of 20 patients with TWN (85%) and in 6 out of 16 (38%) without TWN ($p=0.004$). Ischemic score was significantly higher in patients with TWN (table II). In patients with TWN and ischaemia on SPECT, reversible perfusion defects occurred in myocardial segments corresponding to ECG sites of TWN in 15 of 17 patients (88%).

Stress Echocardiography: The distribution of the echocardiographic patterns in patients with and without TWN is depicted in Figure 1b. Consistent with the history of myocardial infarction and SPECT findings, few patients had a normal resting echocardiogram. New or worsened wall motion abnormalities occurred in 14 out of 20 patients with TWN (70%) and in 5 out of 16 (32%) without TWN ($p=0.02$). Δ wall motion score was significantly higher in patients with TWN (table II). In patients with TWN and ischaemia on echocardiography, stress-induced wall motion abnormalities occurred in myocardial segments corresponding to ECG sites of TWN in 12 of 14 patients (86%).In the 36

patients studied, 30 had resting wall motion abnormalities. Worsening of these abnormalities at peak stress was more frequent in patients with TWN: 11/16 (69%) vs 4/14 (29%), p = 0.03. Reversible perfusion defects occurred in the corresponding myocardial segments (on the 6 segment model) with baseline dyssynergy on echocardiography in 15 of 30 patients. The prevalence of these defects was significantly higher in patients with TWN: 12/16 (75%) vs 3/14 (21%), p = 0.005. The correlation between TWN, transient perfusion defects (scintigraphic "ischaemia") and new or worsening wall motion abnormalities (echocardiographic "ischaemia") is shown in Figures 2a and 2b. The diagnostic accuracy of TWN to predict the echocardiographic and scintigraphic ischaemia is summarized in table III.

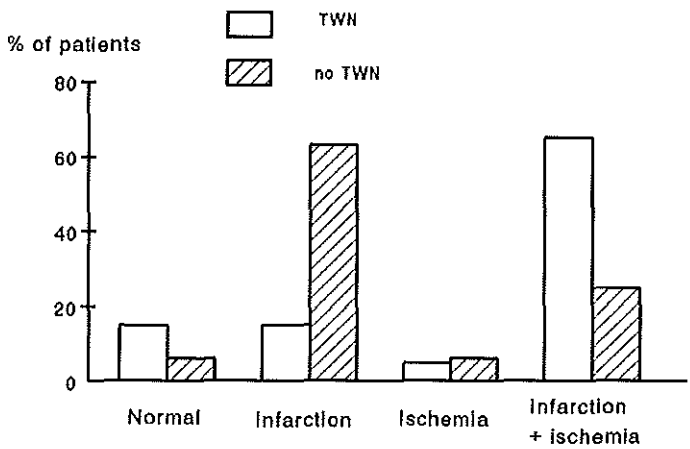

Figure 2. Distribution of the echocardiographic patterns in patients with (open bars) and without (dashed bars) T wave normalization.

Coronary angiography: Group 1 (patients with TWN): Significant coronary stenosis was detected 12 of the 14 patients who underwent coronary angiography; 6 patients had a single vessel disease, 4 had 2 vessel disease, and 2 had 3 vessel disease. The remaining 2 patient had <50% lesions in the left anterior descending coronary artery. All patients with significant coronary stenosis had TWN in a corresponding myocardial segment. Group 2 (patients without TWN): Significant coronary stenosis was detected in 8 of the 10 patients who underwent coronary angiography; 5 patients had a 2 vessel disease, and 1 had 3 vessel disease. One patient had <50% lesions in the LAD and the RCA and the remaining patient had a normal coronary angiogram.

TABLE I. Demographic data, stress test results, and coronary anglographic findings in the study group

Nr	T wave inversion, location	TWN, location	max HR, bpm	max BP, mmHg	RPD, location	stress WMA, location	coronary stenosis
1	2	2	125	170/85	2	2	RCA
2	1, 2	1,2	140	180/70	0	0	RCA
3	2	2	150	160/115	2	2	Cx, RCA
5	1, 2	2	128	100/65	2	2	LAD
6	2	2	122	180/80	1	1	LAD, Cx, RCA
7	1, 2	1	137	160/60	1	0	LAD <50%
8	2	2	137	145/90	1	1	LAD, Cx
9	1, 2	1, 2	150	85/51	1, 2	1	LAD
10	1, 2	1, 2	152	171/75	1, 2	1, 2	RCA, Cx
11	1, 2	1	162	164/76	0	0	LAD <50%
12	2	2	152	151/80	2	1, 2	RCA,LAD, Cx
13	2	2	92	128/79	2	2	-
14	1, 2	2	142	121/75	2	2	Cx
15	1	1	142	127/66	0	0	-
16	1	1	134	105/52	1	0	LAD
17	1	1	136	138/73	1	1	-
18	1, 2	1, 2	125	143/80	1, 2	1, 2	-
19	1,2	1,2	135	138/88	1,2	1	-
20	2	2	131	140/80	2	2	-
21	1, 2	0	110	160/70	0	0	-
22	2	0	160	120/80	0	0	-
23	2	0	110	140/90	0	0	RCA
24	1, 2	0	100	135/80	2	0	RCA <50%
25	1, 2	0	136	190/70	0	0	-
26	1, 2	0	96	160/80	2	0	LAD
27	2	0	128	128/70	0	1	LAD, Cx
28	2	0	148	140/58	1, 2	0	-
29	1, 2	0	125	130/73	2	2	LAD
30	2	0	20	130/84	1, 2	1	-
31	2	0	143	145/101	0	1	LAD, RCA
32	2	0	139	90/54	0	0	LAD, Cx, RCA
33	1, 2	0	124	124/58	0	0	LAD
34	2	0	127	130/80	0	0	RCA
35	2	0	133	125/70	1,2	1,2	normal
36	1,2	0	140	120/83	0	0	-

Location: 1=anterior; 2=infero-lateral; 0=absence. LAD=left anterior descending; Cx=circumflex; RCA=right coronary artery; WMA=wall motion abnormalities;HR=heart rate; BP=blood pressure; + present; 0 absent; - not performed; RPD=reversible perfusion defect; bpm=beats per minute; TWN=T wave normalization.

Table II. Wall motion and perfusion score at rest and peak stress with and without T wave normalization (TWN).

	TWN	no TWN	P value
Rest wall motion score	21.0 ± 4.2	21.7 ± 7.3	NS
Peak wall motion score	23.1 ± 6.4	21.9 ± 5.3	NS
Δ wall motion score	2.1 ± 3.9	0.2 ± 2.1	0.03
Stress perfusion score	7.15 ± 4.6	5.25 ± 4.2	NS
Rest perfusion score	3.9 ± 3.3	3.8 ± 3.6	NS
Δ perfusion score	3.3 ± 2.9	1.5 ± 2.3	0.04

Δ = stress-rest

TABLE III. Diagnostic accuracy of T wave normalization to predict reversible perfusion defects (RPD) and stress-induced wall motion abnormalities (WMA) % and 95% C.I., (confidence intervals).

	RPD		WMA	
	%	95% C.I.	%	95% C.I.
Sensitivity	74	60-88	74	59-88
Specificity	77	63-91	65	59-80
Accuracy	75	61-89	69	54-84
Positive predictive value	85	73-97	70	55-85
Negative predictive value	63	47-78	69	54-84

DISCUSSION

The results of dobutamine stress test mostly rely on the interpretation of different imaging modalities, since ST-segment changes have been reported to be less accurate for the diagnosis of coronary artery disease (9). However, no information are available on the functional significance of TWN during dobutamine stress test. The data available based on exercise stress test mostly indicate a poor positive predictive value and a low specificity for myocardial

ischaemia. However, such data were obtained in non homogeneous populations with different prevalence of coronary disease, often with concomitant ECG abnormalities, and different reference methods for ischaemia (1-5). All these factors make the comparison difficult between the previous data and those in the present study. Since the mechanism of TWN can be related to myocardial ischaemia but also to the direct effect of the sympathetic stimulation in otherwise normal myocardium (6,7), it can be expected that TWN is more frequently related to ischaemia in a population with proven coronary disease. The results of the present study, including a well defined homogeneous population and state-of-the-art methods for the noninvasive functional assessment of myocardial ischaemia (9-12), confirm this hypothesis. Indeed, we found a strong association between TWN and the imaging markers of myocardial ischaemia in particular, a high positive predictive value of TWN (85%) for the presence of reversible perfusion defects was detected. The specificity of TWN was slightly higher for the detection of transient perfusion defects than new wall motion abnormalities (Table II). This can be explained by the known higher prevalence of perfusion defects compared to wall motion abnormalities (11). This is due to the fact that perfusion scintigraphy may detect both malperfusion and true ischaemia. In contrast, stress echocardiography is more specific for true myocardial ischaemia.

The high prevalence of myocardial ischaemia in segments with baseline dyssynergy both by echocardiography and SPECT in patients with TWN compared to patients with persistent negative T waves is an indicator of the presence of jeopardized viable myocardium in the peri-infarction zone. This is supported by the agreement between the sites of TWN in the ECG, myocardial ischaemia and coronary stenosis. We have previously reported that in patients with recent myocardial infarction, T wave normalization at low dose dobutamine infusion is a predictor of myocardial viability and spontaneous improvement of function (13). The results of both studies underscore a relation between TWN and two different signs of myocardial viability: spontaneous recovery of function of the stunned myocardium and peri-infarction ischaemia in a stunned or hibernating myocardium subtended by a stenosed coronary artery.

Limitations of the study

We have evaluated a patient population with a previous myocardial infarction and suspected myocardial ischaemia. A high prevalence of ischaemia would be expected in such population. However, specificity of TWN in our study was derived from a control group with persistent negative T wave and similar clinical characteristics. To our knowledge, no previous study utilized a similar approach to derive specificity of TWN. Coronary angiography was not used as a gold standard. However, the aim of the study was to assess the relationship between TWN and stress-induced ischaemia using accurate markers of ischaemia which have been previously validated (7-9) rather than defining the relation with coronary anatomy. A significant coronary stenosis, particularly in

infarct related artery may not necessarily be associated with stress-induced ischaemia. Furthermore, non-invasive stress testing is frequently used to assess the functional significance of a documented coronary stenosis in patients with previous myocardial infarction.

In conclusion, in patients with previous non-Q wave myocardial infarction, isolated TWN during dobutamine stress test is associated with the presence of echocardiographic and scintigraphic myocardial ischaemia. In this specific group of patients, this ancillary electrocardiographic pattern should not be disregarded as an indicator of myocardial ischaemia in cases with poor or difficultly interpretable cardiac stress images.

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CHAPTER 4

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Stress-Induced Left Ventricular Dysfunction in Silent and Symptomatic Myocardial Ischemia During Dobutamine Stress Test

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The extent and severity of dobutamine-induced left ventricular (LV) dysfunction with and without angina were evaluated in 105 consecutive patients with significant coronary artery disease and a positive dobutamine stress echocardiographic test, defined as new or worsening wall motion abnormalities during high-dose dobutamine stress (up to 40 μg/kg/min). Wall motion score (WMS) was derived using a 16-segment, 4-grade scoring method. The difference between stress and rest WMS (ΔWMS) was derived as a global measure of stress-induced LV dysfunction. Typical angina occurred in 61 patients (58%) during the test. There was no significant difference between patients with or without angina with respect to age, gender, prevalence of previous myocardial infarction, multivessel disease, or number of diseased coronary arteries. Patients with angina had a higher prevalence of a history of angina before the test. Rest, stress, and ΔWMS, number and distribution of ischemic segments, and number of segments with an increase in regional WMS of ≥2 were not significantly different in patients with or without angina. ST-segment depression was more frequent in patients with angina (56% vs 29%, p <0.05). Patients with (vs those without) ST-segment depression had a significantly higher number of ischemic segments with normal baseline contraction, an equal total number of ischemic segments, and a similar ΔWMS. It is concluded that in patients with anatomically and functionally significant coronary artery disease, the amount of stress-induced LV dysfunction evaluated by dobutamine stress echocardiography is similar in patients with or without angina. ST-segment depression is more common in patients with angina and is associated with more extensive ischemia in normally contracting segments at rest.

(Am J Cardiol 1995;75:1112–1115)

Silent ischemia may be expressed as asymptomatic ST-segment depression, reversible perfusion defects, or transient wall motion abnormalities in patients with coronary artery disease.[1–11] Available data regarding the influence of the severity of ischemia on the development of pain are conflicting.[1–8] The dobutamine stress test (DST) is an accurate method for the functional evaluation of patients with known or suspected coronary artery disease, especially in those with limited exercise capacity.[12–14] It has been reported that ischemia, manifested as transient wall motion abnormalities during a DST, may occur without symptoms.[12,13] However, it is not known if there is a difference in the amount of abnormally contracting myocardium in patients with or without angina during a positive DST. The latter is important for prognostic stratification.[15,16] Consequently, the aim of this study was to compare the clinical characteristics and extent of myocardial ischemia during a positive DST in patients with or without angina.

METHODS

Patient population: The study population comprised 105 consecutive patients with significant coronary artery disease and a positive dobutamine stress echocardiographic test, defined as new or worsened wall motion abnormalities during a DST. All patients had a limited exercise capacity and were referred for a DST for diagnostic evaluation of myocardial ischemia. Significant coronary artery disease was defined as ≥50% luminal diameter stenosis of ≥1 major coronary artery detected at angiography within 3 months of a DST.

Mean age was 60 ± 9 years; 83 patients (79%) were men. Seventy-two patients (69%) had a previous myocardial infarction.

The baseline electrocardiogram was interpretable for ischemia in 92 patients (absence of electrocardiographic evidence of left ventricular [LV] hypertrophy or bundle branch block). Eighty-two patients (78%) were receiving antianginal medications; 50 of them were taking beta blockers. A history of typical exertional angina in the pretest period was obtained in 51 patients (49%).

Dobutamine stress test: Dobutamine was infused as an incremental dose of 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given to patients not achieving 85% of their age-predicted maximal heart rate. The electrocardiogram was monitored throughout dobutamine infusion and a 12-lead electrocardiogram was recorded each minute.

Echocardiographic images were acquired at rest and during the test and recovery. For both rest and stress studies, the LV wall was divided into 16 segments and scored using a 4-point scale of wall motion and thickening: 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. The diagnosis of ischemia was based on the occurrence of new or worsening wall motion abnormalities during DST. Wall motion score (WMS) was derived as a measure of global LV function by summation of the

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TABLE I Clinical Characteristics of Patients With and Without Angina During a Positive Dobutamine Stress Echocardiographic Test

	Angina (n = 61)	Silent (n = 44)
Age (yr)	61	58
Male gender	50 (82)	33 (75)
Beta-blocker therapy	27 (44)	23 (52)
History of angina pectoris	36 (59)	15 (34)*
Previous myocardial infarction	40 (66)	32 (72)
Multivessel disease	43 (70)	25 (57)
No. of diseased arteries	2.1 ± 0.8	1.9 ± 0.9
Peak heart rate (beats/min)	131 ± 16	141 ± 10†
Peak systolic blood pressure (mm Hg)	139 ± 26	133 ± 29
Peak rate-pressure product	18,215 ± 3,970	18,834 ± 3,892
Peak dobutamine dose (μg/kg/min)	38 ± 7	39 ± 3
Atropine administration	29 (48)	23 (52)
Atropine dose (mg/patient)	0.6 ± 0.3	0.7 ± 0.3
ST-segment depression‡	30/54 (56)	11/38 (29)*

*p <0.05; †p <0.0005.
‡Values derived from interpretable electrocardiograms.
Values are expressed as number (%) or mean ± SD.

score of the 16 segments both at rest and at peak stress. The difference between stress and rest WMS (ΔWMS) was used as a global measurement of the amount of stress-induced LV dysfunction. Image interpretation was performed by 2 experienced observers without the knowledge of the patients' clinical data. In case of disagreement, a third investigator reviewed the images and a majority decision was achieved. In our laboratory, inter- and intraobserver agreement for stress echocardiographic assessment are 91% and 92%, respectively.[17]

The test was interrupted if severe chest pain, ST-segment depression >2 mm, ST-segment elevation >2 mm in patients with normal baseline electrocardiogram, significant ventricular or supraventricular arrhythmia, or a systolic blood pressure decrease of >40 mm Hg occurred during the test.

Statistical analysis: Unless specified, data are presented as mean ± SD. The chi-square and Fisher's exact tests 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

The test was performed in all patients without serious complications. The test was interrupted prematurely before reaching the maximal dose or the target heart rate in 18 patients. Reasons for premature termination of the test were angina (n = 9), ST-segment depression (n = 3), and hypotension (n = 6). The test was not interrupted because of stress-induced wall motion abnormalities in any patient. Typical angina was provoked in 61 patients (58%) during the test. The remaining 44 patients (42%) were considered to have silent ischemia. Age, gender, prevalence of previous myocardial infarction, diabetes mellitus, hypertension, smoking, multivessel disease, and number and distribution of stenosed coronary arteries were not significantly different between both groups. Clinical characteristics of both groups are listed in Table I.

Patients with dobutamine-induced angina had a higher prevalence of typical effort angina before the test (59% vs 34%, p <0.05). There was no significant difference between both groups with respect to the use of antianginal medication at the time of the test, the use of atropine, peak dobutamine and atropine doses, or peak systolic blood pressure. Peak heart rate was significantly lower in patients with angina (131 ± 16 vs 141 ± 10 beats/min, p <0.0005). However, peak rate-pressure product was not significantly different in patients with or without angina.

TABLE II Echocardiographic Findings of Patients With and Without Angina During a Positive Dobutamine Stress Echocardiographic Test

	Angina (n = 61)	Silent (n = 44)
Rest WMS	23.6 ± 7	24.3 ± 6
Stress WMS	28.0 ± 8	27.9 ± 7
ΔWMS	4.4 ± 3	3.6 ± 2
Total no. of ischemic segments	3.3 ± 2	2.8 ± 2
No. of ischemic segments with dyssynergy at rest	1.5 ± 1.9	1.4 ± 1.5
No. of ischemic segments normal at rest	1.8 ± 1.9	1.4 ± 1.2
No. of segments with regional ΔWMS ≥2	0.33 ± 0.8	0.25 ± 0.5

Values are expressed as mean ± SD.
WMS = wall motion score; ΔWMS = difference between stress and rest wall motion score.

ST-segment depression (≥1 mm horizontal or downsloping depression 80 ms after the J point below the resting baseline level) occurred in 41 of the 92 patients (45%) who had an interpretable electrocardiogram. ST-segment depression was more frequent in patients with angina (56% vs 29%, p <0.05).

Stress echocardiography: There was no significant difference between patients with or without angina with respect to rest WMS (23.6 ± 7 vs 24.3 ± 6), stress WMS (28 ± 8 vs 27.9 ± 7), ΔWMS (4.4 ± 3 vs 3.6 ± 2), number of overall ischemic myocardial segments (3.3 ± 2 vs 2.8 ± 2), ischemic segments with an increase in regional score of ≥2 during stress (0.33 ± 0.8 vs 0.25 ± 0.5), ischemic segments with normal baseline contraction (1.8 ± 1.9 vs 1.4 ± 1.2), or ischemic segments exhibiting dys-

synergy at rest (1.5 ± 1.9 vs 1.4 ± 1.5). The difference was still not significant after exclusion of patients whose test was interrupted before reaching the target heart rate. Distribution of ischemia in the vascular territories of individual coronary arteries was not different with or without chest pain. Reclassification of patients defining silent ischemia as absence of both angina and ST-segment depression did not alter the comparable findings of rest, stress, and ΔWMS, and number of ischemic segments in the silent and symptomatic groups. Echocardiographic findings of both groups are listed in Table II.

In patients with an interpretable electrocardiogram, there was no significant difference between patients with or without ST-segment depression with respect to rest WMS (23.2 ± 6 vs 23.4 ± 7), stress WMS (27.4 ± 7 vs 26.6 ± 8), ΔWMS (4.2 ± 2.5 vs 3.3 ± 2.5), or total number of ischemic segments (3.6 ± 2 vs 2.9 ± 1.9). ST-segment depression was associated with a significantly higher number of ischemic segments with normal baseline contraction (2.3 ± 2 vs 1.3 ± 1.4, $p < 0.05$).

DISCUSSION

The results of our study are derived from a population with inadequate exercise capacity undergoing a DST for diagnostic evaluation of myocardial ischemia. Our data show that in patients with anatomically and functionally significant coronary artery disease documented by coronary angiography and a positive dobutamine stress echocardiographic test, the occurrence of angina during the test is not related to the extent or the severity of stress-induced LV dysfunction or the extent of coronary artery disease. Angina was more likely to occur in patients with a history of angina in the pretest period. Patients with or without angina have otherwise comparable clinical characteristics. ST-segment depression was more common in patients with angina and was associated with a higher extent of stress-induced LV dysfunction in myocardial segments with normal baseline contraction. However, the overall extent and severity of stress-induced LV dysfunction were not significantly different with or without ST-segment depression.

Comparison with previous studies: Some investigators have reported a greater extent and severity of ischemia in symptomatic patients than in those with silent ischemia. Iskandrian and Hakki[2] reported that angina correlated with more severe deterioration of regional function using first-pass radionuclide ventriculography. Travin et al[4] reported that patients with exercise-induced thallium redistribution without angina had less ischemia than patients with angina. Klein et al[1] reported that the induction of chest pain is associated with more extensive thallium perfusion abnormalities when analyzed in a broad-spectrum population with coronary artery disease. The analysis of chest pain tended to lose its value when it was restricted to a coronary artery disease population with a greater prior likelihood of inducible ischemia.

In contrast, numerous studies have failed to find a difference in the amount of ischemic myocardium between patients with silent and symptomatic ischemia during exercise stress testing.[3-9]

The diagnosis of ischemia by myocardial perfusion scintigraphy relies on the detection of stress-induced hypoperfusion[4,7,8]; however, this does not always signify ischemia. Stress-induced LV dysfunction, which represents true ischemia, can be accurately detected by echocardiographic evaluation of wall motion and thickening during stress test. Silent ischemia during exercise stress testing was evaluated by echocardiography only in 2 studies. Marwick et al[3] reported a similar extent and severity of exercise-induced wall motion abnormalities and a similar prevalence of ST-segment depression in patients with or without chest pain. However, evaluation of wall motion immediately after exercise may not allow for evaluation of peak ischemic burden in these patients because of a possibly rapid, complete, or partial recovery of wall motion in the immediate postexercise period. In our study, symptomatic ischemia was associated with a higher prevalence of ST-segment depression than silent ischemia. This finding may suggest a common pathway for both the electrical and painful response to ischemic stimulus.[7] Our findings are consistent with other reports that described a higher prevalence of ST-segment depression in patients with versus without angina during ischemic episodes.[4,5,7,8]

Hecht et al[5] concluded that exercise-induced ST-segment depression is the single most significant variable related to the amount of ischemia evaluated by supine bicycle stress echocardiography, and that exercise chest pain had no significant relation. In our study, ST-segment depression was associated with more extensive ischemia in myocardial segments with normal baseline contraction. However, the total number of ischemic segments as well as the ΔWMS were not significantly different with or without ST-segment depression. This may be explained by a lower sensitivity of ST-segment depression for detecting ischemia in segments with baseline dyssynergy. The greater the amount of ischemic segments with normal baseline contraction, the more chance of involvement of more "non-electrically silent areas" of myocardium, and consequently the development of ST-segment depression. The discrepancy between our findings and those of Hecht et al may be explained by a difference in the relative proportion of normal and dyssynergic segments at rest that developed ischemia during stress.

Dobutamine stress echocardiography allows evaluation of regional wall motion and thickening in multiple planes during peak stress without the interference of rapid respiratory movements as with exercise. We are not aware of other studies in which the relation between chest pain and ST-segment depression and the extent and severity of dobutamine-induced LV dysfunction were studied in patients with coronary artery disease and a positive dobutamine stress echocardiographic test.

Clinical implications: The absence of chest pain during a positive dobutamine stress echocardiographic test should not be interpreted as evidence of less severe ischemia. Consequently, greater attention should be paid to the amount of stress-induced myocardial dysfunction in the management of patients with a positive test rather

than to the occurrence of symptoms. The prognostic significance of silent wall motion abnormalities induced by dobutamine stress remains to be determined.

Study limitations: Despite the fact that echocardiographic evaluation of wall motion is an accurate method for evaluating the extent of stress-induced ischemia, evaluation of the severity of wall motion abnormalities relies upon a semiquantitative visual analysis of images. However, this is the routinely applied method in most clinical laboratories. Most patients were receiving antianginal medication, which may have decreased the prevalence of angina or ST-segment depression and influenced the extent and severity of ischemia. Nevertheless, the percentage of patients with or without angina who received medication was not different, and the effect of medications in both groups can be expected to be similar.

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CHAPTER 5

ALTERED MYOCARDIAL PERFUSION DURING DOBUTAMINE STRESS TEST IN SILENT VERSUS SYMPTOMATIC MYOCARDIAL ISCHEMIA ASSESSED BY QUANTITATIVE SPECT IMAGING[1]

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ABSTRACT

Aim of the study was to compare the extent and severity of reversible underperfusion in silent versus painful myocardial ischemia during dobutamine stress test. A consecutive series of 161 patients with significant coronary artery disease and reversible perfusion defects on 201 thallium or 99m technetium MIBI SPECT performed at rest and at high dose dobutamine stress (up to 40 μg/kg/min) were studied. The left ventricle was divided into 6 segments. Ischemic score was derived by subtracting rest from stress defect score using quantitative measurements. Results were derived separately for MIBI and thallium studies. Patients with multivessel disease had a higher ischemic score and a higher number of reversible perfusion defects than patients with single vessel disease. Typical angina occurred in 82 patient (51%) during the test. There was no significant difference between patients with or without angina with respect to age, gender, peak rate-pressure product, prevalence of previous myocardial infarction, diabetes mellitus, multivessel disease, number of stenotic coronary arteries or the percentage diameter of the most severe stenosis. Stress, rest, and ischemic score as well as number and distribution of reversible defects were not different with or without angina. Patients with angina had more frequently a history of typical angina before the test (67% vs 38%, $p<0.0005$) and ST-segment depression during the test (50% vs % 33%, $p<0.01$). It is concluded that in patients with coronary artery disease and ischemia detected by

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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 ischemia, dobutamine stress test, SPECT imaging.

INTRODUCTION

Pharmacological stress testing with dobutamine is increasingly used for non-invasive diagnosis and evaluation of coronary artery disease in patients with suspected myocardial ischemia and inadequate exercise capacity (1-8). The induction of myocardial ischemia with dobutamine infusion is mainly due to an increase of myocardial contractility and heart rate (9). Dobutamine was also reported to induce coronary blood flow heterogeneity (10). Recent studies showed that dobutamine stress test in conjunction with 99m technetium MIBI or 201 thallium single photon emission computed tomographic imaging is an accurate method for the diagnosis and localization of myocardial ischemia 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 has not been compared in 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 test in patients with coronary artery disease.

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 canter for diagnostic evaluation of myocardial ischemia. All patients underwent dobutamine stress test in conjunction with 99m-technetium MIBI or 201 thallium SPECT. One hundred sixty one patients were included according to the following criteria: 1) significant coronary artery disease defined as $\geq 50\%$ diameter stenosis of one or more major epicardial arteries. 2) the occurrence of myocardial ischemia during the test defined as reversible perfusion defects on MIBI or thallium SPECT in the distribution of ≥ 1 stenotic coronary artery. Mean age was 59 $\pm$ 10 years; 129 (80%) were males. A history and/or an electrocardiographic evidence of a previous myocardial infarction were present in 105 patients (65%). Nine patients had left ventricular hypertrophy and 18 had left bundle branch block by electrocardiographic criteria. The remaining 134

patients (83%) had a resting electrocardiogram interpretable for ischemia. A history of typical effort angina before the test was obtained in 85 patients (53%). On the day of the test, 120 patients (75%) were receiving antianginal medication; including beta blocker therapy in 62.

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 5 μg/kg/min for 3 minutes, 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. 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 minutes. Significant ST-segment depression was defined as ≥ 1mm horizontal or downsloping 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, significant ventricular or supraventricular tachyarrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test.

SPECT imaging

Approximately 1 minute before the termination of the stress test, an intravenous dose of 370 MBq of MIBI (77 patients) or 74 MBq of thallium (84 patients) was administered. The acquisition of stress SPECT imaging was started immediately after thallium and one hour after MIBI injection. For the resting MIBI studies, 370 MBq were injected at least 24 hour after the first study. For the resting thallium studies, imaging was acquired 4 hours after the stress test, 20 minutes after the reinjection of 37 MBq of thallium. Image acquisition and interpretation were performed according to a previously described protocol (5). The left ventricular images were divided into 6 segments: anterior, septal (subdivided in anterior and posterior septum), lateral, infero-posterior and apical. A persistent perfusion defect on both stress and resting 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 resting imaging. This was considered diagnostic of ischemia. An experienced observer, unaware of patients' clinical or angiographic data reviewed the images. The interpretation was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Each of the 6 left ventricular segments was scored on a 4 grade score where 0 = normal and 3 = severely reduced or absent uptake. Visual perfusion defect score was derived by the summation of the individual score of the 6 myocardial segments for both rest and stress imaging. The difference between stress and rest score (ischemic score) was considered representative of the total amount of stress-induced underperfusion. Perfusion defect score was quantitatively calculated at rest and at stress images

by measuring the area between the lower limit of normal values (± 2 standard deviations) and the actual circumferential profile in 6 short axis slices. Ischemic perfusion score was derived by subtracting rest from stress score only in segments with reversible defects. Because of the potential difference in the size of perfusion defects between MIBI and thallium studies (13), quantitative perfusion defect score was studied separately with each tracer.

Quantitative coronary angiography

All patients underwent coronary angiography within 3 months of dobutamine stress test. Coronary lesions were quantified using a previously described method from our canter (14).

Statistical analysis

Unless specified, data are presented as mean values ± SD. The chi square test and Fisher exact test were used to compare differences between proportions. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant.

RESULTS

Hemodynamic response

Heart rate increased from 71 ± 13 to 138 ± 17 beats /min at peak stress ($p < 0.0001$) and systolic blood pressure from 129 ± 21 to 134 ± 32 mm Hg ($p < 0.05$). Atropine was administered in 70 patients (mean dose = 0.65 mg). In 31 patients, the test was interrupted prematurely before reaching the maximal dose or the target heart rate because of a limiting side effect. Reasons for premature termination of the test were angina in 18 patients, ST-segment depression in 3 patients, hypotension in 8 patients and tachyarrhythmias in 2 patients. ST-segment depression occurred in 56 (43%) of 134 patients with interpretable electrocardiogram. Eighty-two patients (51%) developed typical angina during the test (symptomatic ischemia group). The remaining 79 patients (49%) without angina during the test constituted the silent ischemia group.

Demographic, hemodynamic and angiographic characteristics (table I)

There was no significant difference between patients with or 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 systolic blood pressure and peak rate pressure product were not significantly different in both groups. In patients with interpretable electrocardiogram, ST-segment depression occurred in 35 of 70 patients with and in 21 of 64 patients without angina (50% vs 33%, $p < 0.05$).Prevalence of multivessel disease, number of coronary arteries with significant stenosis,

percentage diameter of most severe stenosis and distribution of individual coronary artery stenosis were not significantly different between the two groups.

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

	Angina, N=82	Silent, N=79
Age, years	59 ± 9	58 ± 10
Male gender	67 (81%)	62 (78%)
Beta blocker therapy	30 (37%)	32 (40%)
History of angina pectoris	55 (67%)	30 (38%)*
Previous myocardial infarction	50 (61%)	55 (69%)
Multivessel disease	56 (68%)	49 (62%)
Number of stenotic arteries	2.03 ± 0.8	1.96 ± 0.9
% diameter of most severe stenosis	88 ± 17%	91 ± 13%
Peak heart rate (beats/min)	131 ± 17	139 ± 17**
Peak SBP, mm Hg	139 ± 32	130 ± 31
Peak rate pressure product	18175 ± 4279	17896 ± 4555
Peak dobutamine dose, μg/kg/min	38 ± 6	39 ± 4

SBP = systolic blood pressure, * $p<0.0005$, ** $p<0.01$.

SPECT results (table II)

There was no significant difference between patients with or without angina with respect to total number of myocardial segments with reversible defects, completely reversible defects, number of segments with perfusion defects on resting imaging, stress perfusion defect score, rest score, ischemic score by both visual and quantitative analysis. Exclusion of patients in whom the test was interrupted prematurely or patients in whom the electrocardiogram was not interpretable did not alter the comparable extent and severity of underperfusion with or without angina. The regional distribution of reversible defects was not different in both groups (table III).

Table II. Scintigraphic data of patients with coronary artery disease and reversible perfusion defects with and without angina during dobutamine stress test.

	Angina N = 82	Silent N = 79
Stress score	9.1 ± 4.4	9.6 ± 4.2
Rest score	4.9 ± 3.1	5.3 ± 3.1
Ischemic score	4.2 ± 2.3	4.3 ± 2.6
Number of reversible defects	2.0 ± 1.1	2.0 ± 1.0
Number of completely reversible defects	1.0 ± 0.9	1.0 ± 0.8
Number of fixed defects on rest imaging	1.7 ± 1.4	1.8 ± 1.5
Quantitative stress defect (MIBI)	1326 ± 1251	1251 ± 1354
Quantitative rest defect (MIBI)	963 ± 1189	825 ± 965
Quantitative ischemic defect (MIBI)	472 ± 630	458 ± 671
Quantitative stress defect (Tl)	2116 ± 1662	2356 ± 1498
Quantitative rest defect (Tl)	1546 ± 1002	1884 ± 1285
Quantitative ischemic defect (Tl)	803 ± 870	710 ± 674

Tl = 201 thallium, MIBI = technetium-99m methoxyl isobutyle isonitrile.

Table III. Distribution of reversible perfusion defects in patients with or without angina during dobutamine stress test.

	Angina, N = 82	Silent, N = 79
Anterior	23 (28%)	23 (29%)
Septal anterior	29 (35%)	20 (25%)
Septal posterior	30 (37%)	25 (32%)
Infero-posterior	52 (63%)	49 (62%)
Lateral	12 (15%)	16 (20%)
Apex	17 (21%)	25 (32%)

Values are expressed as number and % of patients with reversible defects.

Patients with ST-segment depression: In the 134 patients with interpretable electrocardiogram, there was no significant difference between patients with or without ST-segment depression with respect to total number of reversible defects (2.0 ± 1.2 vs 1.8 ± 0.8), completely reversible defects (1.1 ± 1.0 vs 0.9 ± 0.7), visual ischemic score (4.3 ± 2.6 vs 4.0 ± 2.0) or quantitative ischemic score (table IV). Reversible perfusion defects without angina or ST-segment depression occurred in 43 of 134 patients with interpretable electrocardiogram (32%), whereas a combination of angina and ST-segment depression occurred in 35 patients (26). Parameters of reversible hypoperfusion were not different in various combinations of angina and ST-segment depression compared to patients without these findings (table IV).

Table IV: Quantitative ischemic perfusion defect score in patients with different combinations of angina and ST-segment depression during dobutamine stress test.

	yes	no	tracer
ST depression	485 ± 645	430 ± 654	MIBI
	859 ± 701	765 ± 836	Thallium
ST depression and Angina	441 ± 614	465 ± 679	MIBI
	858 ± 767	820 ± 909	Thallium
ST depression and/or Angina	502 ± 699	420 ± 571	MIBI
	902 ± 956	753 ± 626	Thallium

Extent and severity of ischemia in single versus multivessel disease: Patients with multivessel disease (N = 105) had a significantly higher number of reversible perfusion defects (2.3 ± 1.2 vs 1.8 ± 0.8, $p < 0.01$), visual ischemic score (4.7 ± 2.7 vs 3.7 ± 1.9, $p < 0.01$), quantitative ischemic thallium score (956 ± 1081 vs 478 ± 643, $p < 0.05$) and ischemic MIBI score (590 ± 760 vs 310 ± 409, $p < 0.05$) compared to patients with single vessel disease (figure 1).

DISCUSSION

Evaluation of the extent and severity of reversible perfusion defects during stress testing is important for prognostic stratification of patients with coronary artery disease (11-12). In our study, the additional value of angina and/or ST-segment depression in patients with coronary artery disease and

dobutamine-induced ischemia manifested as reversible perfusion defects on thallium or sestamibi SPECT was evaluated. Our finding of a higher number of reversible perfusion defects and ischemic score in patients with multi- versus single vessel disease validates the use of perfusion scintigraphy in the assessment of the extent of myocardial ischemia. Our results show that in patients with significant coronary artery disease and myocardial ischemia detected by dobutamine perfusion scintigraphy, the extent and severity of coronary artery disease and reversible underperfusion is not different with or without angina during the test. Parameters of reversible underperfusion were also similar in patients who had both angina and ST-segment depression compared to other 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 or without angina during dobutamine stress test.

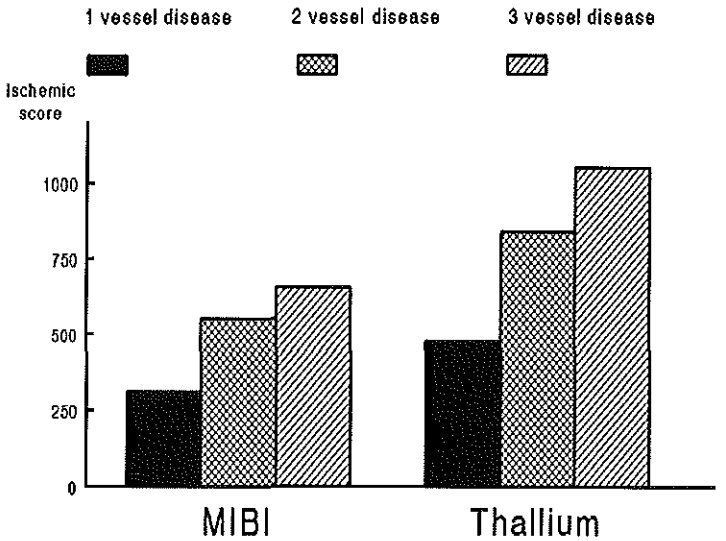

Figure 1. Ischemic perfusion defect score in patients with single, two and three vessel disease showing a positive correlation between the defect severity and number of stenotic coronary arteries.

Comparison with previous studies

To our knowledge, this is the first study in which the extent and severity of underperfusion in silent and symptomatic ischemia during dobutamine stress test were evaluated. Discordant results have been published about the functional significance of silent versus symptomatic ischemia during exercise stress test (15-20). Reversible exercise-thallium defects were reported

to be more extensive and severe in patients with compared to those without angina in studies of Klein et al. (15) and Travin et al. (16), while others failed to demonstrate that 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 loose its apparent value when its analysis is restricted to coronary artery disease population with a greater pre-test likelihood of manifesting ischemia.

Studies of left ventricular function: Various studies compared the amount of abnormally contracting myocardium in silent and painful ischemia during exercise stress test using radionuclide ventriculography (21-23) or echocardiography (24-26). Iskandrian and Hakki (21) and recently Nihoyannopolos et al. (26) reported that angina correlated with more severe deterioration of regional function. Other studies demonstrated a comparable segmental and global exercise-induced left ventricular dysfunction in silent and symptomatic ischemia 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 are not different with or without angina (27). The results of this scintigraphic study confirm our previous findings. Despite that stress-induced wall motion abnormalities are highly specific for myocardial ischemia, this study on a larger patient population 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 ischemia in akinetic segments. 3) the less operator dependent characteristics of perfusion imaging technique. 4) the higher sensitivity of perfusion scintigraphy than echocardiography at submaximal stress (28).

Hemodynamic 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 or 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. This higher prevalence of electrically silent ischemia in asymptomatic patients has been reported during dobutamine (27) and exercise stress test as well (17,20,25) which may suggest a common pathway for both the electrocardiographic and pain response to ischemic stimulus (20).

ST-segment depression and the amount of ischemia

In our study, the extent and severity of reversible underperfusion during dobutamine stress test were not different with or without ST-segment depression. We have previous reported a similar ischemic wall motion score with or without ST-segment depression during dobutamine stress test and a higher number of ischemic 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 segments with completely reversible defect with or without ST-segment depression. This contradiction may be explained by the fact that a partially reversible defect may represent ischemia in absence of baseline wall motion abnormalities. 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 ischemia assessed by 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 ischemic myocardium assessed by exercise echocardiography.

Limitations of the study

We assessed myocardial ischemia on basis of reversible perfusion defects which may represent flow malperfusion as well as true ischemia. The detection of reversible perfusion defects in severely dyssynergic segments may represent a clinical challenge (29). However, a recent study showed a high sensitivity of dobutamine thallium scintigraphy for the detection of peri-infarction ischemia (30). An other limitation of the study is that most of patients were receiving antianginal medications which may modify symptoms and signs of ischemia. We have previously shown that the adminstration of atropine enhances the detection of myocardial ischemia during dobutamine stress test especially in patients receiving beta blockers (31,32). Furthermore, the percentage of patients receiving medications was not different on both group. Finally, ST-segment depression in patients with myocardial infarction may represent reciprocal changes without ischemia. Despite this limitation, exercise-induced ST-segment depression after myocardial infarction was generally considered as a marker of a positive test associated with an adverse outcome (33).

Conclusions

In patients with coronary artery disease and ischemia manifested as transient perfusion defects on dobutamine SPECT imaging, the extent and severity of coronary artery disease and reversible underperfusion are comparable in patients with or without angina during the test. Patients with symptomatic ischemia have a higher prevalence of typical effort angina before the test and a higher prevalence of ST-segment depression during the test. The amount of

ischemic myocardium is similar in patients with or without ST-segment depression. The absence of angina and/or ST-segment depression in a population with anatomically and functionally significant coronary artery disease should be disregarded as a marker of less severe ischemia.

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CHAPTER 6

DOBUTAMINE-INDUCED HYPOPERFUSION WITHOUT TRANSIENT WALL MOTION ABNORMALITIES: LESS SEVERE ISCHEMIA OR LESS SEVERE STRESS?[1]

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ABSTRACT

Rationale. Aim of the study was to compare the clinical characteristics, hemodynamic response and severity of ischemia in patients with coronary artery disease and reversible perfusion defects on dobutamine MIBI SPECT with or without transient wall motion abnormalities.

Background. The occurrence of reversible perfusion defects without concomitant wall motion abnormalities in patients with coronary artery disease was attributed to less severe ischemia. However, little data are available to support this observation.

Methods. Fifty four consecutive patients with significant coronary artery disease and reversible perfusion defects on dobutamine (up to 40 μg/kg/min) MIBI SPECT were studied (mean [$\pm$ SD] age 59 $\pm$ 11 years, 38 men). All patients underwent simultaneous echocardiography. The myocardium was divided into 6 matched segments and ischemic perfusion score was quantitatively derived in myocardial segments with reversible defects.

Results. New or worsening wall motion abnormalities occurred in 40 (74%) patients (group A) and were absent in 14 (26%) patients (group B). There was no significant difference between both groups with respect to age, previous myocardial infarction, number of abnormal coronary arteries (1.8 $\pm$ 0.8 $\pm$ 1.6 $\pm$ 0.9), number of reversible perfusion defects (1.6 $\pm$ 0.9 vs 1.8 $\pm$ 0.7) or ischemic perfusion score (412 $\pm$ 750 vs 526 $\pm$ 553). Patients of group A had a higher prevalence of male gender (80% vs 43%, $p<0.01$) a higher peak systolic blood pressure (147 $\pm$ 30 vs 127 $\pm$ 31 mm Hg, $p<0.05$), a higher

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peak rate pressure product (19,632 ± 4,081 vs 16,939 ± 4,344, $p < 0.01$), and a higher prevalence of angina (53% vs 14%) and ST-segment depression (55% vs 14%) $p < 0.05$ in both.
Conclusions. In patients with coronary artery disease and ischemia on dobutamine MIBI SPECT, the absence of transient wall motion abnormalities is associated with a similar extent and severity of reversible perfusion defects, a lower stress rate-pressure product and a higher prevalence of female gender compared to patients with transient wall motion abnormalities. Mechanically silent ischemia should be disregarded as a marker of less severe ischemia on myocardial perfusion scintigraphy.

Key words: Dobutamine stress echocardiography-MIBI SPECT imaging-Myocardial ischemia.

INTRODUCTION

The diagnosis of myocardial ischemia relies upon the detection of different pathophysiologic sequela of coronary artery disease. These include reversible hypoperfusion and wall motion abnormalities, ST-segment depression and typical anginal pain (1-3). Reversible perfusion and wall motion abnormalities during exercise or pharmacological stress testing are the most accurate markers of myocardial ischemia in patients referred for evaluation of coronary artery disease (1-14). It has been demonstrated that hypoperfusion precedes the occurrence of wall motion abnormalities in the ischemic cascade (15-16). The severity of myocardial ischemia assessed by thallium scintigraphy has been reported to determine the occurrence or absence of concomitant transient wall motion abnormalities during dobutamine stress test (17). If this is confirmed by other studies, a combination of reversible perfusion defects and transient wall motion abnormalities would identify patients with severe ischemia and provide additional data for the management and prognostic stratification of patients with coronary artery disease. In this study we compare the clinical, hemodynamic and scintigraphic variables in patients with coronary artery disease and reversible perfusion defects on dobutamine MIBI SPECT with and without transient wall motion abnormalities on simultaneous echocardiography.

METHODS

Patients selection

The study population comprised 54 consecutive patients with chest pain and inability to perform an adequate exercise test, referred to our cardiac stress imaging laboratory who underwent dobutamine stress echocardiography in conjunction with MIBI SPECT myocardial perfusion imaging. All patients fulfilled the following criteria: 1) The presence of reversible perfusion defects on MIBI SPECT in the vascular territory of ≥ 1 stenotic coronary artery. 3) Adequate imaging quality. Mean age was 59 ± 11 years. There were 38 men

and 16 women. Thirty one patients (57%) were receiving antianginal medications including beta blockers in 28 (52%). Thirty seven patients (69%) had a previous myocardial infarction.

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 10 μg/kg/min, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age and sex predicted maximal heart rate (18). The ECG was monitored continuously and recorded each minute. Blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant tachyarrhythmias or systolic blood pressure fall >40 mm Hg occurred during the test.

Stress echocardiography

Echocardiographic images were acquired at rest and during the test and recovery. Left ventricular wall was divided into 16 segments (19) and scored using a 4-point scale, where 1=normal, 2=hypokinesis, 3=akinesis, 4 = dyskinesis (4-5). Both wall motion and thickening were considered for analysis. Wall motion score was obtained by the summation of the individual score of the 16 segments. The diagnosis of ischemia relied upon the occurrence of wall motion abnormalities in one or more normal segment and/or the occurrence of akinesis or dyskinesis in one or more hypokinetic segment at rest. As we have previously concluded, ischemia was not considered if akinetic segments became dyskinetic without improvement at low-dose dobutamine (20). The echocardiograms were recorded on video tapes and digitized on optical disk (Vingmed CFM 800). Images were compared side by side in quad-screen format. Images interpretation was performed by 2 experienced observers without the knowledge of the patients' clinical, demographic or scintigraphic data. In case of disagreement, a majority decision was achieved by a third investigator. We have previously reported an inter-and intra-observer agreement for dobutamine stress echocardiographic assessment in our laboratory of 91% and 92% respectively (21).

SPECT imaging

Approximately 1 minute before the termination of the stress test, an intravenous dose of 370 MBq of MIBI was administered. Stress images were acquired 1 hour after termination of dobutamine infusion. For resting studies 370 MBq of MIBI were injected at least 24 hours after the stress study (8). For each study 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 were defined. Each of the 6 short axis slices was divided into 8 equal segments. The interpretation of the scan was semiquantitatively performed by visual analysis

assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed in side by side pair by an experienced observer who was unaware of the patients' clinical or echocardiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in 2 or more contiguous segments or slices. This was considered diagnostic of ischemia. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments or slices which persists on rest images. Echocardiographic and scintigraphic images were matched into 6 major segments: anterior, inferior, septal (subdivided into anterior and posterior) posterolateral and apical. To assess the severity of hypoperfusion, each of the 6 major left ventricular segments was scored on a 4 grade score where 0 = normal and 3 = severely reduced or absent uptake. Perfusion score was derived by the summation of the score of the 6 myocardial segments. Visual ischemic score was obtained by subtracting rest from stress score. Perfusion defect score was quantitatively calculated by measuring the area between the lower limit of normal values ($\pm$ 2 standard deviations) and the actual circumferential profile in 6 short axis slices. Ischemic score was derived by subtracting rest from stress score in segments with reversible defects.

Coronary angiography

Coronary angiography was performed, using the Judkins technique, within 3 months in all patients. Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$ in one or more major epicardial arteries. Coronary arteries were assigned to particular myocardial segments as previously described (4).

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. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant.

RESULTS

Dobutamine stress test

Heart rate increased from 69 $\pm$ 12 at rest to 131 $\pm$ 18 beats /min at peak stress ($p < 0.0001$) and systolic blood pressure from 129 $\pm$ 20 at rest to 141 $\pm$ 30 mm Hg at peak stress, $p < 0.01$).

MIBI SPECT results

Reversible perfusion defects were detected in all patients (by inclusion criteria). A total of 97 reversible defects were identified. Those were completely reversible in 53 (55%) segments (34 patients) and partially reversible in 44 (45%) segments (32 patients). In 30 segments, a fixed perfusion defect was

detected (21 patients). Among 97 segments with a reversible defects 8 (8%) were not associated with a significant stenosis of the related artery (7 in the inferior wall and one in the anterior septum). These defects were not included in the calculation of ischemic perfusion defect score.

Stress echocardiography

Wall motion abnormalities were detected in 35 patients (65%) at rest. New or worsening wall motion abnormalities were detected in 40 patients (74%). These patients comprised group A. Group B comprised 14 patients (26%) without stress-induced wall motion abnormalities. Nine patients in group B had baseline wall motion abnormalities, which were confined to the infarct region in all of them. 4 of these patients showed improvement of contraction in the infarct region; whereas 5 patients had unchanged wall motion during dobutamine infusion. In group A, all patients had transient wall motion abnormalities in the vascular territories of ≥ 1 abnormal coronary artery. A total of 83 ischemic segments were detected, 6 of them (7%) were not in the vascular territory of an abnormal artery (3 inferior, 1 lateral and 2 anterior segments). In group B, a negative echocardiogram was associated with a reversible perfusion defect confined to a dyssynergic segment in 4 patients (29%). The involved segments were hypokinetic in 3 patients and akinetic in one patient. 2 of these patients had improvement of thickening during dobutamine infusion.

Clinical characteristics and hemodynamic response

There was no significant difference between group A and B with respect to age, previous myocardial infarction, risk factors or beta blocker therapy. In patients with previous myocardial infarction, the infarct location was anterior in 13 (50%) of group A and 3 (27%) in group B. Patients of group B had a higher prevalence of female sex, a lower peak rate pressure product, a lower peak systolic blood pressure, a lower incidence of angina and ST-segment depression during the test (table 1) and a trend to a lower peak dobutamine dose (37.9 ± 5.8 vs 39.8 ± 1.6, $p = 0.06$) compared to group A. Systolic blood pressure increased significantly from rest to peak stress in group A ($p < 0.01$) but not in group B. Atropine was given in 20 patients in group A (50%) and in 6 patients in group B (43%).

A drop or failure of increase of systolic blood pressure from rest to peak stress occurred in 12 patients (30%) in group A and in 9 patients (64%) in group B ($p < 0.05$). The test was interrupted in 9 (23%) patients in group A (angina in 6 patients and ST-segment depression in 3 patients) and in 3 (21%) patients (all with angina) in group B (p = NS). Twenty two patients in group A (55%) and 4 patients of group B (29%) achieved 85% of the maximal exercise heart rate predicted for age and sex ($p = 0.09$).

Table 1: Clinical features and hemodynamic data in patients with reversible perfusion defects on dobutamine MIBI SPECT with and without transient wall motion abnormalities.

	Transient WMA + (N = 40)	Transient WMA - (N = 14)
Age (years)	61 ± 10	57 ± 12
Female sex	8 (20%)	8 (57%)*
Previous infarction	26 (65%)	11 (79%)
Beta blocker medication	23 (58%)	5 (36%)
Rest HR	70 ± 13	68 ± 11
Peak HR	134 ± 16	125 ± 18
Rest SBP	130 ± 18	128 ± 23
Peak SB	147 ± 3	127 ± 31 **
Rest rate-pressure product	9,160 ± 2,553	8,765 ± 2,535
Peak rate-pressure product	19,632 ± 4,081	16,939 ± 4,344 *
85% of target HR achieved	22 (55%)	4 (29%)
Angina during the test	21 (53%)	2 (14%)**
ST-segment depression	17 (55%)#	2 (14%)**

SBP = systolic blood pressure (mm Hg), HR = heart rate (beats/min), WMA = wall motion abnormalities, * $p<0.01$, ** $p<0.05$, # = in patients with interpretable ECG.

Echocardiographic, angiographic and scintigraphic data

There was no significant difference between both groups with respect to prevalence of multivessel disease, number and distribution of abnormal coronary arteries or resting wall motion score. Peak wall motion score was higher in group A. The number of reversible perfusion defects as well as stress, rest and ischemic perfusion score were not different in both group (table 2). The distribution of reversible defects in the 6 segments was similar (table 3) except for a higher prevalence of anterior defects in group B ($p<0.01$). Inclusion of the 5 patients of group B who had unchanged wall motion during dobutamine infusion in group A did not change the comparable parameters of reversible hypoperfusion in the 2 groups. All patients with left bundle branch block (N = 6) and left ventricular hypertrophy (N = 3) had transient wall motion abnormalities.

Table 2: Echocardiographic and angiographic data in patients with reversible perfusion defects on dobutamine MIBI SPECT with and without transient wall motion abnormalities.

	Transient WMA + (N = 40)	Transient WMA - (N = 14)
Resting WMA	26 (65%)	9 (64%)
Resting wall motion score	22 ± 6	20 ± 4
Stress wall motion score	26 ± 7	20 ± 4 *
Multivessel disease	22 (55%)	5 (37%)
Number of stenotic arteries	1.8 ± 0.8	1.6 ± 0.9
LAD disease	27 (68%)	10 (71%)
LCx disease	18 (45%)	5 (36%)
RCA disease	25 (63%)	7 (50%)

LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery, WMA = wall motion abnormalities, * $p<0.01$.

Variables associated with female gender:

A negative stress echocardiogram was obtained in 8 of 16 females and in 6 of 38 males (50 % vs 16%, $p<0.01$). The following variables were not different between females and males: age (62 ± 13 vs 58 ± 9 years), resting wall motion score (19.7 ± 4.5 vs 22.7 ± 5.9), peak systolic blood pressure (140 ± 28 vs 142 ± 32 mm Hg), rate pressure product (17,403 ± 4,385 vs 19,210 ± 4,384, $p = 0.2$), number of abnormal coronary arteries (1.5 ± 0.9 vs 1.8 ± 0.8, $p = 0.2$) and number of reversible defects (1.8 ± 0.8 vs 1.6 ± 0.9). Male gender was associated with a higher peak heart rate (135 ± 15 vs 124 ± 16 beats/min, $p<0.05$), peak wall motion score (25.6 ± 7 vs 21.2 ± 0.5, $p<0.05$), a higher prevalence of multivessel disease (61% vs 25%, $p<0.05$), a trend to a higher prevalence of previous infarction (76% vs 50%, $p = 0.06$), a higher stress perfusion score (1609 ± 1590 vs 598 ± 937, $p<0.05$), rest score (1132 ± 1212 vs 416 ± 832, $p<0.05$) and ischemic score (554 ± 795 vs 181 ± 172, $p<0.05$).

Patients on beta blocker therapy: There was no significant difference between patients with or without beta blocker therapy with regard to age, gender, extent of coronary artery disease, prevalence of ischemia on echocardiography, or quantitative perfusion defect score. Patients on beta blockers had a lower peak heart rate (126 ± 17 vs 139 ± 15, $p<0.01$), a lower peak rate pressure product

(17869 ± 4250 vs 20116 ± 3706, $p<0.05$) and a higher maximal dobutamine dose (40 ± 0 vs 37 ± 6 μg/kg/min, $p<0.05$). Among patients receiving beta blockers, peak heart rate was higher in group A compared to group B (130 ± 18 vs 108 ± 16, $p<0.05$).

Table 3: Distribution of reversible perfusion defects and perfusion defect score in patients with and without transient wall motion abnormalities.

	Transient WMA + (N = 40)	Transient WMA - (N = 14)
Anterior	10 (25%)	9 (64%) *
Inferior	18 (45%)	6 (36%)
Posterolateral	8 (20%)	1 (7%)
anterior septum	8 (20%)	4 (29%)
Posterior septum	9 (23%)	3 (21%)
Apex	11 (28%)	3 (21%)
Number of reversible defects	1.6 ± 0.9	1.8 ± 0.7
Rest perfusion defect score	1,032 ± 1,286	600 ± 559
Stress perfusion defect score	1,362 ± 1,642	1,135 ± 988
Quantitative ischemic score	412 ± 750	526 ± 553
Visual ischemic score	3.5 ± 2	3.8 ± 1.2

* $p<0.01$.

DISCUSSION

Identification of stress test variables associated with more severe ischemia is important in the management and prognostic stratification of patients with coronary artery disease especially in the presence of equivocal indications for revascularization (22). The echocardiographic method of evaluation of wall motion during stress test employed in clinical practice depends upon a semiquantitative visual evaluation with a limited scoring scale of different grades of dyssynergy (4-12). Conversely, the detection of a reversible perfusion defect with the relatively automated myocardial SPECT imaging is assisted by quantitative analysis of perfusion defect size. Theoretically, this can explain the lack of stress-induced wall motion abnormalities in patients with reversible hypoperfusion on basis of less severe flow malperfusion and presumably less severe ischemia (14). Therefore, it is important to find whether the absence of

inducible wall motion abnormalities identifies a population with different clinical characteristics, extent and severity of ischemia, different hemodynamic response to dobutamine or extent of coronary artery disease.

The results of our study are derived from a symptomatic patient population with coronary artery disease and reversible defects on dobutamine perfusion scintigraphy. The data show that the presence or absence of transient wall motion abnormalities in conjunction with a reversible perfusion defect is not related to the severity of ischemia assessed by quantitative MIBI SPECT imaging. The absence of transient wall motion abnormalities correlated with a lower peak rate pressure product, impaired systolic blood pressure response at peak stress, and higher prevalence of female sex. The lower rate pressure product in the group with a negative echocardiogram can be explained by the occurrence of hypoperfusion earlier than wall motion abnormalities in the ischemic cascade (15-16). Consequently, diagnostic techniques dependent on the detection of wall motion abnormalities may be more vulnerable to a submaximal stress compared to perfusion imaging techniques (12). The association between transient wall motion abnormalities and a higher prevalence of both ST-segments depression and/or angina during stress may be explained by the late occurrence of angina and ST-segment depression following impairment of perfusion and function in the ischemic cascade (15,16,23). Since the latter stops before the occurrence of mechanical dysfunction in patients without transient wall motion abnormalities, theses patients were more likely to have less angina and ST-segment depression. There was a higher prevalence of reversible perfusion defects in the anterior wall in patients with than without transient wall motion abnormalities, which may be due to the difficulties in delineation of the entire endocardium of the anterior wall in the apical 2 chamber view. The apparent trend to a higher resting wall motion and perfusion defect score in patients with transient wall motion abnormalities may be due to the relatively higher prevalence of anterior myocardial infarction in the former group. All patients with left bundle branch block or left ventricular hypertrophy had a positive echocardiographic study. This is not surprising, since diagnostic problems in this population were described with scintigraphy (24,25) and not with echocardiography which was reported to be more accurate in patients with than without left ventricular hypertrophy (11).

Comparison with previous studies

This is the first study which evaluates the severity of myocardial ischemia in patients with reversible perfusion defects in presence or absence of simultaneous transient wall motion abnormalities during stress test. Coma-Canella et al. (17) studied patients after recent myocardial infarction by dobutamine stress with radionuclide angiography and 201 thallium SPECT in 2 separate days. They concluded that mild to moderate ischemia on basis of visual analysis of reversible thallium defects is compatible with improvement or no

change of regional function whereas severe ischemia results in worsening of function. Unlike radionuclide angiography, echocardiography allows tomographic evaluation of both endocardial excursion and wall thickening improving the detection of mechanical dysfunction. The difference between the 2 studies may be explained by the tomographic assessment of wall motion and quantitative assessment of perfusion in our study.

Accuracy of dobutamine stress testing in females

Despite that exercise perfusion scintigraphy is more accurate than electrocardiography in females (26), there are some inherent diagnostic problems of perfusion scintigraphy in females including a false positive test due to a shifting breast artifact. In our study, females had a higher incidence of a negative echocardiogram, a lower peak heart rate, a lower peak wall motion score and a lower ischemic perfusion defect score. It can not be precisely concluded whether these findings are due to the lower prevalence of multivessel disease, a lower peak heart rate or due to a difference in inducibility and/or detection of wall motion abnormalities in females. It has been reported that exercise echocardiography is an accurate method for the diagnosis of coronary artery disease in females (27). As the predicted maximal exercise heart rate is higher in males than females at a given age (28), a similar calculation of the maximal heart rate during dobutamine stress test may not be appropriate for females undergoing dobutamine stress echocardiography in which the detection of ischemia may be critically dependent on heart rate increment.

Accuracy of dobutamine stress testing at various levels of stress

Previous studies have shown that a submaximal dobutamine stress test, defined as a test in patients receiving beta blockers or inability to compete the standard protocol is associated with a reduced sensitivity of echocardiography whereas the effect on sensitivity of perfusion scintigraphy was less prominent (11,12). Since dobutamine stress test is an exercise simulator stress modality, an important increase of rate pressure product is required to have a high accuracy especially for the detection of abnormal wall motion. We have previously shown that in unselected patient population with suspected myocardial ischemia who underwent dobutamine stress echocardiography with simultaneous MIBI SPECT, the addition of MIBI studies to echocardiographic studies which are negative for ischemia at submaximal test was particularly useful for the prediction of cardiac events (29).

The effect of beta blockers

In our study the prevalence ischemia detected at echocardiography was not different with or without beta blocker therapy. This may be due to the adminstration of atropine which was reported to increase sensitivity particularly in patients receiving beta blockers (30), and the higher dobutamine dose in

patients receiving beta blockers which may compensate for the lower rate pressure product by exerting more positive inotropic effect. Additionally, in patients receiving beta blockers, peak heart rate was higher in patients with than without ischemia on echocardiography.

The role of systolic blood pressure response

High dose dobutamine infusion induces myocardial ischemia by increasing metabolic demand due to an increase of heart rate and myocardial contractility (31-33). Coronary vasodilatation and flow heterogeneity results from the increased myocardial demand and a weak vasodilator effect (33). The effect of dobutamine on systolic blood pressure is influenced by mechanisms related to contractility and systemic vascular resistance (34). Therefore, the importance of systolic blood pressure response in the attainment of an adequate stress test level has not been proven. An interesting finding of our study is that patients with a negative echocardiogram had impaired systolic blood pressure response in contrary to those with a positive test. This difference is unlikely to be due to myocardial ischemia because in this situation, impaired systolic blood pressure response is expected to occur in the group with rather than without mechanical dysfunction. Conversely, impaired systolic blood pressure response is most probably a reason of a negative echocardiogram and can be explained by a possible predominant peripheral vasodilator response in these particular patients. The role of systolic blood pressure response is supported by the reported findings of a significant increase of systolic blood pressure with dobutamine, even comparable to that obtained with exercise in some studies (7,35). Echocardiography was reported to have a good sensitivity comparable to that of perfusion scintigraphy when applied with stress modalities associated with heart rate and systolic blood pressure increase like exercise (1-2) and dobutamine (8-9), whereas sensitivity is low compared to perfusion scintigraphy when applied with vasodilator stress testing with dipyridamole (36) in which there is a mild increase of heart rate meanwhile, systolic blood pressure drops or does not change. For echocardiographic imaging, sensitivity of dobutamine and exercise was found to be higher than dipyridamole (37). It can be postulated that in particular patients, a modest but a critical increment of systolic blood pressure during dobutamine infusion is required to increase the left ventricular wall stress to result in subendocardial ischemia and deterioration of function that can be detected by visual assessment. This may not be as critical for reversible hypoperfusion which occurs at a lower stress level.

Limitations of the study

The number of patients with a negative echocardiogram was small. Patient population was heterogenous including some patients with previous myocardial infarction. However, only one patient had a negative echocardiographic study and a reversible perfusion defect confined to an akinetic

segment. The assessment of the severity of ischemia by perfusion scintigraphy may have some pitfalls as the latter detects flow malperfusion as well as true ischemia. Difference in perfusion may be attenuated in patients with multivessel disease (17). Finally, some patients were receiving medications including beta blockers. Nevertheless, we have shown previously that the addition of atropine increases the sensitivity of dobutamine echocardiography especially in patients receiving beta blockers.

Clinical implication

Since a lower peak rate pressure product correlated with a negative dobutamine echocardiographic test in patients with reversible perfusion defects, great attention should be given to achieve a higher product in patients undergoing dobutamine stress echocardiography alone. This may include stopping beta blockers and implement of stress protocol aiming at the attainment of a higher heart rate like atropine adminstration (18,30) or the use of longer dobutamine infusion time (38). The occurrence of mechanically silent ischemia manifested as reversible perfusion defects without transient wall motion abnormalities should be disregarded in the management of patients with coronary artery disease as a marker of less severe ischemia as assessed by myocardial perfusion scintigraphy.

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CHAPTER 7

FUNCTIONAL ASSESSMENT OF PATIENTS AFTER CORONARY ARTERY BYPASS GRAFTING BY DOBUTAMINE STRESS ECHOCARDIOGRAPHY[1]

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ABSTRACT

Exercise echocardiography is an accurate technique for the assessment of graft function after coronary artery bypass grafting (CABG). Although dobutamine stress echocardiography is a feasible alternative in patients with limited exercise capacity, its value in this particular patient population has not been assessed. Dobutamine (up to 40 μg/kg/min) stress echocardiography was performed in 50 patients at (mean [$\pm$ SD]) 5.1 $\pm$ 5.4 years (range 3 months to 19 years) after CABG. Ischemia was defined as new or worsened wall motion abnormalities. Significant vascular compromise was defined by quantitative measurements as $\geq$50% luminal diameter stenosis in a graft or in a native coronary artery if the stenosis was distal to the graft or involved non grafted artery.

Ischemia was detected in 25 of 32 patients with and in 2 of the 18 patients without vascular compromise (sensitivity = 78%; CI 67-90, specificity = 89%; CI 80-98, positive predictive value = 93%; CI 85-100, negative predictive value = 70%; CI = 57-82; accuracy = 82%; CI 71-93). The sensitivity was 64% (7/11) in patients with vascular compromise in one region, 83% (10/12) in 2 regions and 89% (8/9) in 3 regions. Sensitivity was 86% in patients who achieved 85% of the target heart rate. Dobutamine stress echocardiography is an accurate method for the assessment of graft function in patients after CABG and provides useful data for the selection of patients in whom coronary angiography may be indicated.

Key Words: Dobutamine stress echocardiography - Coronary artery bypass grafting

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[1] *Submited for publication.*

INTRODUCTION

The detection of myocardial ischemia is the hallmark of the non-invasive evaluation of graft function (1-5) after coronary artery bypass grafting (CABG). Exercise electrocardiography was shown to have a limited accuracy in this clinical setting (3). Recent studies have demonstrated a high accuracy of exercise echocardiography for the detection of myocardial ischemia in patients with significant graft or progressive native coronary artery stenosis (3-5). However, in patients with limited exercise capacity, an alternative stress modality is required for the functional evaluation of these patients.

The value of dobutamine echocardiography in the diagnosis and functional assessment of coronary artery disease has been established in various clinical indications including the assessment of the results of coronary angioplasty (6-11). However, its role in the assessment of adequate myocardial perfusion in patients after CABG has not been studied. Therefore, the aim of this study was to assess the value of dobutamine stress echocardiography in the functional evaluation of patients after CABG unable to perform exercise stress testing.

METHODS

Patient selection

Study population comprised 50 patients unable to perform exercise stress test who were studied by dobutamine stress echocardiography 3 months to 19 years after coronary artery bypass grafting (mean = 5.1 $\pm$ 5.4 years, range 3 months to 19 years). Reasons for stress testing were chest pain in 36 patients and exertional dyspnea in 2 patients, whereas in 12 patients, the test was performed for routine functional assessment. All patients gave an informed consent to undergo the test. Mean age was 58 $\pm$ 9 years. There were 41 men and 9 women. Thirty five patients (70%) were receiving oral nitrates and/or calcium antagonists and 15 (30%) were receiving beta blockers at the day of the test. A history or an electrocardiographic evidence of myocardial infarction was present in 39 patients.

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 5 followed by 10 μg/kg/min (3 minutes stages), increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age predicted maximal heart rate at the maximal dobutamine dose (12). The electrocardiogram was monitored throughout dobutamine infusion and was recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test. Ischemia at the electrocardiogram was defined as ≥ 0.1 mV horizontal or

downsloping ST-segment depression 80 mS from the J point compared to baseline level or ≥ 0.1mV ST-segment elevation in electrocardiogram leads corresponding to non infarcted myocardium (13).

Stress echocardiography

Echocardiographic images were acquired at rest and during stress and recovery. The echocardiograms were recorded on video tapes and were also digitized on optical disk and displayed side by side in quad-screen format (Vingmed CFM 800) to facilitate the comparison of rest and stress images. Left ventricular wall was divided into 16 segments (14) and scored using a 4-point scale, where 1=normal, 2= hypokinesis, 3 = akinesis, 4 = dyskinesis. The interpretation of images was performed by 2 experienced observers without the knowledge of the patients' angiographic data. In case of disagreement, a third reviewer revised images and a majority decision was achieved. In our laboratory, inter-and intra-observer agreement for stress echocardiographic assessment are 92% and 94% respectively (15). Both wall motion and thickening were considered for analysis. The diagnosis of ischemia was based on the occurrence of new or worsening wall motion abnormalities in one or more segments. As previously reported, ischemia was not considered when akinetic segments at rest became dyskinetic without improvement at low-dose dobutamine (16).

Coronary angiography

Coronary angiography was performed, using the Judkins technique, within 3 months in all patients. The clinical course was stable in the period between coronary angiography and dobutamine stress testing. Coronary stenosis was quantified using a previously described method from our center (17). Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$ in a graft or in a native coronary artery if the stenosis was distal to the graft or involved non grafted artery. Coronary arteries were assigned to particular myocardial segments as previously described (9).

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. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant. Sensitivity, specificity, predictive value and accuracy were derived according to standard definition and presented with their corresponding 95% confidence interval (CI).

RESULTS

Coronary angiography

There was no significant vascular compromise in 18 patients, whereas

in 32 patients significant graft or native non grafted coronary artery stenosis was detected. Vascular compromise was detected in one region in 11 patients (22%), in 2 regions in 12 patients (24%) and in 3 regions in 9 patients (18%). Significant stenosis of the left anterior descending coronary artery (LAD) region was detected in 22 patients (44%), of the right coronary artery (RCA) in 20 patients (40%) and of the left circumflex coronary artery (LCX) in 20 patients (40%).

Dobutamine stress test

Heart rate increased from 70 ± 12 at rest to 135 ± 18 beats /min at peak stress ($p<0.001$) and rate pressure product from 9013 ± 2212 to 17065 ± 9129 ($p<0.001$) whereas systolic blood pressure did not change significantly (128 ± 20 at rest vs 127 ± 26 mm Hg at peak stress). Angina occurred in 15 (30%) patients, ST-segment depression in 13 (26%) and ST-segment elevation in 10 (20%) patients, which was confined to infarction leads in all of them. In 8 (16%) patients, the test was interrupted prematurely before reaching the maximal dose or the target heart rate because of a limiting side effect. Reasons for premature termination of the test were angina (5 patients), ST-segment depression (1 patients), hypotension (2 patients) and significant tachyarrhythmias (1 patient). ST-segment depression occurred in 10 patients with vascular compromise (3 with single region and 7 with multi-region compromise) and in 3 patients without vascular compromise (sensitivity = 31%; CI 18-44, specificity = 83%; CI 73-94, positive predictive value = 77%; CI 65-89, negative predictive value = 41%; CI = 27-54; accuracy = 50%; CI 36-64).

Stress echocardiography

Ischemia was detected in 25 of 32 patients with and in 2 of the 18 patients without vascular compromise (sensitivity = 78%; CI 67-90, specificity = 89%; CI 80-98, positive predictive value = 93%; CI 85-100, negative predictive value = 70%; CI = 57-82; accuracy = 82%; CI 71-93). Sensitivity and accuracy were significantly higher than electrocardiography ($p<0.0001$ and <0.001 respectively). The sensitivity was 64% (7/11) in patients with vascular compromise in one region, 83% (10/12) in 2 regions and 89% (8/9) in 3 regions. There was a trend to a higher sensitivity in patients with multivessel compared to those with single vessel compromise (86% [18/21] vs 64% [7/11], $p<0.1$).

The impact of maximal stress heart rate

In patients with vascular compromise, peak heart rate was significantly higher in patients with than without ischemia at echocardiography (135 ± 22 vs 120 ± 18, $p<0.05$). The sensitivity was relatively higher with than without the achievement of 85% of the target heart rate (86% [19/22] vs 60% [6/10]) respectively.

Prediction of the extent of vascular compromise

An ischemic pattern in 2 different vascular territories, suggestive of multivessel compromise occurred in 12 of 21 patients (57%) with multivessel and in 2 of 11 patients with single vessel compromise (sensitivity = 57%; CI 40-74, specificity = 82%; CI 68-95, positive predictive value = 86%; CI 74-98, negative predictive value = 50%; CI = 33-67; accuracy = 66%; CI 49-82). The sensitivity, specificity, and accuracy of dobutamine stress echocardiography for the detection of vascular compromise in the LAD, LCX and RCA regions are shown in the table 1. Sensitivity and specificity improved by considering the RCA and LCX together, probably due to the frequent overlap in their territories. By the use of 2 myocardial regions (LAD and combined LCX and RCA), ischemia was detected in 30 of 47 regions with and in 8 of 53 regions without vascular compromise (sensitivity = 64%, specificity = 85%). Sensitivity in each vascular region was not different in presence or absence of myocardial infarction in the same region (60% vs 65% in LAD and 69% vs 58% in the RCA-LCX region respectively, p = NS). Of the 8 false positive regional diagnose, 3 occurred in relation to lesions between 40 and 50% and 4 occurred in regions with normal baseline contraction. A false positive diagnosis of ischemia in the septum was encountered in 2 patients. Septal motion at rest was normal in one patient and abnormal in the other.

Table 1. Sensitivity, specificity and accuracy of dobutamine stress echocardiography for the diagnosis of significant stenosis in individual vascular regions in patients with previous coronary artery bypass grafting.

	sensitivity	specificity	accuracy
LAD	64 (50-77)	86 (76-95)	76 (64-88)
LCX	50 (36-64)	80 (69-91)	68 (55-81)
RCA	45 (31-59)	76 (64-88)	63 (50-77)
RCA ± LCX	64 (51-77)	84 (74-94)	74 (62-86)

LAD = left anterior descending, LCX = left circumflex, RCA = right coronary artery

DISCUSSION

Coronary artery bypass grafting is an effective intervention for symptomatic relief, prolongation of survival and improvement of left ventricular function in particular subset of patients with coronary artery disease (18). However, myocardial perfusion after surgery may be compromised by late graft occlusion and progression of coronary artery disease in non-grafted or in grafted

coronary arteries distal to the bypass (19). Therefore, the assessment of myocardial ischemia in this population is important to detect vascular compromise and to select patients in whom coronary angiography may be indicated. The value of exercise echocardiography in this clinical setting has been established (3-5). In patients with limited exercise capacity, pharmacological stress testing may represent a feasible alternative. Although the value of dobutamine stress echocardiography in the detection of myocardial ischemia has been assessed in a variety of clinical situations (6-11), its role in the assessment of patients after CABG has not been studied. Our study shows that dobutamine stress echocardiography is a moderately sensitive and highly specific technique for the detection of vascular compromise in patients after CABG. Sensitivity was relatively high in presence of vascular compromise in more than one region and in patients who achieved 85% of the maximal heart rate. In individual vascular territories, sensitivity was not different in presence or absence of myocardial infarction in the corresponding region. Despite the known effect of CABG on the motion of the septum (20), only one of the 8 false positive results involved the septum with abnormal wall motion at rest.

Comparison with previous studies

This is the first study in which the value of dobutamine stress echocardiography in the functional evaluation of patients after CABG was assessed. The sensitivity (78%) and specificity (89%) of dobutamine echocardiography for the detection of vascular compromise are aligned with those of the largest exercise echocardiographic study by Kafka et al. (79% and 82% respectively) in patients after CABG (3). The sensitivity was not reduced in presence of wall motion abnormalities in our patients despite that we used the criteria of new or additional wall motion abnormalities only to define an ischemic response. Kafka et al. (3) reported that the use of failure of improvement of dyssynergic segments during exercise as a criterion for ischemia increased the sensitivity at the expense of specificity. Similar findings have been reported by Marcovitz et al. with dobutamine stress echocardiography (7). This may be explained by the possibility that failure of improvement may signify ischemia or myocardial necrosis. Overall sensitivity and specificity of dobutamine echocardiography in our study are comparable to those reported on dobutamine echocardiography in patients without CABG (6-10) denoting the absence of particular limitations of the technique in patients after CABG.

The detection of regional vascular compromise

The localization of inducible wall motion abnormalities identified the area of vascular compromise in a high proportion of segments. Improvement of regional sensitivity and specificity by combining the RCA and LCX territories can be explained by the vascular overlap described previously in these regions (4). Using the 2 segment model (anterior for LAD and infero-posterolateral for

the RCA and LCX) gave an equal sensitivity in both regions. Kafaka et al. (3) reported a low sensitivity in the LCX region. The difference may be explained by separate analysis of the LCX in the latter study with the possibility of missing some diagnostic results in the inferior wall which was assigned only to the RCA. Furthermore, the lateral wall may be more vulnerable to respiratory artifacts in the postexercise period imposing a difficulty of interpretation of wall motion in this particular region. There was a relatively low sensitivity of dobutamine echocardiography for identifying multivessel disease on basis of inducible abnormalities in more than one region (57%), which is slightly lower than that of exercise echocardiography reported by Kafka et al. (69%). This can be explained by vascular overlap and different threshold for ischemia in different vascular territories with the potential to reach an end point of the test (e.g angina, electrocardiographic or hemodynamic changes and maximal dobutamine dose) before the occurrence of ischemia in other territories. This may also explain the relatively low sensitivity for detecting individual coronary artery stenosis in this population with high prevalence of multivessel disease.

Influence of hemodynamic response

In patients with vascular compromise, peak heart rate was higher in patients with than without ischemia at echocardiography. The importance of the maximal stress heart rate for the occurrence of ischemia at exercise (21) or dobutamine echocardiography (9) has been previously demonstrated.

Limitations of the study

The number of patients without vascular compromise was relatively small. However, this number was even higher compared to most of previous studies on exercise echocardiography after CABG (4,5). Some patients were receiving medications including beta blockers in 30%, which may decrease the sensitivity of dobutamine stress echocardiography. Nevertheless, we have previously shown that the adminstration of atropine at peak dobutamine dose enhances the sensitivity of dobutamine stress echocardiography especially in patients receiving beta blockers (12).

Conclusion

Dobutamine stress echocardiography is an accurate method for the diagnosis of vascular compromise in patients after CABG and provides useful data for the selection of patients in whom coronary angiography may be indicated.

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CHAPTER 8

ACCURACY OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF CORONARY ARTERY STENOSIS IN PATIENTS WITH MYOCARDIAL INFARCTION: THE IMPACT OF EXTENT AND SEVERITY OF LEFT VENTRICULAR DYSFUNCTION[1]

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ABSTRACT

Background. Though the presence of baseline left ventricular dysfunction was postulated to represent a limitation of stress echocardiography for the detection of ischemia, the influence of baseline dysfunction on the test accuracy has not been assessed. Aim of the study was to evaluate the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis in symptomatic patients with old myocardial infarction and to assess the influence of the severity of left ventricular dysfunction on the accuracy for the detection of individual coronary artery stenosis.

Methods. Dobutamine (up to 40 μg/kg/min) stress echocardiography was performed in 132 symptomatic patients with old myocardial infarction. Ischemia was defined as new or worsened wall motion abnormalities. For each coronary artery, regional wall motion in the corresponding territory was classified as normal, mildly, moderately or severely impaired on basis of wall motion score index. Significant coronary stenosis was defined as $\geq$50% diameter stenosis.

Results. Ischemia was detected in 87 of 111 patients with, and 3 of 21 patients without coronary artery stenosis (sensitivity = 78%; CI 71-86, specificity = 86%; CI 79-92, accuracy = 80%; CI 73-87). The accuracy for the diagnosis of individual coronary stenosis was 69%, 74%, 74% and 61% in presence of normal wall motion, mild, moderate and severe wall motion abnormalities in the

[1] *Submitted for publication.*

corresponding territories respectively (p = NS). The sensitivity was higher in presence of mild or moderate wall motion abnormalities (73%) than with normal wall motion (53%) or severe wall motion abnormalities (56%, $p < 0.05$ in both). In territories subtended by a stenotic artery, regional wall motion score index, percentage of dyssynergic segments and percentage of akinetic and dyskinetic segments was not different with or without ischemia.
Conclusion. Dobutamine stress echocardiography has a good overall accuracy for the diagnosis of coronary artery stenosis in symptomatic patients with old myocardial infarction. Accuracy for individual coronary artery is not influenced by the degree of regional dysfunction. The presence of baseline dysfunction should be disregarded as a limitation of dobutamine stress echocardiography for eliciting myocardial ischemia and the diagnosis of significant coronary artery stenosis in this population.

Key Words: coronary artery disease, myocardial infarction, dobutamine stress echocardiography, ischemia.

INTRODUCTION

Previous studies have demonstrated the value of dobutamine stress echocardiography for the detection of peri-infarction and remote ischemia (1-3) and the assessment of myocardial viability in patients with myocardial infarction (4,5). However, most of these studies were performed for routine predischarge functional assessment of patients with recent myocardial infarction (1-3). The value of dobutamine stress echocardiography has not been assessed in a homogenous population of symptomatic patients with old myocardial infarction and suspected myocardial ischemia who represent a substantial proportion of patients referred the functional assessment of coronary artery disease. Furthermore, the influence of the extent and severity of baseline left ventricular dysfunction on the accuracy of the test for the diagnosis of myocardial ischemia and significant coronary artery stenosis has not been assessed. The latter is important, since echocardiographic diagnosis of myocardial ischemia relies upon the occurrence and/or worsening of wall motion abnormalities (6-8), which may be difficult to elicit, in presence of severe baseline dyssynergy (9). In some studies, the presence of baseline dyssynergy was considered diagnostic for significant coronary artery stenosis (10-11). This approach, does not disclose the relation between the patient symptoms and myocardial ischemia and may be confounding after thrombolytic therapy or revascularization of infarct-related artery. Therefore, the aim of this study was to assess the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis on basis of inducible ischemia and to find whether baseline left ventricular dysfunction influence the accuracy of the test for the diagnosis of individual coronary artery stenosis in symptomatic patients with old myocardial infarction.

METHODS

Patient selection

Study population comprised 132 consecutive patients with chest pain, unable to perform an adequate exercise test, who were referred to our imaging laboratory for evaluation of myocardial ischemia. All patients fulfilled the following criteria: 1) previous myocardial infarction >3 months. The diagnosis of myocardial infarction relied upon the standard criteria of prolonged chest pain, a diagnostic rise (at least twice the normal value) and fall of serum creatine kinase and serial electrocardiographic changes. 2) the presence of wall motion abnormalities at baseline echocardiogram. 3) absence of severe heart failure, severe valvular heart disease, hypertension, hypotension or a history of sustained ventricular tachyarrhythmias. All patients gave an informed consent to undergo dobutamine stress echocardiography.

Mean age was 60 ± 9 years. There were 101 men and 31 women. Ninety patients (68%) were receiving oral nitrates and/or calcium antagonists and 38 (29%) were receiving beta blockers at the day of the test. Q waves, in the electrocardiogram were present in 88 patients (67%). Those were detected in the anterior (or anterolateral) leads in 40 patients, inferior (or inferolateral) leads in 31 patients and in both locations in 17 patients.

Dobutamine stress test: Dobutamine was infused through an antecubital vein starting at a dose of 5 followed by 10 μg/kg/min (3 minutes sages), increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age predicted maximal heart rate (12). The electrocardiogram was monitored throughout dobutamine infusion and was recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test.

Stress echocardiography: Echocardiographic images were acquired at rest and during stress and recovery. The echocardiograms were recorded on video tapes and were also digitized on optical disk and displayed side by side in quad-screen format (Vingmed CFM 800) to facilitate the comparison of rest and stress images. For both rest and stress studies, left ventricular wall was divided into 16 segments and scored using a 4-point scale, where 1=normal, 2=hypokinesis, 3=akinesis, 4 = dyskinesis (7,13). The interpretation of images was performed by 2 experienced observers without the knowledge of the patients' angiographic data. In case of disagreement, a third reviewer revised images and a majority decision was achieved. In our laboratory, inter-and intra-observer agreement for stress echocardiographic assessment is 92% and 94% respectively (14). Both

wall motion and thickening were considered for analysis. Wall motion score index was derived by dividing the summation of individual score of the 16 segments by 16. For each vascular territory, regional wall motion score index was derived by the summation of the score of segments in the related territory and dividing the summation by the number of segments. According to this index, 3 grades of regional dysfunction were defined: 1) >1 to 1.7, classified as mild. 2) >1.7-2.3, moderate. 3) >2.3, severe regional dysfunction. The accuracy of dobutamine stress echocardiography for detecting individual coronary artery stenosis was assessed in absence of baseline wall motion abnormalities and in presence of different grades of regional dysfunction. Dyssynergy index was derived by dividing the number of dyssynergic segments by the total number of segments in each vascular territory. Similarly, akinesis-dyskinesis index was derived by dividing the number of akinetic and dyskinetic segments by the total number of segments in the same territory. Diagnostic criteria of ischemia were the appearance of wall motion abnormalities during stress in one or more normal segment at rest and/or the occurrence of akinesis or dyskinesis during stress in one or more hypokinetic segments at rest. As we have previously concluded (15), ischemia was not considered when akinetic segments at rest became dyskinetic during stress without improvement at low-dose dobutamine (5-10 μg/kg/min).

Coronary angiography: Coronary angiography was performed, using the Judkins technique, within 3 months in all patients. Coronary stenosis was quantified using a previously described
method from our center (16). Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$ in one or more major epicardial arteries. Coronary arteries were assigned to particular myocardial segments at echocardiography as previously described (17): 1) the left anterior descending coronary artery (LAD) was assigned to the anterior wall, anterior septum, posterior septum (except for the basal segment) apical anterior and apical septal segments. 2) the left circumflex coronary artery (LCx) was assigned to the lateral and the posterior wall. 3) the right coronary artery (RCA) was assigned to the inferior wall and the basal part of the posterior septum. The apical lateral segment was considered as an overlap segment between the LAD and the LCx, and if abnormal, it was assigned to the abnormal artery. Similarly, the apical inferior segment was considered as an overlap segment between the LAD and RCA. Due to the possible overlap between the RCA and LCx in the posteroinferior region (11), these 2 arteries were also analyzed together by grouping their vascular territories and assigning abnormalities to the LCx and/or RCA.

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. The Student *t* test was used for analysis of continuous data. A $p<0.05$ was considered statistically significant. Sensitivity, specificity, predictive value and accuracy were derived according to standard definition and presented with their corresponding 95% confidence interval (CI).

RESULTS

Dobutamine stress test: Heart rate increased from 70 ± 13 at rest to 136 ± 16 beats /min at peak stress ($p<0.0001$) and rate pressure product from 9003 ± 2563 to 17707 ± 9204 ($p<0.0001$) whereas systolic blood pressure did not change significantly (128 ± 19 at rest vs 131 ± 28 mm Hg at peak stress). Angina occurred in 62 (47%) patients, ST-segment depression in 46 (35%) and ST-segment elevation in 40 (30%) patients (with or without concomitant ST-segment depression). In 28 (21%) patients, the test was interrupted prematurely before reaching the maximal dose or the target heart rate because of a limiting side effect. Reasons for premature termination of the test were angina (13 patients), ST-segment depression (3 patients), hypotension (10 patients) and significant tachyarrhythmias (2 patients).

Table 1. Accuracy of dobutamine stress echocardiography for the diagnosis of significant LAD stenosis on basis of inducible ischemia in presence or absence of regional wall motion abnormalities in the corresponding territories.

		Sensitivity	Specificity	Accuracy
Overall	% (CI)	59 (51-67)	82 (75-88)	67 (59-76)
	number of pts	49/83	40/49	89/132
Normal wall motion	% (CI)	50 (33-67)	83 (70-96)	69 (53-85)
	number of pts	7/14	15/18	22/32
Mild WMA	% (CI)	71 (56-87)	85 (72-97)	76 (62-91)
	number of pts	15/21	11/13	26/34
Moderate WMA	% (CI)	55 (36-74)	75 (59-91)	61 (43-79)
	number of pts	11/20	6/8	17/28
Severe WMA	% (CI)	57 (41-73)	80 (67-83)	63 (48-78)
	number of pts	16/28	8/10	24/38

CI = 95% confidence interval, pts = patients, WMA = wall motion abnormalities.

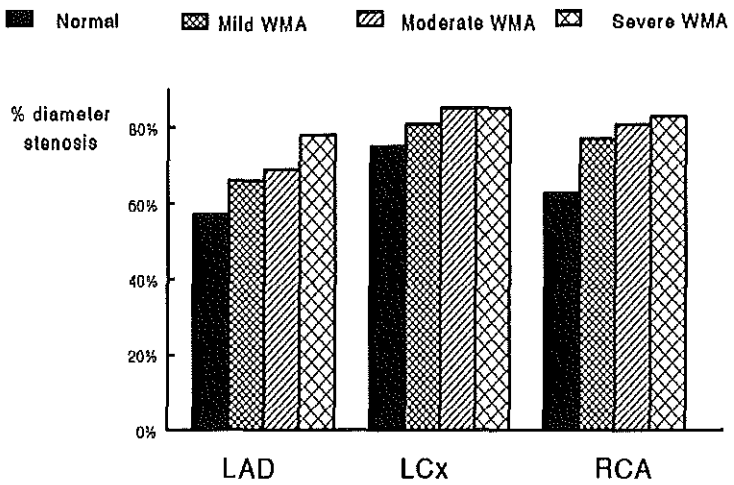

Figure 1. Percentage diameter stenosis of the related artery in territories with and without baseline wall motion abnormalities (WMA), derived only in arteries with ≥50% stenosis.

Table 2: Accuracy of dobutamine stress echocardiography for the diagnosis of significant LCx stenosis on basis of inducible ischemia in presence or absence of regional wall motion abnormalities in the corresponding territories.

		Sensitivity	Specificity	Accuracy
Overall	% (CI)	53 (45-62)	82 (76-89)	68 (60-76)
	number of pts	34/64	56/68	90/132
Normal wall motion	% (CI)	39 (27-51)	90 (82-97)	71 (60-82)
	number of pts	9/23	35/39	44/62
Mild WMA	% (CI)	47 (28-66)	78 (62-94)	58 (39-77)
	number of pts	8/17	7/9	15/26
Moderate WMA	% (CI)	73 (57-89)	71 (55-88)	72 (56-89)
	number of pts	11/15	10/14	21/29
Severe WMA	% (CI)	67 (43-91)	67 (43-91)	67 (43-91)
	number of pts	6/9	4/6	10/15

CI = 95% confidence interval, WMA = wall motion abnormalities.
Coronary angiography: Significant coronary artery disease was detected in 111 patients (84%). Thirty two patients (24%) had single vessel disease, 45 (34%) had 2 vessel disease and 34 (26%) had 3 vessel disease. Significant stenosis of the LAD was detected in 77 patients (58%), of the RCA in 83 patients (63%) and of the LCx in 64 patients (48%). Twenty one patients had normal coronary arteries or $<50\%$ lesions. In coronary arteries with significant stenosis, the mean percentage diameter stenosis was significantly higher in arteries with than without wall motion abnormalities in the corresponding territories ($p<0.01$ in the LAD and RCA, $p<0.05$ in LCx territories) and showed a trend to more severe stenosis with more severe regional wall motion abnormalities (figure 1).

Stress echocardiography
Baseline: Wall motion abnormalities at baseline echocardiography were detected in all patients. Mean wall motion score was 1.71 ± 0.46 (range 1.13 to 2.75) in the whole left ventricular myocardium, 1.78 ± 0.66 (range 1 to 2.8) in LAD territories, 1.47 ± 0.57 (range 1-2.8) in LCx territories and 1.81 ± 0.65 (range 1 to 2.9) in RCA territories.

Stress: Wall motion score index increased significantly from baseline (1.71 ± 0.46) to peak stress (1.90 ± 0.52, $p<0.001$). Ischemia was detected in 87 of 111 patients with significant coronary artery stenosis (78%) and in 3 of the 21 patients (14%) without significant coronary artery disease; 2 of them had lesions between 40 and 45% in the related artery (sensitivity = 78%; CI 71-86, specificity = 86%; CI 79-92, positive predictive value = 97%; CI 93-100, negative predictive value = 43%; CI = 34-51; accuracy = 80%; CI 73-87).

The sensitivity was 66% in patients with single vessel disease, 82% in 2 vessel disease and 85% in 3 vessel disease. The sensitivity was significantly higher in patients with multivessel than with single vessel disease (84% vs 66%, $p<0.05$). An ischemic pattern in 2 different vascular territories, suggestive of multivessel involvement occurred in 37 of 79 patients with multivessel disease and in 6 of 53 patients with single vessel or without coronary artery stenosis (sensitivity = 47%; CI 38-55, specificity = 89%; CI 83-94, positive predictive value = 86%; CI 80-92, negative predictive value = 53%; CI = 44-61; accuracy = 64%; CI 55-72). The mean number of stenotic coronary arteries was 1.9 ± 0.8 in patients with mild, and 2.1 ± 0.8 with moderate or severe wall motion abnormalities ($p=NS$). Sensitivity was 73% (43/58) in patients with mild, 87% (34/39) with moderate and 75% (10/14) with severe wall motion abnormalities ($p = NS$). Ischemia was detected in 74 of 98 patients with and in 5 of 34 patients without significant stenosis of the infarct-related artery (sensitivity = 76; CI 68-83, specificity = 85; CI 79-92, accuracy = 78%; CI = 71-85). Ischemia was detected in 54 of 74 patients with and in 5 of 41 patients without remote coronary artery stenosis, after exclusion of 17 patients

with extensive infarction and wall motion abnormalities involving the 3 vascular territories (sensitivity = 73; CI 69-81, specificity = 88; CI 82-94, accuracy = 78%; CI = 71-86).

Table 3: Accuracy of dobutamine stress echocardiography for the diagnosis of significant RCA stenosis on basis of inducible ischemia in presence or absence of regional wall motion abnormalities in the corresponding territories.

		Sensitivity	Specificity	Accuracy
Overall	% (CI) pts nr	62 (54-71) 48/77	69 (61-77) 38/55	65 (57-73) 86/132
Normal wall motion	% (CI) pts nr	46 (29-63) 6/13	76 (62-91) 16/21	65 (49-81) 22/34
Mild WMA	% (CI) pts nr	71 (55-86) 12/17	60 (43-77) 9/15	66 (49-82) 21/32
Moderate WMA	% (CI) pts nr	83 (68-98) 15/18	67 (48-86) 4/6	79 (63-95) 19/24
Severe WMA	% (CI) pts nr	52 (37-67) 15/29	69 (55-83) 9/13	57 (42-72) 24/42

CI = 95% confidence interval, pts = patients, WMA = wall motion abnormalities.

The sensitivity, specificity, and accuracy of dobutamine stress echocardiography for the detection of individual stenosis of the LAD, LCx and RCA are shown in table 1,2 and 3 respectively. Accuracy was calculated in absence and in presence of different grades of baseline dysfunction in the corresponding territory. Sensitivity was not different in the 3 vascular territories. There was a trend to a lower specificity in the RCA compared to other territories. Because some of the false positive results in the inferior wall may be attributed to LCx disease, the vascular territories of RCA and LCx were grouped and abnormalities were assigned to a disease in either of them (table 4). This approach increased the specificity of the RCA from 69% to 76%, meanwhile the specificity of the LCx decreased from 82% to 76%. The overall accuracy for detection individual coronary artery stenosis was derived by adding the accuracy for LAD to the accuracy in the combined RCA and LCx segment (table 5). Twenty eight % of false positive results occurred in relation to arteries with stenosis between 40% and 50%. There was no significant difference in the diagnostic accuracy in presence or absence of baseline wall motion abnormalities

and in various grades of regional dyssynergy in the related vascular territories (figure 2). However, the sensitivity in territories with mild and moderate wall motion abnormalities (added together) was higher than in territories with severe wall motion abnormalities (73% vs 56%, $p<0.05$) and in those with normal baseline contraction (73% vs 53%, $p<0.05$).

Table 4: Accuracy of dobutamine stress echocardiography for the diagnosis of significant RCA and/or LCx stenosis on basis of inducible ischemia in presence or absence of regional wall motion abnormalities in the corresponding territories.

		Sensitivity	Specificity	Accuracy
Overall	% (CI)	72 (64-79)	76 (68-83)	73 (65-80)
	number of pts	68/95	28/37	96/132
Normal	% (CI)	56 (38-74)	86 (73-98)	70 (54-86)
wall motion	number of pts	9/16	12/14	21/30
Mild WMA	% (CI)	73 (60-87)	67 (52-81)	71 (58-85)
	number of pts	22/30	8/12	30/42
Moderate	% (CI)	85 (74-96)	71 (58-85)	83 (71-94)
WMA	number of pts	29/34	5/7	34/41
Severe	% (CI)	53 (31-76)	75 (55-95)	58 (36-80)
WMA	number of pts	8/15	3/4	11/19

CI = 95% confidence interval, pts = patients, WMA = wall motion abnormalities.

In individual vascular territories, subtended by a stenotic coronary artery, there was no significant difference in baseline regional wall motion score index (figure 3), dyssynergy index (figure 4), akinesis-dyskinesis index (figure 5) in presence (true positive) or absence (false negative) of ischemia at echocardiography in the same vascular territories. Similarly, in absence of significant stenosis, none of these indices was significantly different between the false positive and true negative studies (figure 3-5). However, there was a small trend to higher percentage of dyssynergic segments in both true and false positive studies (figure 4) and a trend to a higher percentage of akinetic-dyskinetic segments in the false negative studies (figure 5).

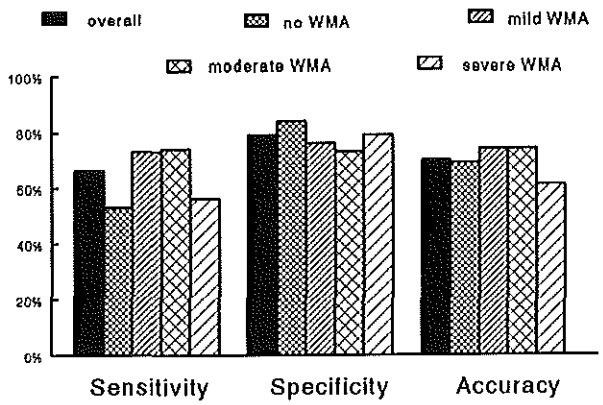

Figure 2. Accuracy of dobutamine stress echocardiography for the diagnosis of coronary stenosis in territories with normal wall motion, mild, moderate and severe wall motion abnormalities (WMA).

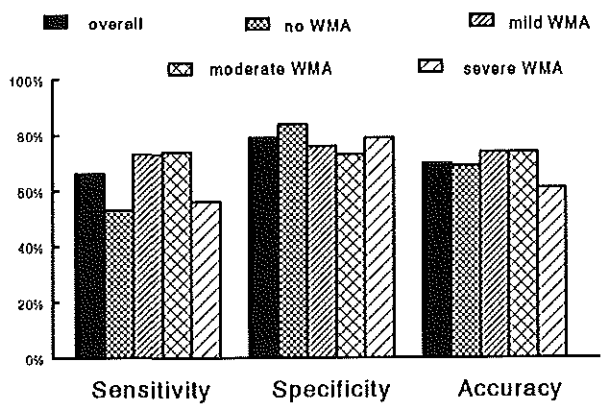

Figure 3. Regional wall motion score index (WMSI) in vascular territories with or without stenosis of the related artery, in presence or absence of regional ischemia at dobutamine echocardiography.

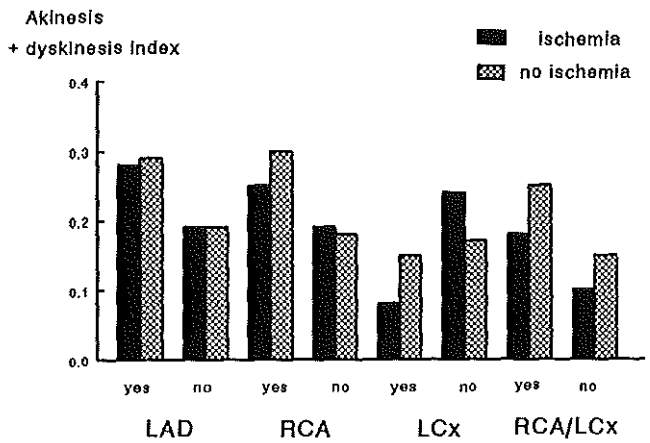

Figure 4. Regional akinesis + dyskinesis index in vascular territories with or without significant stenosis of the related artery, in presence or absence of regional ischemia at dobutamine echocardiography.

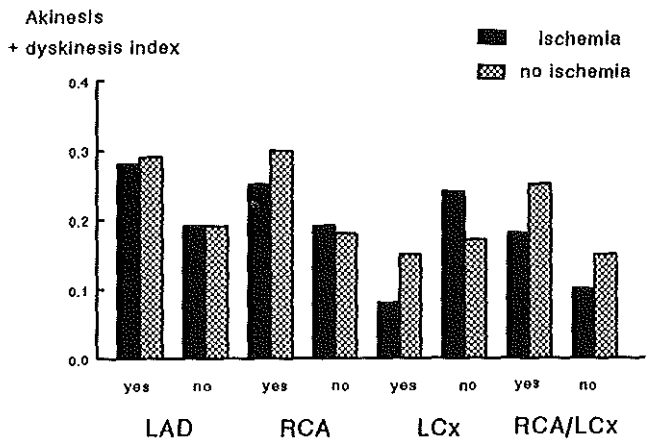

Figure 5. Regional akinesis + dyskinesis index in vascular territories with or without significant stenosis of the related artery, in presence or absence of regional ischemia at dobutamine echocardiography.

Table 5: Accuracy of dobutamine stress echocardiography for the diagnosis of individual coronary artery stenosis in presence or absence of regional wall motion abnormalities in the corresponding territories, derived by adding LAD to the combined RCA and LCx territories.

		Sensitivity	Specificity	Accuracy
Overall	% (CI)	66 (60-72)	79 (74-84)	70 (64-76)
	number of pts	117/178	68/86	185/264
Normal	% (CI	53 (41-66)	84 (75-93)	69 (58-81)
wall motion	number of pts	16/30	27/32	43/62
Mild WMA	% (CI)	73 (62-83)	76 (66-86)	74 (64-84)
	number of pts	37/51	19/25	56/76
Moderate	% (CI)	74 (64-84)	73 (63-84)	74 (64-84)
WMA	number of pts	40/54	11/15	51/69
Severe	% (CI)	56 (43-69)	79 (68-89)	61 (49-74)
WMA	number of pts	24/43	11/14	35/57

CI = 95% confidence interval, pts = patients, WMA = wall motion abnormalities.

DISCUSSION

The assessment of myocardial ischemia provides a valuable data regarding the function of coronary arteries that can not be obtained by routine angiography. Therefore, patients with previous myocardial infarction are frequently referred for the assessment of the functional significance of coronary stenosis documented at angiography. The detection of myocardial ischemia in that setting confirms the relationship between the patient symptoms and coronary artery disease and helps in decision making regarding revascularization which is likely to improve symptoms.

Because of the ability of dobutamine stress echocardiography to assess left ventricular function and to detect ischemia at high dose, it is increasingly used for functional evaluation of patients after myocardial infarction (1-5). However, previous studies have focused mainly on the assessment of patients after a recent myocardial infarction, mostly for routine evaluation in absence of symptoms (1-3). The extension of these studies to a large homogenous population of symptomatic patients with old myocardial infarction has not been carried out. Exercise performance in these patients may be limited by pulmonary

and joint disease, physical deconditioning and particularly exertional dyspnea due to left ventricular dysfunction. Furthermore, the accuracy of the electrocardiography for the diagnosis of ischemia may be reduced due to the presence of pathological Q-waves or conduction abnormalities, the low specificity of ST segment elevation for ischemia and the confounding occurrence of reciprocal ST-segment depression without true ischemia (18). Therefore, the assessment of the value of dobutamine stress echocardiography for the diagnosis of ischemia in this population appears to be a clinically relevant issue. However, in presence of baseline dyssynergy, the detection of coronary artery stenosis may be influenced by various factors, including the encroachment on the number of segments in which ischemia can be elicited and the tethering effect of a dyssynergic segments during stress on an adjacent normal segment which can mimic ischemia. Because of these potential limitations, it was suggested that patients with left ventricular dysfunction represent a population in whom perfusion may be preferred to echocardiographic imaging (9).

The present study

Our study shows a good overall accuracy of dobutamine stress echocardiography, based on the detection of inducible ischemia, for the diagnosis of significant coronary artery stenosis in symptomatic patients with regional left ventricular dysfunction after myocardial infarction. Sensitivity was higher in multivessel versus single vessel disease which can be explained by a larger amount of jeopardized myocardium with multivessel disease. The high sensitivity in multivessel disease is an advantage for the technique, since the sequela of a false negative test in patients with multivessel disease are more serious than in patients with single vessel disease who were shown to have a better prognosis (19).

Effect of baseline wall motion abnormalities

There was no significant difference in the accuracy for the detection of significant stenosis in an individual artery in presence or absence of wall motion abnormalities in the corresponding territories. Furthermore, the accuracy was not different in presence of mild, moderate or severe wall motion abnormalities. However, the sensitivity in vascular territories with mild and moderate wall motion abnormalities was higher compared to those with severe abnormalities (73% vs 56%) and those with normal wall motion (73% vs 53%). This may be explained by many factors including a high prevalence of non-transmural infarction in territories with mild and moderate wall motion abnormalities, which is known to be associated with a high prevalence of myocardial ischemia (20). A recent study showed that the sensitivity of ischemia assessed by dobutamine thallium scintigraphy for the diagnosis of significant coronary stenosis was significantly higher in the peri-infarction compared to remote segments (21). The presence of baseline dyssynergy in some of the analyzed

segments may be due to severe ischemia rather than myocardial infarction (22). The differentiation between theses 2 situations may be difficult in this population due to the low sensitivity of Q waves for the detection of wall motion abnormalities (23). If baseline dyssynergy is a manifestation of severe ischemia, the latter may be more inducible during stress in these vascular territories. The finding of more severe coronary stenosis in arteries with than without wall motion abnormalities in the related territories and the trend to more severe stenosis in association with more severe wall motion abnormalities may enhance sensitivity in dyssynergic territories and maintain a similar sensitivity in normal segments compared to severely dyssynergic segments by compensating for the reduced number of myocardial segments in which ischemia can be detected. Despite the lack of echocardiographic criteria for the diagnosis of ischemia in akinetic and dyskinetic segments, the latter does not usually involve the entire vascular territory. Finally, ischemia can be detected in hypokinetic segments when akinesis or dyskinesis occur during stress.

Wall motion score index, representing an overall estimation of the extent and severity of baseline dysfunction, did not influence the stress results in presence or absence of significant stenosis. This was demonstrated by the similar wall motion score index in true positive, compared to false negative and in true negative compared to false positive results. However, there was a constant trend to a higher percentage of dyssynergic segment in association with both true and false positive results. This may be explained by a the possible confounding effect of tethering in presence of extensive wall motion abnormalities which may passively increase sensitivity by reducing specificity. A constant trend to a higher number of akinetic and dyskinetic segments in false negative compared to true positive results was also observed. However, the difference was small and did not reach a statistical significance.

Comparison with previous studies

This is the first study which evaluates the accuracy of dobutamine stress echocardiography for the detection of coronary artery stenosis in a homogenous patients population with old myocardial infarction. A limited number of studies were reported in patients after a recent myocardial infarction. Berthe et al. (1) reported an accuracy of 87% for dobutamine stress echocardiography in the detection of multivessel disease in 30 patients after a recent myocardial infarction. Takeuchi et al. (2) reported a sensitivity and specificity of 93% and 91% of dobutamine stress echocardiography for the detection of significant infract related artery stenosis after a recent myocardial infarction. Sawada et al. (7) reported that in 41 patients with baseline
wall motion abnormalities, the sensitivity and specificity of dobutamine stress echocardiography for the detection of coronary artery disease in remote segments were 81% and 87% respectively. However, none of theses studies assessed both remote and peri-infarction ischemia and there are no reports

concerning the overall accuracy in patients with baseline left ventricular dysfunction.

Marcovitz et al. (10) reported that in a heterogenous patient population with or without baseline wall motion abnormalities undergoing dobutamine stress echocardiography, most of the false positive results were encountered in patients with baseline wall motion abnormalities. Conversely, Armstrong et al. (11) reported a trend to a higher accuracy in patients with than without baseline wall motion abnormalities undergoing exercise echocardiography. However, these 2 study considered the diagnosis of coronary artery stenosis in presence of baseline wall motion abnormalities that did not change during stress. The contradiction may be explained by a difference in proportion of patients with wall motion abnormalities who had no significant stenosis of the infarct related artery as occurs after thrombolysis or revascularization procedures. Wall motion abnormalities due to reasons other than coronary artery disease will further compromise the specificity of this approach which has also the limitation of failure to disclose the relationship between the patient symptoms and inducible ischemia.

The overall sensitivity and specificity of dobutamine stress echocardiography for the detection of coronary artery disease in our study in patients with old infarction are aligned with those found in large studies in population without previous myocardialinfarction (17,24,25) and in heterogenous population (8,10,26).

Accuracy for individual coronary artery disease

There was no significant difference in the sensitivity for detecting individual coronary stenosis in the 3 territories. A similar finding has been reported by Marwick et Al (17). In contrast, Armstrong et al. (11) found a lower sensitivity of exercise echocardiography for LCx. This may be related to the post exercise acquisition of images and the interfering effect of respiratory movement on the lateral wall.

In our study, the assignment of the inferior wall to the RCA and posterior wall to the LCx was associated with a relatively low sensitivity for LCx disease and a low specificity for RCA. This can be explained by vascular overlap in the inferior wall described by other investigators (11,27). When RCA and LCx were considered together, specificity increased only for the RCA and was slightly reduced for the LCx. Theses findings suggest that a significant proportion of inferior ischemia is due to LCx disease, meanwhile a relation between posterior ischemia and RCA disease may not be equally significant.

Limitations of the study: Most patients had multivessel disease which may influence the sensitivity and specificity for the diagnosis of individual coronary artery disease, due to overlap of vascular territories. Most patients were receiving antianginal therapy including beta blocking agents in 29% which may

reduce the prevalence of ischemia and decrease the sensitivity of the test. However, these limitations are expected to a have a uniform influence on all segments rather than a particular group of segments. Furthermore, we have previously shown that atropine increases the sensitivity of dobutamine echocardiography especially in patients receiving beta blockers (12). Finally, the number of patients without significant coronary artery disease was relatively small. This is expected in symptomatic population after myocardial infarction. Therefore we performed analysis on segmental basis to avoid this limitation which is related to the nature of the selected patient group.

Summary and conclusion

Our results are derived from a consecutive series of symptomatic patients with previous myocardial infarction, referred for non-invasive evaluation of coronary artery disease and comprised a wide range of baseline left ventricular dysfunction. The theoretical limitation of echocardiographic detection of ischemia in presence of baseline dyssynergy could not hold in our study. Conversely, the presence of mild or moderate abnormalities was associated with a higher sensitivity compared to normal segments and severely dyssynergic segments. Dobutamine stress echocardiography is an accurate method for the detection of functionally significant coronary artery disease in patients with myocardial infarction. In this population, the presence of baseline dyssynergy should be disregarded as a limitation of the test for the detection of myocardial ischemia and the diagnosis of significant coronary artery stenosis.

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CHAPTER 9

DOBUTAMINE 201-THALLIUM SPECT IMAGING FOR THE ASSESSMENT OF PERI-INFARCTION AND REMOTE MYOCARDIAL ISCHEMIA IN SYMPTOMATIC PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION[1]

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ABSTRACT

Aim of the study was to assess the value of dobutamine 201 thallium scintigraphy for the diagnosis of infarct-related and remote coronary artery stenosis in symptomatic patients with left ventricular dysfunction late after acute myocardial infarction. Dobutamine (up to 40 μg/kg/min) - atropine (up to 1 mg) stress test in conjunction with stress-reinjection 201 thallium SPECT was performed in 71 symptomatic patients with left ventricular dysfunction >3 months after myocardial infarction. Ischemia was defined as reversible perfusion defects. Results: Significant coronary stenosis ($\geq$50% luminal diameter stenosis) was detected in all patients. Sensitivity of reversible thallium defects for the diagnosis of coronary stenosis was 80% in all patients, 70% in patients with 1-vessel disease, 79% with 2-vessel disease, and 86% with 3-vessel disease. The sensitivity for detecting infarct-related artery stenosis was 71% (95% CI, 60-81), specificity = 83%; (95% CI, 75-92) and accuracy = 72%; (95% CI, 61-82). Those for remote coronary stenosis were 74%; (95% CI, 63-86), 80%; (95% CI, 70-90) and 76%; (95% CI, 65-87) respectively. Ischemic perfusion score was significantly higher in patients with multi-versus single vessel disease. Dobutamine thallium scintigraphy is an accurate method for the diagnosis of coronary stenosis on basis of reversible hypoperfusion in symptomatic patients late after myocardial infarction with a comparable sensitivity for detecting remote and infarct-related artery stenosis.

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[1] *Submitted for publication.*

Key words:
Dobutamine stress test - 201 thallium SPECT - Myocardial infarction

INTRODUCTION

Exercise 201 thallium perfusion scintigraphy is a widely used technique for the diagnosis and functional assessment of coronary artery disease (1-4). The presence of scintigraphic markers of myocardial ischemia after myocardial infarction, based on reversible hypoperfusion, is a predictor of future cardiac events (3,4). In symptomatic patients with impaired systolic function, the detection of myocardial ischemia identifies myocardial segments at jeopardy and identifies patients in whom symptoms may improve after revascularization.

Since exercise tolerance may be reduced in patients with left ventricular dysfunction, dobutamine stress testing represents a feasible and safe alternative (5-11). However, in presence of severe myocardial dysfunction and severe perfusion abnormalities at rest, the detection of reversible perfusion defects represents a technical challenge for thallium scintigraphic techniques (12,13). Conversely, a recent study in patients after a recent myocardial infarction has shown that the sensitivity of dobutamine thallium scintigraphy for the diagnosis of infarct-related artery stenosis was high compared to poor sensitivity for remote coronary artery stenosis (14). Accordingly, the aim of this study was to assess the value of dobutamine 201 thallium single photon emission computed tomographic (SPECT) imaging for the detection of myocardial ischemia in symptomatic patients with left ventricular dysfunction late after acute myocardial infarction and to assess to which extent can the severity of persistent perfusion abnormalities influence the accuracy of the technique for the detection of individual coronary artery stenosis, based on reversible perfusion defects.

METHODS

Patients selection

Study population comprised 71 patients, referred to our nuclear imaging laboratory for evaluation of myocardial ischemia who fulfilled the following criteria:

1) previous myocardial infarction >3 months. The diagnosis of myocardial infarction relied upon the standard criteria of prolonged chest pain, a diagnostic rise (at least twice the normal value) and fall of serum creatine kinase and serial electrocardiographic changes. Mean time from the infarction was 5.3 ± 6.1 years.

2) the presence of wall motion abnormalities on resting echocardiogram. 3) absence of left bundle branch block, left ventricular hypertrophy, severe heart failure, valvular heart disease, severe hypertension, hypotension, or a history of sustained ventricular tachyarrhythmias. All patients gave an informed consent to undergo dobutamine stress testing in conjunction with 201-thallium perfusion

scintigraphy. Mean age was 59 ± 9 years. There were 58 men and 13 women. Forty seven (66%) patients were receiving oral nitrates and/or calcium antagonists and 38 patients (54%) were receiving angiotensin converting enzyme inhibitors at the day of the test. Beta blocking agents were stopped 2 days before the test. Symptoms before testing included typical angina in 57 patients, atypical chest pain in 3 patients and exertional dyspnea in 25 patients. Myocardial infarction was anterior (or anterolateral) in 39 patients, inferior (or inferolateral) in 20 patients and combined anterior and inferior in 12 patients.

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 5 followed by 10 μg/kg/min (3 minutes stages), increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of age predicted maximal heart rate (15). The ECG was monitored during dobutamine infusion and a 12-lead ECG was recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test. Ischemia at the ECG was defined as ≥0.1 mV horizontal or downsloping ST-segment depression 80 mS from the J point compared to baseline level or ≥0.1mV ST-segment elevation in ECG leads corresponding to myocardial regions without infarction (16).

Echocardiography

Echocardiographic images were acquired in the standard views. Left ventricular wall was divided into 16 segments and scored using a 4-point scale, where 1=normal, 2=hypokinesis, 3=akinesis, 4 = dyskinesis (16). Both wall motion and thickening were considered for analysis. Wall motions score index was derived by dividing the summation of the score of the 16 segments by 16. Regional wall motion score index was derived by dividing the score of the segments in each vascular territory by the number of segments in that territory.

Thallium SPECT imaging

Approximately 1 minute before the termination of the stress test, an intravenous dose of 74 MBq of 201 Tl was administered (17). The acquisition of stress SPECT imaging was started immediately after the test. For the reinjection studies, imaging was acquired 4 hours after the stress test, 20 minutes after the reinjection of 37 MBq of Tl. Image acquisition was performed with a Siemens Gammasonics single-head Rota Camera. For each study 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 were defined. Each of the 6 short axis slices was divided into 8 equal segments. The interpretation of the scan was performed by visual analysis assisted by the circumferential profiles

analysis. All tomographic views were reviewed in side by side pair (stress and reinjection) by an experienced observer who was unaware of the patients' clinical or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at reinjection imaging in 2 or more contiguous segments or slices. This was considered diagnostic of ischemia. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments or slices which persists on reinjection images. To assess perfusion defect size, perfusion defect score was quantitatively calculated by measuring the area between the lower limit of normal values ($\pm$ 2 standard deviations) and the actual circumferential profile at reinjection and stress images. Ischemic perfusion score was derived by subtracting rest from stress score in segments with reversible defects. Reinjection (fixed) defect score was derived in the peri-infarction area and was compared in vascular territories with and without reversible perfusion defects, in presence of significant stenosis of the related artery.

Coronary angiography

Coronary angiography and left ventriculography were performed, using the Judkins technique, within 3 months in all patients. Coronary artery lesions were quantified as discussed previously (18). Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$ in one or more major epicardial arteries. Coronary arteries were assigned to particular myocardial segments as follows: 1) the left anterior descending (LAD) coronary artery was assigned to the anterior wall, anterior septum, posterior septum (except for the basal segment) apical anterior and apical septal segments. 2) the left circumflex (LCX) coronary artery was assigned to the lateral and posterior wall. 3) the right coronary artery (RCA) was assigned to the inferior wall and the basal part of the posterior septum. The apical lateral segment was considered as an overlap segment between the LAD and the LCX and was assigned to the abnormal artery. Similarly, the apical inferior segment was considered as an overlap segment between the LAD and RCA.

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. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant. Sensitivity, specificity, predictive value and accuracy were derived according to standard definition and presented with their corresponding 95% confidence interval (CI).

RESULTS

Coronary angiography

Significant coronary artery disease was detected in all patients. Ten patients (14%) had single vessel disease, 33 (46%) had 2 vessel disease and 28 (39%) had 3 vessel disease. Significant stenosis of the LAD was detected in 62 patients (87%), of the RCA in 52 patients (73%) and of the LCX in 46 patients (65%). Significant stenosis of LCX and/or RCA was detected 61 patients (86%). In stenotic coronary arteries, the mean percentage diameter stenosis was significantly higher in infarct-related than remote coronary arteries (78 $\pm$ 21 vs 62 $\pm$ 25%, $p<0.05$).

Dobutamine stress test

Heart rate increased from 72 $\pm$ 13 at rest to 139 $\pm$ 15 beats /min at peak stress ($p<0.0001$) whereas systolic blood pressure did not change (125 $\pm$ 21 at rest vs 123 $\pm$ 25 mm Hg at peak stress). Atropine was administered in 27 (38%) patients. Angina occurred in 41 (58%) patients, ST-segment depression in 24 (32%) of whom, 2 had 1-vessel and 22 had multivessel disease. ST-segment elevation occurred in 32 (44%) patients, all of them had baseline wall motion abnormalities in the related segment. In 15 (21%) 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 (5 patients), ST-segment depression (1 patients), hypotension (8 patients) and significant tachyarrhythmias (1 patient).

201 Thallium SPECT

All patients had abnormal perfusion scintigraphy (fixed with or without reversible perfusion defects) in ≥ 1 vascular territory. Ischemia (partially or completely reversible perfusion defects) was detected in 57 patients (80%). There was no significant difference between patients with or without ischemia with respect to mean ejection fraction (40 $\pm$ 13 vs 35 $\pm$ 10%), peak heart rate (139 $\pm$ 13 vs 138 $\pm$ 13) or peak rate pressure product (16931 $\pm$ 3856 vs 17035 $\pm$ 3207). The sensitivity of dobutamine 201 thallium scintigraphy for the detection of coronary artery disease, on basis of reversible perfusion defects was 80% in all patients, 70% in patients with single vessel disease, 79% in patients with 2-vessel disease, and 86% in patients with 3 vessel disease. Sensitivity was relatively higher in multivessel versus single vessel disease (82% vs 70%), though the difference was not statistically significant. The sensitivity was higher than electrocardiography ($p<0.0001$). The sensitivity and specificity for the detection of significant stenosis in individual arteries on basis of reversible perfusion defects are shown in table 1. Because of the overlap between the LCX and RCA in the posteroinferior region, the sensitivity and specificity for detecting stenosis in either arteries were calculated by combining both vascular territories.

Ischemia was detected in more than one vascular territory in 39 of 61 patients with multivessel disease and in 2 of 10 patients with single vessel disease (sensitivity for detecting coronary stenosis in >1 region = 64%; CI, 53-75, specificity = 80%; CI, 71-89 and accuracy = 66%; CI, 55-77). Peri-infarction ischemia was detected in 46 of 65 patients with and in 1 of 6 patients without significant stenosis of the infarct-related artery (sensitivity = 71%; CI, 60-81, specificity = 83%; CI, 75-92 and accuracy = 72%; CI, 61-82). In the 59 patients who had infarction confined to the anterior or inferior location, remote ischemia was detected in 29 of 39 patients with and in 4 of 20 patients without remote coronary stenosis (sensitivity = 74%; CI, 63-86, specificity = 80%; CI, 70-90 and accuracy = 76%; CI, 65-87)[table 1].

Table 1. Sensitivity, specificity and accuracy of reversible perfusion defects on dobutamine thallium scintigraphy for the diagnosis of significant stenosis in individual regions in patients with previous myocardial infarction.

stenosis	yes	no	sensitivity	specificity	accuracy
LAD	62	9	65 (53-76)	89 (81-96)	68 (57-79)
LCX	46	25	61 (50-72)	76 (66-86)	66 (55-77)
RCA	52	19	67 (56-78)	74 (63-84)	69 (85-80)
RCA ± LCX	61	10	74 (64-84)	80 (71-89)	75 (65-85)
Infarct-related artery	65	6	71 (60-81)	83 (75-92)	72 (61-82)
Remote coronary artery	39	20	74 (63-86)	80(70-90)	76(65-87)

LAD = left anterior descending, LCX = left circumflex, RCA = right coronary artery. Sensitivity, specificity and accuracy are presented as percentage and (95% confidence interval).

Effect of fixed wall motion and perfusion abnormalities

In infarct regions subtended by a stenotic coronary artery, regional quantitative perfusion defect score at reinjection (figure 1) and regional wall motion score index on resting echocardiogram (figure 2) were significantly lower in presence than in absence of reversible perfusion defects in the same vascular territory only in the LCX and RCA territories; whereas no difference was found in the LAD territories.

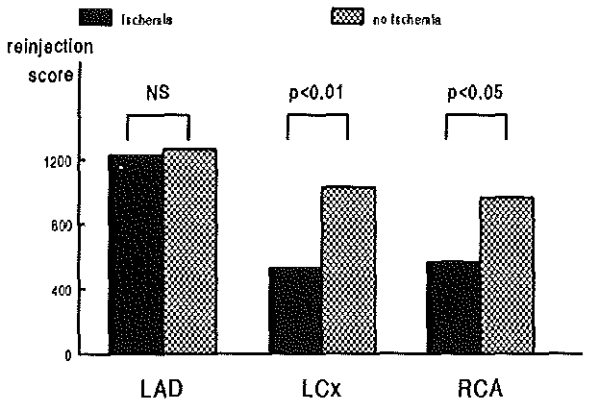

Figure 1. Regional perfusion defect score after reinjection in infarct regions with significant stenosis of the related artery, in presence or absence of peri-infarction ischemia at dobutamine thallium SPECT.

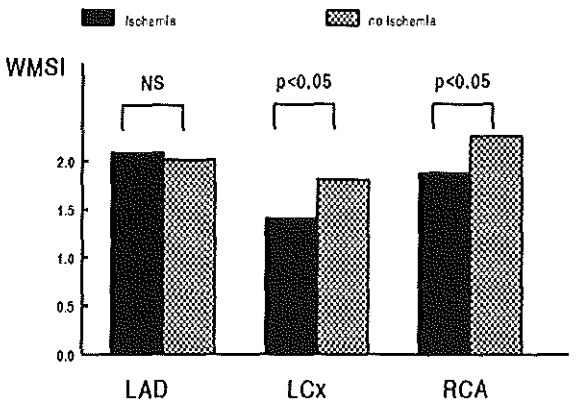

Figure 2. Regional wall motion score index (WMSI) in infarct regions with significant stenosis of the related artery, in presence or absence of peri-infarction ischemia at dobutamine thallium SPECT.

Extent and severity of ischemia in single versus multivessel disease

Patients with multivessel disease had a higher number of segments with reversible perfusion defects (2.5 ± 1.3 vs 1.7 ± 0.9, $p < 0.01$) and a higher ischemic defect score (1056 ± 1021 vs 423 ± 633, $p < 0.01$) compared to patients with single vessel disease.

DISCUSSION

The diagnosis of myocardial ischemia is important for the management and prognostic stratification of patients after myocardial infarction. The presence of thallium redistribution on exercise thallium scintigraphy in this population identifies patients at a higher risk of cardiac events (3,4).

Dobutamine stress testing is an exercise simulator used as a safe and feasible alternative for exercise in patients with limited exercise capacity. High dose dobutamine infusion may induce myocardial ischemia in presence of fixed coronary artery stenosis due to an increase of myocardial oxygen demand and induction of flow heterogeneity (19-20). Recent studies have demonstrated the value of dobutamine perfusion scintigraphy in the diagnosis and localization of coronary artery disease, based on the occurrence of reversible hypoperfusion during the test in patients without previous myocardial infarction (5-11). The role of dobutamine thallium scintigraphy in the assessment of myocardial viability and the prediction of improvement of left ventricular function after revascularization has been previously studied (17). However, little is known about the value of dobutamine perfusion scintigraphy for the diagnosis of peri-infarction and remote ischemia in patients with previous myocardial infarction. A recent study has shown a poor sensitivity of dobutamine thallium scintigraphy for the diagnosis of remote coronary artery stenosis early after myocardial infarction (14). Therefore, the diagnostic accuracy of dobutamine thallium scintigraphy in patients with myocardial infarction needs further assessment.

The present study

The results of our study show a good overall sensitivity of dobutamine thallium SPECT myocardial perfusion scintigraphy for the diagnosis of significant coronary artery stenosis on basis of reversible hypoperfusion in a well defined symptomatic patient population with left ventricular dysfunction late after myocardial infarction. The sensitivity for the detection of remote coronary artery stenosis was comparable to that for the infarct-related artery. The relatively low sensitivity for the detection of individual coronary stenosis and multivessel involvement on basis of inducible ischemia in more than one vascular territory can be explained by the possible attenuation of differences in perfusion in presence of multivessel disease and that remote ischemic segments may appear as contiguous. An other explanation is a different threshold for

ischemia in different territories in the same patients, with a possibility of reaching an end point of symptoms, hemodynamic or electrical changes following the occurrence of ischemia in one territory before others. Exercise thallium scintigraphy has been reported to underestimate the extent of coronary artery disease after myocardial infarction (21). Similar findings were reported with adenosine thallium (22) and dobutamine MIBI scintigraphy (8) in patients without previous myocardial infarction. The vascular overlap between the LCX and RCA in the posteroinferior region (9,23) may explain the low accuracy when each artery was analyzed separately.

Influence of the severity of resting perfusion abnormalities on the diagnosis of ischemia

In presence of infarct-related artery stenosis, the severity of fixed wall motion and perfusion abnormalities contributed to a lower prevalence of peri-infarct redistribution only in the LCX and RCA territories, while the severity of resting abnormalities was not different with or without reversible perfusion defects in territories with LAD stenosis. This can be explained by the large myocardial mass in the LAD territories comprising the anterior wall, anterior and posterior septum and apex, which maintains an adequate substrate for ischemia even in presence of a relatively large infarction in contrast to RCA and LCX which supply a smaller myocardial mass in which the induction of myocardial ischemia may be critically dependent on the extent of intact myocardium in the related territories. Despite that the severity of resting perfusion abnormalities was a factor reducing the sensitivity for the diagnosis of significant RCA or LCX stenosis, the sensitivity for the diagnosis of peri-infarction and remote ischemia was not different. This can be explained by the more severe diameter stenosis of the infarct-related compared to remote stenosis which may compensate for the reduction of myocardial mass functioning as a substrate for ischemia in the peri-infarction region. Mean ejection fraction was not different with or without ischemia. Similar results were reported by Sutton et al. in patients with residual critical stenosis after thrombolysis for acute myocardial infarction, undergoing exercise thallium scintigraphy, although mean peak creatine kinase level was lower in patients with ischemia (24). Our findings of a similar peak heart rate and rate pressure product in patients with or without ischemia are consistent with the findings of Sutton et al (24).

Comparison with previous studies

This is the first study which evaluates the accuracy of dobutamine perfusion scintigraphy for the diagnosis of peri-infarct and remote coronary artery stenosis in a symptomatic population late after acute myocardial infarction.

Coma-Canella et al. (14) studied 63 patients with dobutamine thallium SPECT early after a recent myocardial infarction. The sensitivity of thallium

scintigraphy for the detection of coronary stenosis was 75% for infarct-related and 18% for remote coronary artery stenosis. The low sensitivity for remote stenosis compared to our results may be related to the inclusion of predominantly asymptomatic population as opposed to our patients which can be expected to influence the inducibility of ischemia. An other factor may be related to the use of quantitative assessment of perfusion in all patients in our study which may enhance the detection of mild reversible defects. The higher sensitivity for remote coronary artery stenosis in our study (74% vs 18% in the other study) is concordant with our finding of a higher quantitative ischemic perfusion defect score in patients with multivessel compared to single vessel disease; whereas the previous study, based on visual semiquantitaive assessment failed to find such difference. It has been demonstrated that quantitative analysis is superior to visual analysis of exercise thallium images in the diagnosis of coronary artery stenosis in patients with known or suspected coronary artery disease (25). The overall accuracy of dobutamine thallium scintigraphy for the diagnosis of significant coronary artery stenosis in patients with previous myocardial infarction is aligned with previous studies on dobutamine perfusion scintigraphy in patients without previous myocardial infarction (5-11).

Limitations of the study

All patients had significant coronary artery stenosis precluding evaluation of the overall specificity of the technique. However, coronary stenosis was not an inclusion criteria and this finding represents the high predictive value of the clinical status of this population for significant coronary stenosis. Nevertheless, we have demonstrated a good regional specificity of the technique. Despite that thallium reinjection improves the detection of ischemia in dyssynergic segments (12), it has been reported that some reversible defects at redistribution may become fixed after reinjection with a possibility of underestimating ischemia if redistribution images were not acquired (13).

Summary and conclusion

Dobutamine thallium scintigraphy is an accurate method for the diagnosis of coronary stenosis on basis of reversible hypoperfusion in symptomatic patients with left ventricular dysfunction late after myocardial infarction with a comparable sensitivity for the detection of remote and infarct-related artery stenosis. The severity of fixed wall motion and perfusion abnormalities contributes to a lower prevalence of peri-infarction ischemia only in the circumflex and right coronary artery territories probably due to the a smaller myocardial mass compared to the territories of the left anterior descending coronary artery.

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CHAPTER 10

RELATIONSHIP BETWEEN CONTRACTILE RESPONSE OF AKINETIC SEGMENTS DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY AND ISCHEMIA ASSESSED BY SIMULTANEOUS 201 THALLIUM SPECT[1]

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ABSTRACT

There are no standard criteria for the diagnosis of myocardial ischemia in akinetic segments during dobutamine stress echocardiography (DSE). The aim of the study was to assess the relation between different responses of akinetic segments during DSE and ischemia assessed by 201 Tl SPECT. DSE (up to 40 μg/kg/min) with simultaneous stress-reinjection Tl SPECT was performed in 67 patients with old myocardial infarction and coronary artery stenosis. Fourteen myocardial segments were matched for both DSE and SPECT. Ischemia on SPECT was defined as reversible Tl defects. In 257 akinetic segments, 4 patterns during DSE were identified: I) biphasic in 41 segments (16%), defined as improvement at low-dose (5-10 μg/kg/min) followed by worsening at high-dose. II) persistent akinesis in 155 segments (60%). III) akinesis becoming dyskinesis in 39 segments (15%). IV) sustained improvement in 22 segments (9%). Reversible Tl defects were detected in 21 segments (51%) in group I, 20 segments (13%) in group II, none in group III and in 2 segments in group IV (9%). The prevalence of reversible defects in biphasic segments was higher compared to other patterns ($p < 0.00001$ vs group II and III, $p < 0.005$ vs group IV). Ischemic perfusion defect score was significantly higher in group I than group II. The positive predictive value of biphasic response for reversible Tl defects was similar to that of stress-induced dyssynergy in normal segments at 2rest (51% vs 58%). It is concluded that of the varying responses of akinetic segments to dobutamine infusion, the biphasic response is associated with the highest prevalence and greatest severity of ischemia on Tl SPECT. Observation of contractile response at both low and high dose DSE provides a valuable

[1] *Am J Cardiol; in press.*

approach for the diagnosis of myocardial ischemia in akinetic segments.

Key Words: Dobutamine stress echocardiography - Thallium SPECT imaging

INTRODUCTION

Dobutamine stress test in conjunction with echocardiography or myocardial perfusion scintigraphy is increasingly used for the diagnosis and functional evaluation of coronary artery disease (1-9). The standard echocardiographic criteria for the diagnosis of ischemia rely upon the occurrence of new or worsening wall motion abnormalities (1-4). However, in severely dyssynergic segments, no further deterioration of function can occur during the test and consequently, the diagnosis of ischemia in these segments represents a limitation of the echocardiographic technique. It was suggested that a "biphasic response" manifested as a contractile response at low-dose dobutamine followed by worsening at high dose is a sign of myocardial ischemia (10,11). However, little data are available to confirm this conclusion. The diagnosis of myocardial ischemia by dobutamine perfusion scintigraphy is based on the occurrence of reversible perfusion defects (4-6). Since the technique is independent on interpretation of wall motion, it can be used for evaluation of ischemia in akinetic segments. Therefore, the aim of this study was to assess the relationship between different responses of akinetic segments during dobutamine stress echocardiography (DSE) and ischemia on simultaneous 201 Tl SPECT myocardial perfusion imaging in patients with previous myocardial infarction.

METHODS

Patient selection

Study population comprised 67 consecutive patients with previous myocardial infarction >3 months and exertional chest pain, referred to our imaging laboratory for evaluation of myocardial ischemia, in whom DSE was performed in conjunction with 201 Tl SPECT imaging and had technically interpretable images. The diagnosis of myocardial infarction relied upon the standard criteria of prolonged chest pain, a diagnostic rise of serum creatine kinase and serial electrocardiographic changes. Patients were included if they had $\geq$ 2 akinetic segments on baseline echocardiogram. Mean age was 59 $\pm$ 9 years. There were 55 men and 12 women. Forty seven (70%) patients were receiving oral nitrates and/or calcium antagonists at the day of the test. If administered, beta blockers were stopped 2 days before the test.

Dobutamine stress test

Dobutamine was infused through an antecubital vein in 3 minutes stages starting at a dose of 5 μg/kg/min, 10 μg/kg/min, increasing by 10 μg/kg/min to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age predicted maximal heart rate at peak dobutamine

dose (12). The electrocardiogram was monitored during infusion and recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test.

Stress echocardiography

Echocardiographic images were acquired at rest and during the test and recovery. For both rest and stress studies, left ventricular wall was divided into 16 segments and scored using a 4-point scale, where 1=normal, 2=hypokinesis, 3=akinesis, 4 = dyskinesis (1,3). Both wall motion and thickening were considered for analysis. Each segment was scored at rest, at low dose dobutamine and at peak stress. Criteria of ischemia were the appearance of wall motion abnormalities during stress in one or more normal segment at rest and the occurrence of akinesis or dyskinesis during stress in one or more hypokinetic segment at rest. Images were recorded on video tapes and were also digitized on optical disk-Vingmed CFM 800 and displayed side by side in quad-screen format to facilitate the comparison of rest, low-dose and peak stress images. Images interpretation was performed by 2 experienced observers without the knowledge of the patients scintigraphic data. In case of disagreement, a majority decision was achieved by a third reviewer. In our laboratory, inter-and intra-observer agreement for echocardiographic assessment are 84% and 87% for resting images and 92% and 94% for dobutamine stress images respectively (13). 4 patterns of contractile response in akinetic segments during DSE were identified: I) biphasic response: defined as akinetic segments demonstrating a contractile response at low-dose dobutamine (5-10 μg/kg/min) and becoming akinetic at peak stress. II) persistent akinesis: defined as unchanged akinetic pattern throughout the test. III) akinesis at rest becoming dyskinesis at peak stress. IV) sustained improvement: defined as akinetic segment at rest becoming normal or hypokinetic at low-dose, without worsening at peak stress.

Thallium SPECT imaging

Approximately 1 minute before the termination of the stress test, an intravenous dose of 74 MBq of 201 Tl was administered (13). The acquisition of stress SPECT imaging was started immediately after the test. For the reinjection studies, imaging was acquired 4 hours after the stress test, 20 minutes after the reinjection of 37 MBq of Tl. For each study 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 were defined. Each of the 6 short axis slices was divided into 8 equal segments. The septal part of the 2 basal slices (4 segments) was not considered for analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced

uptake. The interpretation of the scan was performed by visual analysis assisted by the circumferential profiles analysis. Stress and reinjection tomographic views were reviewed in side by side pair by an experienced observer who was unaware of the patients' echocardiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at reinjection imaging in 2 or more contiguous segments or slices. This was considered diagnostic of ischemia. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments or slices which persists on reinjection images. Perfusion defect score was quantitatively calculated by measuring the area between the lower limit of normal values ($\pm$ 2 standard deviations) and the actual circumferential profile in 6 short axis slices. Ischemic perfusion score was derived by subtracting rest from stress score. Myocardial segments identified at scintigraphy were matched with those identified at echocardiography in a 16 segment model. The basal septal segments were excluded from analysis.

Coronary angiography

Coronary angiography was performed, using the Judkins technique, within 3 months in all patients. Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$ in one or more major epicardial arteries using a quantitative method described previously (14). Coronary arteries were assigned to particular myocardial segments as previously described (3,15).

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. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant.

RESULTS

Dobutamine stress test

Heart rate increased from 73 $\pm$ 13 at rest to 137 $\pm$ 15 beats /min at peak stress ($p < 0.0001$) whereas systolic blood pressure did not change (125 $\pm$ 21 at rest vs 123 $\pm$ 25 mm Hg at peak stress). There was no significant increase of heart rate or systolic blood pressure at low dose-dobutamine compared to baseline values (82 $\pm$ 17 beats/min and 124 $\pm$ 23 mm Hg respectively). Angina occurred in 37 (55%) patients, ST-segment depression in 22 (33%) and ST-segment elevation in 28 (42%) patients The test was interrupted before reaching the maximal dose or the target heart rate because of angina in 4 patients, ST-segment depression in 1 patient, hypotension in 7 patients and significant tachyarrhythmias in 1 patient.

Stress echocardiography

A total of 257 akinetic segments were identified on baseline echocardiogram. 4 groups of akinetic segments were identified: I) biphasic response detected in 17 patients (25%); in 41 segments (16%). II) persistent akinesis in 50 patients (75%); in 155 segments (60%). III) akinesis becoming dyskinesis in 14 patients (21%); in 39 segments (15%); none of these segments improved at low-dose. IV) sustained improvement, detected in 10 patients (15%); in 22 segments (9%). Some patients had different responses in different segments. In the 63 segments with contractile response at low dose dobutamine, the response was observed at a dose of 5 μg/kg/min in 18 segments and at 10 μg/kg/min in 45 segments. There was no significant difference between the 4 groups in the corresponding heart rate or systolic blood pressure at rest, low-dose and peak stress. New wall motion abnormalities were detected in 89 of 403 segments (22%) with normal baseline contraction.

Table I: Scintigraphic pattern, quantitative perfusion defect score and prevalence of significant stenosis of the related coronary artery in each group of akinetic segments identified according to the response to dobutamine infusion.

	Group I biphasic N = 41	Group II persistent akinesis N = 155	Group III akinesis dyskinesis N = 39	Group IV sustained improvement N = 22
Reversible defect	21 (51%)	20 (13%)	0	2 (9%)
complete	5 (12%)	6 (4%)	0	2 (9%)
partial	16 (39%)	14 (9%)	0	0
Fixed defect	16 (39%)	127 (82%)	39 (100%)	11 (50%)
Normal	4 (10%)	8 (5%)	0	9 (41%)
Stress defect score	279±220	294±265	307±180	100±130
Reinjection defect score	140±170*	273±255	302±177	90±110*
Ischemic defect score	136±142**	56±90	0	80±16
Coronary stenosis ≥50%	37 (90%)	132 (85%)	35 (89%)	15 (68%)#

* = $p<0.05$ vs II and III, ** = $p<0.05$ vs II (values are derived only in segments with reversible perfusion defects), # = $p<0.05$ vs other groups.

201 thallium SPECT imaging

The distribution of scintigraphic patterns is presented in table I. Group I comprised segments with the highest prevalence of reversible perfusion defects ($p<0.00001$ vs group II and III, $p<0.005$ vs group IV). The prevalence of reversible Tl defects was higher in group II versus III ($p<0.05$) while the

difference was not significant in group II versus IV and in group III versus IV (figure 1). Perfusion defect score at reinjection was lower in group IV than other groups ($p < 0.05$) and lower in group I versus II and III ($p < 0.05$). Normal perfusion was detected in 21 segments (8%) and did not tend to involve a particular anatomic location. Ischemic perfusion score was higher in group I than II ($p < 0.05$) [table I]. In myocardial segments with normal contraction at rest, reversible perfusion defects were detected in 52 of 89 (58%) segments with and in 18 of 314 (6%) segments without stress-induced wall motion abnormalities ($p < 0.00001$). The prevalence of reversible perfusion defects in akinetic biphasic segments was not different compared to segments with normal baseline contraction and stress-induced wall motion abnormalities (51% vs 58%).

Coronary angiography

Significant coronary artery disease was detected in all patients. Twelve patients (18%) had single vessel disease, 25 (37%) had two-vessel disease and 30 (45%) had 3 vessel disease. There was no significant difference between group I, II or III with respect to prevalence of stenosis in the related artery, whereas the prevalence was higher in each of these groups compared to group IV ($p < 0.05$ in all) [table I].

DISCUSSION

Our results show that among the 4 different contractile responses of akinetic segments during DSE, a biphasic response was associated with the highest prevalence of reversible perfusion defects (and presumably ischemia) compared to segments with persistent akinesis, sustained improvement and akinesis becoming dyskinesis. The degree of reversibility as measured by ischemic perfusion score was greater in segments with biphasic response compared to those with persistent akinesis by quantitative analysis. Furthermore, the use of a biphasic response in akinetic segments as a criterion for ischemia gave a positive predictive value comparable to the standard criterion of a normal segment becoming dyssynergic during stress. The relation between a biphasic response and ischemia can be explained by the presence of a hibernating viable myocardium subtended by a stenotic coronary artery, which exhibits a contractile response to low-dose dobutamine and ischemia provoked by an increase of heart rate and flow maldistribution at high-dose dobutamine (16). Nevertheless, 51% of reversible perfusion defects in akinetic segments were not in the biphasic group. Reversible Tl defects occurred infrequently in akinetic segments with sustained improvement (9%) and in persistently akinetic segments (13%). Segments with persistent akinesis and reversible 201 Tl defects may represent a hibernating myocardium unresponsive to dobutamine or severely necrotic myocardium with small amount of viable, ischemic myocardium resulting in reversible hypoperfusion meanwhile incapable of demonstrating a

contractile response at low-dose dobutamine. Panza et al. have concluded that the cellular mechanism responsible for thallium uptake requires less degree of myocyte functional integrity compared to mechanism responsible for positive inotropic response to dobutamine (17) which may explain the presence of reversible perfusion defects in some segments with persistent akinesis. These investigators demonstrated that the positive inotropic response of dyssynergic myocardium to low-dose dobutamine is directly related to thallium uptake (17) which is compatible with our findings of more severe fixed perfusion defects and less severe reversible perfusion defects in persistently akinetic compared to biphasic segments. The absence of reversible perfusion defects in akinetic segments becoming dyskinetic at high dose dobutamine supports our previous report in which this pattern was attributed to passive myocardial bulging unrelated to myocardial ischemia (18). The presence of normal perfusion in 8% of akinetic segments in our study is difficult to explain. Myocardial stunning is a possible mechanism, which may be supported by the finding of the highest prevalence of normal perfusion and lowest prevalence of significant coronary stenosis in segments with persistent improvement. However, it is not known if myocardial stunning can exist more than 3 months after infarction. Other explanations may include methodological limitations in detecting reversible defects and difficulties in registration of images obtained with different methodologies.

Comparison with previous studies

Senior and Lahiri (10) reported that the use of biphasic response increased the sensitivity of DSE for the detection of reversible defects on simultaneous MIBI or tetrofosmin SPECT in 44 patients with left ventricular dysfunction. However, the contribution of other responses of akinetic segments was not studied. Furthermore, a global rather than a matched segmental analysis was used. Biphasic response to dobutamine infusion in animal studies was shown to be characteristic of ischemic or short term hibernation. Worsening of wall motion at high dose was associated with myocardial acidosis and lactate accumulation (19). lack of improvement of contractility during DSE was described as a sign of ischemia due to exhaustion of coronary reserve (5,6,20). However, this is more likely to be applicable to normal or hypokinetic rather than akinetic segments.

Limitations of the study

Myocardial ischemia was assessed by Tl perfusion scintigraphy which detects flow malperfusion as well as true ischemia. Despite that reinjection technique enhances the detection of reversible perfusion defects (21), some of these defects can be missed if redistribution images were not acquired (22). However, it is unlikely that underestimation of defect reversibility will occur more frequently in a particular group of segments. Though biphasic akinetic

segments showed the highest prevalence of reversible Tl defects, the positive predictive value of this pattern for reversible perfusion defects was not high. However, the predictive value was comparable to that of the standard criterion of a normal segment becoming dyssynergic during stress. This may be explained by the previously mentioned limitations of correlating 2 imaging modalities which detect different pathophysiologic sequela of coronary artery disease.

Conclusion

In symptomatic patients with left ventricular dysfunction after myocardial infarction, a biphasic response of akinetic segments during DSE is associated with the highest prevalence and most severe myocardial ischemia on basis of 201 Tl SPECT compared to segments with persistent akinesis, sustained improvement and akinetic segments becoming dyskinetic. The positive predictive value of a biphasic response for reversible Tl defects is comparable to that obtained by the standard echocardiographic criteria for ischemia in segments with normal baseline contraction. Observation of contractile response of akinetic segments at both low and high dose DSE may provide a valuable approach for the echocardiographic diagnosis of myocardial ischemia in akinetic segments.

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CHAPTER 11

IMPAIRED SYSTOLIC BLOOD PRESSURE RESPONSE TO DOBUTAMINE STRESS TEST: A MARKER OF MORE SEVERE FUNCTIONAL ABNORMALITIES IN PATIENTS WITH MYOCARDIAL INFARCTION[1]

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ABSTRACT

Objectives. Aim of the study was to assess the relationship between systolic blood pressure response to high dose dobutamine stress test and the severity of left ventricular dysfunction in patients with myocardial infarction.

Background. Dobutamine-induced hypotension has been disregarded as an indicator of more severe functional abnormalities in patients with known or suspected coronary artery disease. However, the functional significance of systolic blood pressure response to high dose dobutamine has not been assessed in a homogenous population with left ventricular dysfunction.

Methods. Dobutamine stress (up to 40 μg/kg/min) echocardiography was performed in 326 consecutive patients with left ventricular dysfunction after myocardial infarction. Ischemia was defined as new or worsening wall motion abnormalities. Patients were divided into 3 equal groups with mild, moderate and severe wall motion abnormalities according to resting wall motion score index.

Results. Systolic blood pressure and heart rate increased significantly from rest to peak dobutamine stress (127 $\pm$ 22 vs 134 $\pm$ 27 mm Hg and 72 $\pm$ 14 vs 122 $\pm$ 24 beats/minute, $p < 0.00001$ in both). The change of systolic blood pressure from rest to peak dobutamine stress (Δ systolic blood pressure) was significantly higher in patients with mild compared to moderate wall motion abnormalities (16 $\pm$ 29 vs 6 $\pm$ 26 mm Hg, $p < 0.01$), whereas systolic blood pressure dropped in patients with severe wall motion abnormalities (Δ systolic blood pressure = -2 mm Hg, $p < 0.01$ vs moderate and < 0.00001 vs mild wall motion abnormalities). Δ systolic blood pressure $\geq$ 10 mm Hg occurred in 153

[1] *Submitted for publication.*

patients (47%). By multivariate analysis, independent predictors of failure of systolic blood pressure increase were higher wall motion score index at rest and at peak stress ($p<0.00001$ in both), higher resting systolic blood pressure ($p<0.005$), medication with calcium channel blockers ($p<0.005$) and higher age ($p<0.05$). Systolic blood pressure drop ≥ 10 mm Hg occurred in 89 patients (27%). Independent predictors were higher wall motion score index at rest ($p<0.01$) and at peak stress ($p<0.005$), a higher resting systolic blood pressure ($p<0.001$), medication with angiotensin-converting enzyme inhibitors ($p<0.05$) and a higher age ($p<0.05$). Ischemia was detected in 182 patients (56%) and was not an independent predictor of systolic blood pressure increase or decrease.
Conclusion. In patients with myocardial infarction undergoing dobutamine stress echocardiography for the evaluation of myocardial ischemia, left ventricular function is the most powerful predictor of systolic blood pressure response to dobutamine stress.

INTRODUCTION

Exercise-induced hypotension has been recognised as a marker of severe coronary artery disease, extensive functional abnormalities and poor prognosis (1-3). Despite that dobutamine stress testing is an exercise simulator stress modality, previous studies have failed to demonstrate a difference in functional abnormalities between patients with or without dobutamine-induced hypotension (4-9). The development of hypotension in normal subjects during dobutamine stress testing has been attributed to intraventricular obstruction and vagal stimulation due to high cardiac output (8-9). However, previous studies were performed in unselected patient population with or without regional wall motion abnormalities. It is not known if the extent of functional abnormalities may play a role in a selected patient population with left ventricular dysfunction after myocardial infarction in whom intraventricular obstruction and vagal reflexes due to high cardiac output are less likely to occur. Furthermore, previous studies have focused on dobutamine-induced hypotension whereas the significance of failure of systolic blood pressure increase during dobutamine stress test has not been assessed. Therefore, the aim of this study was assess the relationship between systolic blood pressure response and the extent of functional abnormalities in patients with previous myocardial infarction undergoing dobutamine stress testing for evaluation of myocardial ischemia.

METHODS

Patient population

Study population comprised a consecutive series of patients, referred for evaluation of myocardial ischemia who fulfilled the following criteria: 1) previous myocardial infarction based on the standard criteria of prolonged chest

pain, a diagnostic rise of serum enzymes and serial ECG changes. 2) The presence of wall motion abnormalities at resting echocardiogram. 3) absence of severe heart failure, valvular heart disease, severe hypertension, hypotension, or a history of sustained ventricular tachyarrhythmias. Patients in whom the test was terminated before reaching an ischemic end point (angina, ST-segment depression or transient wall motion abnormalities) or the target heart rate because of reasons other than blood pressure changes were excluded. Three hundred-twenty six patients fulfilled the previous criteria. All patients gave an informed consent to undergo dobutamine stress echocardiography. Mean age was 59 $\pm$ 10 years. There were 251 men and 75 women. The test was performed in 111 patients within 1 month from the infarction; whereas the infarction was old in 215 patients (mean time = 4.7 $\pm$ 5.9 years). Symptoms before testing included chest pain in 182 and exertional dyspnea in 21 patients. Ninety patients were referred for routine assessment; whereas 33 patients were referred for the assessment of function after revascularization procedures. Myocardial infarction was anterior (or anterolateral) in 145 patients, inferior (or posterolateral) in 126 patients and in both locations in 55 patients.

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 5 followed by 10 μg/kg/min (3 minutes stages), increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of age predicted maximal heart rate (10). The electrocardiogram was monitored throughout dobutamine infusion and recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test. Ischemia at the ECG was defined as ≥ 0.1 mV horizontal or downsloping ST-segment depression 80 mS from the J point compared to baseline level or ≥ 0.1mV ST-segment elevation in ECG leads corresponding to segments without resting wall motion abnormalities (11).

Stress echocardiography

Echocardiographic images were acquired at rest and during stress and recovery. For both rest and stress studies, left ventricular wall was divided into 16 segments and scored using a 4-point scale, where 1=normal, 2=hypokinesis, 3=akinesis, 4 = dyskinesis. The interpretation of images was performed by 2 experienced observers without the knowledge of the patients' angiographic data. In case of disagreement, a third reviewer revised images and a majority decision was achieved. In our laboratory, inter-and intra-observer agreement for stress echocardiographic assessment is 92% and 94% respectively (12). Both wall motion and thickening were considered for analysis. Wall motion score index was derived by dividing the summation of individual score of the 16 segments

by 16. Ischemia was defined as new or worsening wall motion abnormalities. As we have previously concluded (13), ischemia was not considered when akinetic segments at rest became dyskinetic during stress without improvement at low-dose dobutamine (5-10 μg/kg/min).

Coronary angiography

Coronary angiography was performed, using the Judkins technique, within 3 months in 186 patients (57%). Coronary stenosis was quantified using a previously described method from our center (14). Significant coronary artery disease was defined as a diameter stenosis $\geq$50% in one or more major epicardial arteries.

Statistical analysis

Unless specified, data are presented as mean values $\pm$ SD. The chi square test test was used to compare differences between proportions. ANOVA test was used to determine the differences between groups. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant. Logistic regression analysis was used to determine independent predictors of systolic blood pressure increase or decrease $\geq$ 10mm Hg.

RESULTS

Baseline left ventricular function

3 groups were identified according to resting wall motion:

-Group 1, included 99 patients with mild wall motion abnormalities (wall motion score index between 1.06 and 1.31).

-Group 2, included 110 patients with moderate wall motion abnormalities (wall motion score index between 1.38 and 1.81).

-Group 3, included 117 patients with severe wall motion abnormalities (wall motion score index $\geq$1.88).

Classification of patients aimed at the constitution of 3 equal groups. The presence of some patients with the same wall motion score index resulted in a slight difference in number of patients in each group. Clinical characteristics and medications are shown in table 1. There was no significant difference between the 3 groups with regard to age, gender, risk factor and nitrate therapy. Patients of group 3 had a higher prevalence of a history of angina compared to group 1 ($p < 0.05$). Beta blockers and calcium blockers were more frequently taken in patients of group 1 ($p < 0.005$ vs group 2 and < 0.0001 vs group 3). Intake of diuretics and angiotensin converting enzyme inhibitors was more frequent in group 3 ($p < 00001$ vs group 1 and < 0.005 vs group 2) and in group 2 compared to group 1 ($p < 0.001$).

Table 1. Clinical characteristics of the 3 groups of patients with previous myocardial infarction, classified according to the severity of resting wall motion abnormalities.

	Group 1 (N = 99)	Group 2 (N = 110)	Group 3 (N = 117)
Age	59 ± 11	60 ± 10	58 ± 11
Females	28 (28%)	21 (19%)	26 (22%)
History of chest pain	50 (50%)	57 (52%)	75 (64%)
Beta blockers	47 (47%)	30 (27%)	23 (20%)
Calcium blockers	47 (47%)	30 (27%)	39 (33%)
Nitrates	51 (52%)	50 (45%)	64 (55%)
ACE inhibitors	17 (17%)	49 (45%)	82 (70%)
Diuretics	13 (13%)	36 (33%)	63 (54%)
LVH	2 (2%)	4 (4%)	2 (2%)
Hypertension	34 (34%)	39 (35%)	38 (32%)
Diabetes mellitus	13 (13%)	24 (22%)	22 (19%)

ACE = angiotensin-converting enzyme - LVH = left ventricular hypertrophy

Hemodynamic response and echocardiographic findings in different groups

Systolic blood pressure and heart rate increased significantly from rest to peak dobutamine stress (127 ± 22 vs 134 ± 27 mm Hg, and 72 ± 14 vs 122 ± 24 beats/minute, $p<0.00001$ in both). Atropine increased the heart rate significantly to 136 ± 17 beats/min ($p<0.0001$); whereas systolic blood pressure did not change (134 ± 28 mm Hg). Resting, peak, Δ systolic blood pressure, and percentage of patients with ≥10 mm Hg systolic blood pressure increase or decrease in the 3 groups are shown in table 2.

Peak heart rate and systolic blood pressure are derived at the maximal dose of dobutamine before atropine adminstration. It shows that the more severe the wall motion abnormalities, the lower the Δ systolic blood pressure and the higher the prevalence of drop and failure of increase of systolic blood pressure increase. Δ systolic blood pressure was significantly higher in group 1 compared to group 2 (16 ± 29 vs 6 ± 26 mm Hg, $p<0.01$), whereas systolic blood pressure dropped in group 3 (Δ systolic blood pressure = -2 mm Hg, $p<0.01$ vs group 2 and <0.00001 vs group 1) [figure 1]. The percentage of patients

with ≥10 mm Hg Δ systolic blood pressure was significantly higher in group 1 than 2 and 3 ($p<0.0.05$ and <0.0005 respectively) and in group 2 vs 3 ($p<0.05$). The same significant difference existed with Δ systolic blood pressure ≥20 mm Hg. Systolic blood pressure drop ≥10 mm Hg was more prevalent in group 3 ($p<0.001$ vs group 1, $p<0.05$ vs group 2). Wall motion score index increased significantly in the whole group from rest to peak stress (1.67 ± 0.44 vs 1.79 ± 0.51, $p<0.00001$). Echocardiographic data are shown in table 3. The prevalence of ischemia was significantly lower in group 1 ($p<0.05$ vs group 2, $p<0.0005$ vs group 3).

Table 2. Hemodynamic data of the 3 groups of patients with previous myocardial infarction, classified according to the severity of resting wall motion abnormalities.

	Group 1 (N = 99)	Group 2 (N=110)	Group 3 (N =117)
Resting SBP	130 ± 23	129 ± 20	124 ± 23
Peak dobutamine SBP	145 ± 26	135 ± 27	122 ± 25
Peak dobutamine ± atropine SBP	146 ± 28	135 ± 27	122 ± 26
Δ SBP	16 ± 29	6 ± 26	-2 ± 21
Resting HR	66 ± 13	70 ± 12	78 ± 15
Peak dobutamine HR	114 ± 26	123 ± 25	124 ± 25
Peak stress Heart rate	130 ± 19	136 ± 15	140 ± 17
Δ SBP ≥10	62 (63%)	54 (49%)	39 (32%)
Δ SBP ≥20	41 (41%)	31 (28%)	15 (13%)
Δ SBP ≤-10	17 (17%)	28 (25%)	44 (38%)
Δ SBP ≤-20	11 (11%)	19 (17%)	27 (21%)

SBP = systolic blood pressure (mm Hg), HR = heart rate (beats/minute).

Predictors of systolic blood pressure response

An increase of systolic blood pressure ≥10 mm Hg occurred in 153 patients (48%). Patients with Δ systolic blood pressure ≥10 mm Hg were significantly younger, had a lower resting heart rate, a lower resting systolic blood pressure, a similar maximal heart rate, a higher peak systolic blood pressure, a higher frequency of beta blockers medication, a lower frequency of

calcium channel blockers, angiotensin converting enzyme inhibitor and diuretic medications, a lower wall motion score index at rest and at peak stress, and a lower prevalence of ischemia (table 4).

Table 3. Dobutamine stress data of the 3 groups of patients with previous myocardial infarction, classified according to the severity of resting wall motion abnormalities.

	Group 1 (N = 99)	Group 2 (N = 110)	Group 3 (N = 117)
Peak dobutamine dose	38.4 ± 4.4	38.1 ± 4.8	37.5 ± 6.1
Atropine given	45 (45%)	41 (37%)	30 (26%)
Resting WMSI	1.2 ± 0.8	1.57 ± 0.14	2.18 ± 0.22
Peak WMSI	1.25 ± 0.2	1.71 ± 0.26	2.36 ± 0.31
Ischemia on echocardiogram	41 (41%)	64 (58%)	77 (66%)
ST-segment depression	30 (30%)	35 (32%)	25 (21%)
Angina	20 (20%)	31 (28%)	57 (49%)
Coronary stenosis*	40/50 (80%)	55/60 (92%)	64/76 (86%)
Multivessel disease*	15/50 (30%)	40/60 (67%)	51/76 (67%)

* data are derived only in patients who underwent coronary angiography
WMSI = wall motion score index.

Multivariate analysis of baseline characteristics identified baseline wall motion score index ($p<0.00001$), systolic blood pressure ($p<0.005$), medication with calcium channel blockers ($p<0.005$) and age ($p<0.05$) as independent predictors of a systolic blood pressure increase ≥ 10 m Hg. Multivariate analysis of stress test variables (angina, ST-segment depression, peak heart rate, ischemia at echocardiography and peak wall motion score index) identified peak wall motion score index as an independent predictor ($p<0.00001$).

Systolic blood pressure drop ≥ 10 mm Hg occurred in 89 patients (27%). These patients were significantly older, had a higher resting heart rate, a higher resting systolic blood pressure a similar maximal heart rate, a lower peak systolic blood pressure, a lower frequency of beta blockers medication, a higher frequency of angiotensin converting enzyme inhibitor and diuretic medication, a higher wall motion score index at rest and at peak stress, and a similar prevalence of ischemia (table 5).

Table 4. Clinical, angiographic, echocardiographic and hemodynamic data of patients with or without Δ systolic blood pressure ≥10 mm Hg during dobutamine stress test.

	Δ SBP ≥10 mm Hg (n = 153)	Δ SBP <10 mm Hg (N = 173)	p value
Age	58 ± 11	60 ± 10	0.04
Beta blockers	47 (31%)	30 (17%)	0.0046
Calcium blockers	44 (29%)	72 (42%)	0.015
ACE inhibitors	57 (37%)	91 (53%)	0.0055
Peak dobutamine dose	38.5 ± 4.4	37.5 ± 5.9	0.07
Resting HR	69 ± 13	74 ± 15	0.0008
Peak HR	121 ± 26	123 ± 24	0.35
Resting SBP	123 ± 19	131 ± 23	0.0002
Peak SBP	149 ± 23	120 ± 24	<0.00001
Rest WMSI	1.55 ± 0.38	1.78 ± 0.46	<0.00001
Peak WMSI	1.62 ± 0.46	1.93 ± 0.50	<0.00001
Ischemia	75 (49%)	104 (60%)	0.045
Coronary stenosis	70/78 (90%)	87/106 (82%)	0.14
Multivessel disease	42/78 (54%)	63/106 (59%)	0.45

ACE = angiotensin-converting enzyme, HR = heart rate (beats/minute), SBP = systolic blood pressure (mm Hg), WMSI = wall motion score index.

Multivariate analysis of baseline characteristics identified baseline wall motion score index ($p<0.01$), systolic blood pressure ($p<0.001$), age ($p<0.05$) and medications with angiotensin converting enzyme inhibitors ($p<0.05$) as independent predictors of a systolic blood pressure drop ≥10 m Hg. Multivariate analysis of stress test variables identified peak wall motion score index ($p<0.005$) as an independent predictor. The same findings were obtained by considering peak systolic blood pressure at peak dobutamine ± atropine stress.

Table 5. Clinical, angiographic, echocardiographic and hemodynamic data of patients with or without Δ systolic blood pressure ≤-10 mm Hg during dobutamine stress test.

	Δ SBP ≤-10 mm Hg (n = 89)	ΔSBP >-10 mm Hg (N = 237)	p value
Age	62 ± 9	58 ± 11	0.0016
Beta blockers	18 (20%)	81 (34%)	0.014
Calcium blockers	33 (37%)	83 (35%)	0.72
ACE inhibitors	56 (63%)	92 (39%)	0.0001
Peak dobutamine dose	37.1 ± 6.4	38.3 ± 4.8	0.07
Resting HR	77 ± 15	70 ± 13	0.0001
Peak heart rate	126 ± 23	121 ± 0.25	0.15
Resting SBP	137 ± 23	123 ± 20	0.0001
Peak SBP	115 ± 23	140 ± 26	0.00001
Rest WMSI	1.82 ± 0.44	1.61 ± 0.42	0.005
Peak WMSI	1.97 ± 0.49	1.72 ± 0.50	0.001
Ischemia	54 (61%)	125 (53%)	0.2
Coronary stenosis	45/55 (82%)	112/129 (87%)	0.38
Multivessel disease	34/55 (62%)	61/129 (47%)	0.07

ACE = angiotensin-converting enzyme, HR = heart rate (beats/minute), SBP = systolic blood pressure (mm Hg), WMSI = wall motion score index.

Patients with myocardial ischemia

There was no significant difference between patients with or without ischemia with regard to rest or peak systolic blood pressure before or after atropine. The adminstration of atropine did not change systolic blood pressure significantly in patients with or without ischemia. Patients with ischemia had a higher wall motion score index at rest and at peak stress. The percentage of patients taking calcium blockers or nitrates was higher in patients with than without ischemia (table 6).

Coronary angiography

Coronary angiography was performed in 186 patients (57%). Angiographic data are given in table 3. The prevalence of coronary stenosis was not different in the 3 groups whereas the prevalence of multivessel disease was significantly higher in group 3 and 2 compared to group 1 ($p < 0.0001$, < 0.005 respectively).

Table 6. Clinical, echocardiographic and hemodynamic data of patients with or without myocardial ischemia during dobutamine stress echocardiography.

	Ischemia (N = 182)	no ischemia (N = 144)	p value
Age	59 ± 9	58 ± 11	0.6
Beta blockers	53 (29%)	47 (33%)	0.5
Calcium blockers	79 (43%)	37 (26%)	0.001
Nitrates	108 (59%)	57 (40%)	0.0004
ACE inhibitors	83 (46%)	65 (45%)	0.9
Peak dobutamine dose	38.0 ± 5.3	38.0 ± 5.4	0.99
Resting HR	70 ± 13	74 ± 14	0.02
Peak dobutamine HR	123 ± 24	121 ± 26	0.6
Peak dobutamine ± atropine HR	136 ± 16	135 ± 18	0.7
Resting SBP	127 ± 23	127 ± 22	0.9
Peak dobutamine SBP	131 ± 27	136 ± 27	<0.14
Peak dobutamine ± atropine SBP	132 ± 28	136 ± 29	0.12
Δ systolic blood pressure	04 ± 27	09 ± 25	0.1
Rest WMSI	1.73±0.42	1.61 ± 0.44	0.005
Peak WMSI	1.97± 0.46	1.56 ± 0.47	0.00001

ACE = angiotensin-converting enzyme, HR = heart rate (beats/minute), SBP = systolic blood pressure (mm Hg), WMSI = wall motion score index.

DISCUSSION

Ventricular function is an important determinant of prognosis after acute myocardial infarction (15). Therefore identification of stress test variables

associated with more severe left ventricular dysfunction is a clinically relevant issue. It has been demonstrated that abnormal left ventricular function at rest is an important predictor of exertional hypotension (3). However, a similar significance of dobutamine-induced hypotension has not been proven.

Mechanism of dobutamine-induced hypotension

Systemic vascular resistance was shown to decrease at high dose dobutamine infusion (5). Despite this, all previous clinical studies have demonstrated a significant increase of systolic blood pressure during dobutamine stress test in patients with or without coronary artery disease (10-14,16,17). This would suggest that in most of subjects, an increase in cardiac output corrects for the reduction of systemic vascular resistance. Unlike exercise stress testing, a decrease of systolic blood pressure during dobutamine stress testing was disregarded as a marker of the presence or a measure of the extent of coronary artery disease or its related functional abnormalities. Marcovitz et al.(8) reported that the prevalence and severity of coronary artery disease as well as prognosis were not different in patients with or without hypotension during dobutamine stress testing. Hypotension was associated with higher prevalence of female gender, more advanced age and lower prevalence of beta blockers adminstration. Lieberman et al. (7) reported that in 105 patients with known coronary artery disease evaluated 6 months after coronary angioplasty, dobutamine-induced hypotension was not associated with the presence or severity of coronary artery disease or with echocardiographic wall motion abnormalities. Predictors of dobutamine-induced hypotension were high baseline systolic blood pressure, advanced age and high left ventricular ejection fraction. Pellika et al.(9) reported that dynamic left ventricular obstruction may develop frequently in patients undergoing dobutamine stress echocardiography. They concluded that obstruction rather than ischemia may explain a decrease in blood pressure during dobutamine stress echocardiography. Tanimoto et al.(5) studied the mechanism of hypotension in 59 patients with significant coronary artery stenosis. Contributing mechanism to hypotension were inadequate increase of cardiac output due to impaired systolic reserve, induced myocardial ischemia with abbreviated left ventricular filling period and a decrease of cardiac output due to cavity obliteration and reflex bradycardia. A combination of more than one mechanism was encountered in some patients.

The present study

In this study, we assessed the influence of functional abnormalities on systolic blood pressure response to dobutamine in a defined patients group with a wide range of severity of left ventricular dysfunction after myocardial infarction. Our results show that, a drop or failure of systolic blood pressure to increase at peak dobutamine stress was associated with more severe wall motion abnormalities both at rest and at peak stress. Mean systolic blood pressure

increased in patients with mild compared to moderate wall motion abnormalities, whereas systolic blood pressure dropped in patients with severe wall motion abnormalities. Left ventricular function at rest and at peak stress was the most powerful predictor of systolic blood pressure response at high dose dobutamine. These findings show that systolic blood pressure response to dobutamine is strongly related to the severity of wall motion abnormalities in patients with myocardial infarction.

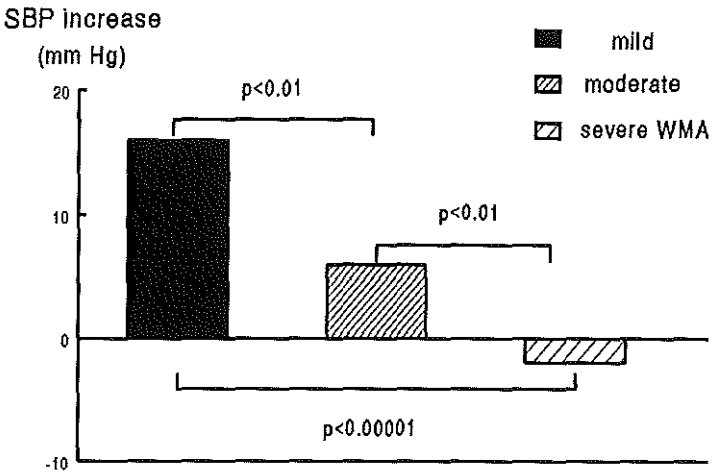

Figure 1. Δ systolic blood pressure (SBP) from rest to high dose dobutamine in patients with mild, moderate and severe resting wall motion abnormalities (WMA).

Comparison with previous studies

The apparent contradiction between our results and the previously mentioned studies may be explained by the presence of 2 major mechanisms contributing to blood pressure response. The first mechanism is related to the increase of myocardial contractility during dobutamine infusion which may cause marked reduction of end-systolic dimensions and stroke volume, cavity obliteration and intraventricular obstruction (5,8,9). The increase of myocardial contractility may be responsible for a brisk increase of cardiac output with reflex vagal induced hypotension. This mechanism is supported by the findings of Tanimoto et al. who described the association between hypotension with greater reduction of left ventricular size (5) and the findings of Lieberman et al. (7) of a higher baseline ejection fraction in patients with hypotension. Beta

blocker adminstration may guard against hypotension by decreasing cavitary obstruction or the peripheral $beta_2$ mediated vasodilatation (5,8). The second mechanism is related to myocardial dysfunction and inability of the dyssynergic myocardium to respond adequately to inotropic stimulation. The reduction of both systemic vascular resistance and ventricular filling with tachycardia at high dose dobutamine will not be compensated with a concomitant increase of contractility which may result in a fall of stroke volume and subsequent hypotension or failure of systolic blood pressure increase. Furthermore, the stroke volume during tachycardia in patients with left ventricular dysfunction may be critically vulnerable to reduced left ventricular filling according to Starling law. This mechanism is supported by the findings of Tanimoto et al. (5) who described an impaired systolic reserve in 42% of patients who developed hypotension in their study. Cohen et al. (18) found that systolic blood pressure response in patients undergoing dobutamine stress test was blunted only in patients with 3-vessel disease. They explained this finding by the lower value of resting ejection fraction in these patients compared to patients with 1 or 2-vessel disease.

The first mechanism is more likely to occur in patients with normal ventricles at rest, whereas it is expected to be less prominent in patients with baseline left ventricular dysfunction in whom cardiac output can not increase equally and end-systolic dimensions can not be reduced critically as in subjects with normal ventricles. Therefore, the second mechanism is more likely to determine systolic blood pressure response in patients with left ventricular dysfunction. When analysis is performed in unselected population with or without baseline wall motion abnormalities (4-9), both mechanisms will tend to keep an equal prevalence of hypotension with or without wall motion abnormalities as shown in previous studies. In contrast, analysis of a particular group with left ventricular dysfunction as shown in our study demonstrated the role of the severity of wall motion abnormalities in the determination of systolic blood pressure response.

The role of myocardial ischemia

Although the prevalence of ischemia was lower in patients with than without Δ systolic blood pressure ≥ 10 mm Hg, ischemia was not an independent variable associated with systolic blood pressure increase in contrast to resting wall motion score index which was an independent predictor of blood pressure increase. While ischemia was defined as transient functional abnormalities, its relation with systolic blood pressure response could not be proven in our study. This can be explained by the fact that at peak stress, the amount of inducible dysfunction was 15% of the total amount of abnormalities (Δ wall motion score index = 0.12 of 0.79 presenting the abnormal score index at peak stress). Additionally, these inducible abnormalities may be counteracted by the increase of contractility in normal segments. Because ischemia was more

prevalent in patients with more severe baseline dysfunction, the contribution of inducible abnormalities may be overshadowed by the highly significant contribution of baseline abnormalities. The trend to a lower Δ systolic blood pressure in patients with than without ischemia can be explained by the relatively higher resting wall motion score index in patients with ischemia.

The extent of coronary artery disease

The extent of coronary artery disease was not different in patients with than without impaired systolic blood pressure response. This can be explained by the possibility that stenotic arteries supplying normal myocardium at rest do not contribute significantly to blood pressure response due to minimal contribution of myocardial ischemia to the latter. The magnitude of left ventricular dysfunction at rest is not always related to the extent of coronary artery disease. For instance, a patient with stenosis of the LAD only may have extensive wall motion abnormalities in the anterior wall, septum and apex; whereas a patient with 2 vessel disease involving the RCA and LCX may have hypokinesis confined to the posterior wall. Additionally, some patient may have persistent severe wall motion abnormalities despite adequate revascularization. Hakki et al. (1) reported that in patients with coronary artery disease, both the extent of coronary artery disease and functional abnormalities were higher in patients with than without exercise-induced hypotension. However, the extent of functional abnormalities was the only independent predictor of hypotension (1).

The effect of medications

The intake of calcium antagonists was an independent predictor of failure of systolic blood pressure increase. This may be explained by the potent arterial vasodilator and the negative inotropic effects of these medications inhibiting adequate increase of contractility. It is to be noted that both the negative inotropic effect of calcium antagonists and the positive inotropic effect of sympathomimetics are achieved by alteration of calcium kinetics (19). Similarly, the intake of angiotensin-converting enzyme inhibitors was an independent predictor of systolic blood pressure drop as reported previously (5). This may be explained by the reduction of both systemic vascular resistance and left ventricular filling due to venous dilatation. Since these medications tend to decrease circulating catecholamine concentration at rest and particularly with exercise (20) and restore towards normal downregulated beta adrenergic receptors in patients with heart failure (21), alteration of the sensitivity of adrenoreceptors to sympathomimetics may also explain the association with dobutamine-induced hypotension.

In contrast with previous reports (5,8), medication with beta blockers was not a predictor of systolic blood pressure increase or decrease in our study. This may show that the protective effect of beta blockers against hypotension is

mainly due to the prevention of marked reduction of ventricular volumes by decreasing the positive inotropic response to dobutamine. Since marked reduction of ventricular volumes is less likely to occur in patients with left ventricular dysfunction, medication with beta blockers was not associated with the favourable systolic blood pressure response described in previous studies which included population with normal resting left ventricular function.

The effect of baseline systolic blood pressure

Hypertension was described as a predisposing factor to dobutamine-induced hypotension (8). We found a strong independent association between a higher systolic blood pressure at rest and drop or failure of systolic blood pressure increase at peak dobutamine stress. Lieberman et al. (7) reported that a high baseline systolic blood pressure was independently predictive of dobutamine-induced hypotension in patients with or without left ventricular dysfunction. However, the higher systolic blood pressure at rest does not imply a clinical definition of hypertension or the presence of left ventricular hypertrophy. The independent association between higher systolic blood pressure at rest and impaired systolic blood pressure response to dobutamine is difficult to explain. It may be postulated that the higher systolic blood pressure at rest is associated with a high sensitivity of the systemic arterioles to sympathetic stimulation (22). Since the net result of high dose dobutamine infusion is a reduction of systemic vascular resistance, this effect may be intensified in patients with higher sensitivity to catecholamine.

Limitations of the study

The interaction between various factors like baseline systolic blood pressure, wall motion abnormalities, medications and myocardial ischemia in patients with moderate and severe left ventricular dysfunction may impose a difficulty in the assessment of the relation between myocardial ischemia and systolic blood pressure response in this population. Further studies may be needed to asses the results of revascularization on blood pressure response of these patients. Global left ventricular function was assessed by semiquantitative evaluation of wall motion and thickening which is not independent on the observer. However, even ejection fraction has its own limitations as a measure of contractility being dependent on loading conditions and heart rate. Wall motion score index has been used as analogous to the ejection fraction with a similar prognostic value in patients with myocardial infarction (23).

Summary and conclusion

In patients with left ventricular dysfunction after myocardial infarction undergoing dobutamine stress echocardiography for evaluation of myocardial ischemia, resting left ventricular function is a powerful predictor of systolic blood pressure response to high dose dobutamine. Further studies are required

to assess the prognostic value of systolic blood pressure response to dobutamine in this population.

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CHAPTER 12

FUNCTIONAL ASSESSMENT OF ALCAPA SYNDROMEBY DOBUTAMINE STRESS 201 THALLIUM SPECT AND ECHOCARDIOGRAPHY[1]

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ABSTRACT

Exercise 201 Tl SPECT has been used as a useful method for the assessment of patients with anomalous left coronary artery communicating to the pulmonary artery (ALCAPA syndrome). In this report, we describe an adult patient with this anomaly who was evaluated by dobutamine stress test in conjunction with simultaneous 201 Tl SPECT and echocardiography before and after surgery. A large perfusion defect in the anterior wall, septum and apex was detected on the preoperative stress scan with partial reversibility on reinjection scan. Worsening of wall motion abnormalities in the septum and anterior wall was detected by stress echocardiography. In the studies performed 3 months and 1 year after reimplantation of the left coronary artery in the aorta, a smaller fixed perfusion defect in the anterior wall and apex was detected without reversibility. No stress-induced wall motion abnormalities were detected. Despite the improvement of perfusion, there was no improvement of regional or global left ventricular function at rest. We report that both dobutamine 201 Tl SPECT and echocardiography were useful for the detection of reversible ischemia and for the assessment of the surgical outcome of an adult patient with ALCAPA syndrome.

Key Words: Dobutamine stress echocardiography, Thallium SPECT, ALCAPA syndrome

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INTRODUCTION

ALCAPA syndrome is a rare congenital anomaly characterised by an anomalous left coronary artery communicating to the pulmonary artery (1). Most of untreated patients with this anomaly die during childhood from myocardial infarction and heart failure. Rarely, some patients survive to adulthood due to extensive collateralization from the right coronary artery to the left coronary artery (1,2). The detection of myocardial ischemia in patients with ALCAPA is important to identify viable left ventricular (LV) myocardium at jeopardy of irreversible damage. Therefore, exercise thallium scintigraphy has been used to assess myocardial perfusion and to evaluate the results of surgery in these patients (3-7). Dobutamine stress test (DST) in conjunction with myocardial perfusion or echocardiographic imaging is increasingly used for evaluation of coronary artery disease (8-11). In patients with LV dysfunction, low-dose dobutamine echocardiography and Tl scintigraphy are useful for the detection of myocardial viability (12-13). In this report we describe an adult patient with ALCAPA in whom DST with simultaneous echocardiography and 201 Tl SPECT was useful for the detection of myocardial ischemia and evaluation of the results of surgery.

Methods: Dobutamine was infused intravenously starting at a dose of 5 μg/kg/min increasing every 3 min to 10, 20, 30 and 40 μg/kg/min. Echocardiography was performed at rest and throughout the test. 1 min before termination of infusion, 80 MBq of 201 Tl were injected intravenously. Images were acquired within 5 minutes after the end of the test and 4 hours following the test, after reinjection of 40 MBq Tl. Image acquisition and interpretation was performed according to a previously described protocol (8). The diagnosis of ischemia relied upon the occurrence of reversible perfusion defects and new or worsened wall motion abnormalities. The diagnosis of viability in dyssynergic segments relied upon the occurrence of a contractile response during low-dose dobutamine (5-10 μg/kg/min) and the presence of reversibility or a fixed defect containing $\geq 50\%$ of the maximal Tl uptake.

Study patient: A 35 year old woman presented with palpitations and atypical chest pain. Physical examination revealed a grade III/VI diastolic murmur in the second left intercostal space. Baseline ECG showed Q waves in I-aVL-V6 and poor R wave progression in precordial leads. Echocardiography revealed a dilated LV, akinetic apex and hypokinetic anterior septum and anterolateral wall. The left coronary artery was seen coming out from the posterior wall of the pulmonary artery with a diastolic flow into the pulmonary artery detected by continuous and colour flow Doppler. Coronary angiography revealed a tortuous widely dilated right coronary artery communicating through extensive collaterals with the left coronary artery which was filling the pulmonary artery (figure IA). Gated blood pool scintigraphy (GBP) showed hypokinesis of the

anterior wall and anterior septum and LV ejection fraction (EF) of 51%. DST with simultaneous Tl SPECT and echocardiography was performed for the detection of myocardial ischemia and viability. Typical angina occurred during the test. A large perfusion defect in the anterior wall, apex and anterior septum was detected on stress imaging with partial reversibility on reinjection (figure II). The apex was considered viable on basis of partial Tl reversibility. Tl counts in the apex was 9116 at stress and 11051 units at reinjection comprising 70% and 85% of the maximal normal counts respectively. Baseline echocardiogram showed akinesis of the apex and hypokinesis of the anterior wall and anterior septum. During low-dose dobutamine, no contractile response was observed in the apex. At peak stress, worsening of wall motion abnormalities was detected in the anterior wall and septum.

The patient underwent reimplantation of the left coronary artery in the aorta. DST was repeated 3 months and 1 year after surgery which revealed a fixed perfusion defect in the anterior wall and the apex without reversibility However, the defect size was smaller compared to preoperative scan by quantitative analysis. No stress-induced wall motion abnormalities were detected. There was no improvement of regional LV wall motion on the echocardiogram or of global function by GBP (EF = 43% after 1 year).

Table I. Left ventricular ejection fraction, quantitative perfusion defect size*and maximal stress heart rate (HR) before and after surgery.

	Ejection fraction %	stress defect	reinjection defect	maximal stress HR
Preoperative	51	2879	1314	130
Postoperative (3 months)	35	661	793	134
Postoperative (1 year)	43	539	627	143

* Defect size is a uniteless measure of the area between the lower limit of normal values (± 2 standard deviations) and the actual circumferential profile in the 6 short axis slices.

The values of EF, quantitative Tl defects and maximal dobutamine stress heart rate before and after surgery are summarized in table I. Follow up coronary angiography performed 14 months after operation showed antegrade filling from the aorta of a dilated left coronary artery with slow flow and abrupt reduction of the calliper distally (figure IB). Collateral circulation resolved completely. Symptoms of palpitations and atypical chest pain did not improve. The course of the patient was uneventful during a follow up period of 2 years with a persistent regional LV dysfunction on serial echocardiograms. Holter monitoring revealed no high grade arrhythmias.

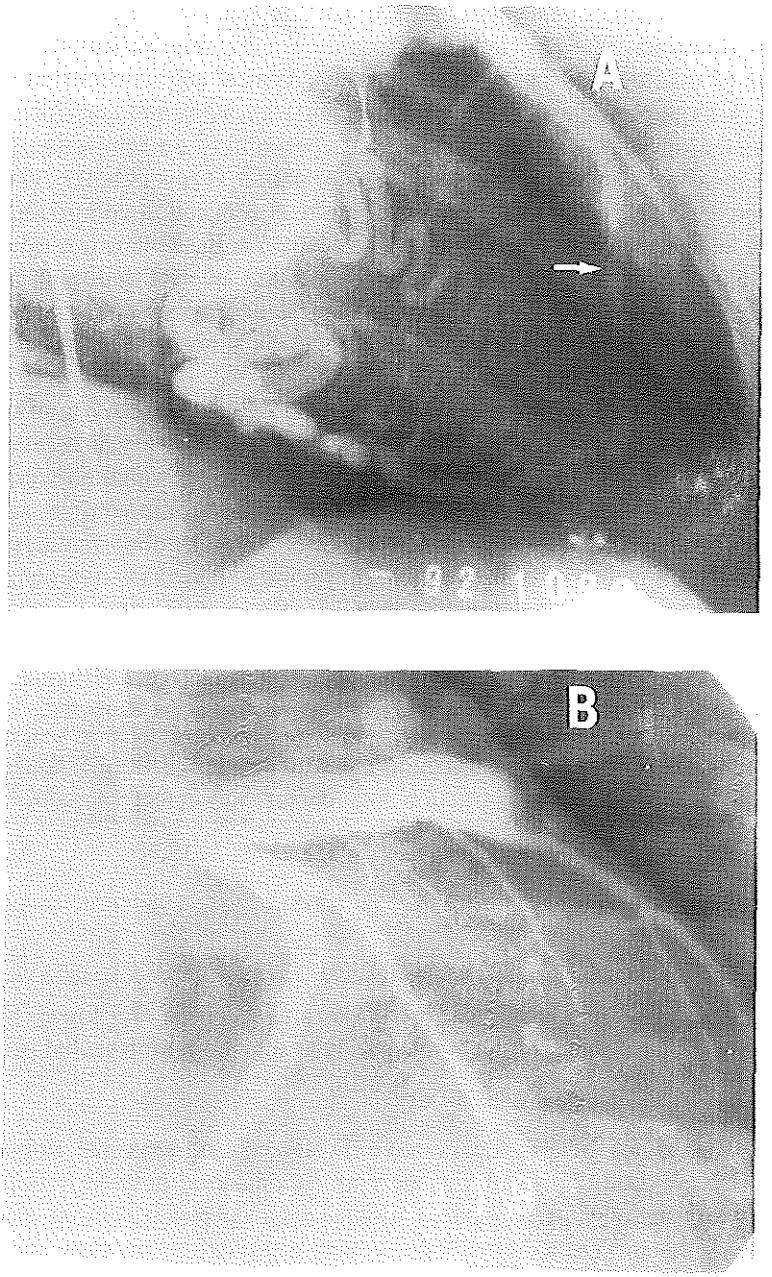

Figure I: A) Preoperative right coronary injection showing a dilated, tortuous right coronary artery filling the left coronary artery (arrow) through extensive collaterals with retrograde filling of the pulmonary artery. B) Postoperative selective left coronary artery injection showing proximal dilatation of the left coronary artery with abrupt calliper reduction distally.

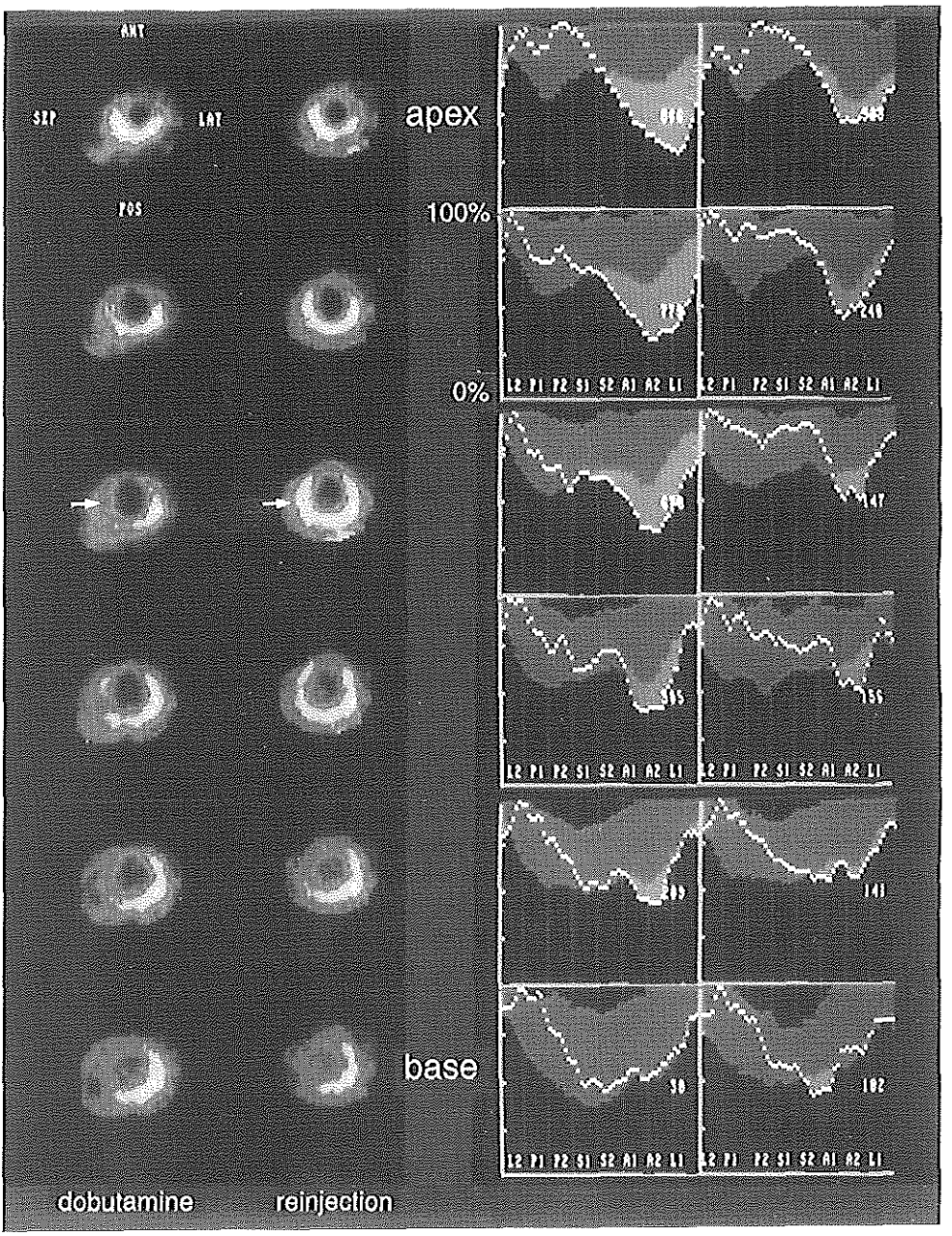

Figure II: Preoperative dobutamine and reinjection 201 thallium SPECT images of the 6 short axis slices, provided with the corresponding circumferential profile. The images show a completely reversible defect in the septum (arrows).

DISCUSSION

The detection of myocardial ischemia in patients with ALCAPA is important to identify the myocardium at risk of irreversible dysfunction. The combined effect of an increase of myocardial oxygen demand and flow malperfusion induced by dobutamine (15,16) may serve as an appropriate mechanism of eliciting ischemia in patients with ALCAPA, in whom the mechanism of ischemia is a combination of coronary steal into the pulmonary artery and inadequate collateral flow in face of an increased demand (6,17). Since these patients may develop an acquired native coronary artery or graft disease, the ability to establish a two coronary artery system provides an advantage over ligation of the left coronary artery (18).

In our study patient, myocardial ischemia could be elicited before surgery during DST as manifested by angina, reversible Tl defect and stress-induced wall motion abnormalities. Echocardiography and Tl SPECT concordantly localized ischemia. The absence of these ischemic markers postoperatively identified a successful surgical correction, which was confirmed by coronary angiography.

A reversible Tl defect without a contractile response to low-dose dobutamine was detected in the apex. This viability pattern on Tl SPECT was predictive of a significant improvement of perfusion postoperatively. However, no improvement of LV function occurred in a follow up period of 2 years. The discrepancy of viability patterns between echocardiography and Tl SPECT may be explained by the high sensitivity of Tl for the detection of small islands of ischemic myocardium which are not capable of restoration of contractility after revascularization of a segment with extensive scarring as we have previously reported (13). The characteristics of chronic ischemia in ALCAPA patients are apparently different from those with atherosclerotic coronary heart disease in terms of the mechanism and duration of ischemia which starts since birth due to a drop of pulmonary artery pressure below coronary perfusion pressure (6). A recent study described a delayed improvement of function up to 3 years after surgery in children with ALCAPA (19). The lack of improvement of LV function after improvement of perfusion has been attributed to a delayed subcellular adaptive response, impairment of energy production and transfer and altered sensitivity of myofilaments to calcium (19-21). The unique anatomy of the left coronary artery with dilatation and slow flow proximally and a small calliper distally, shown in the postoperative angiogram, may have an impaction on functional recovery. The change of the pressure and direction of flow postoperatively may result in a change of vessel morphology on the long term, and consequently improvement of LV function.

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CHAPTER 13

MYOCARDIAL ISCHEMIA ASSESSED BY DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN A PATIENT WITH BI-CORONARY TO PULMONARY ARTERY FISTULAE[1]

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SUMMARY

Congenital coronary artery fistula is a rare anomaly characterised by a communication between one or more coronary arteries with a cardiac chamber, coronary vein or less frequently with the pulmonary artery (1-3). The reported complications of this anomaly are congestive heart failure, infective endocarditis and myocardial infarction (4-5). Although angina is not an infrequent complaint in adult population with coronary to pulmonary artery fistulae (4), objective evidence of myocardial ischemia in absence of concomitant atherosclerotic coronary artery disease has not been described. In this report, we describe an adult patient with chest pain and bi-coronary to pulmonary artery fistulae in whom myocardial ischemia was documented by high dose dobutamine stress echocardiography.

STUDY PATIENT

A 48 years old woman presented with exertional chest pain progressing to occur at rest. She was admitted to the intensive care unit with the diagnosis of unstable angina. Physical examination was unremarkable apart from a systolic murmur grade II/VI in the 2nd left intercostal space. The electrocardiogram during chest pain revealed T wave inversion in precordial leads reverting to the upright position after the episodes of pain. Cardiac enzymes were normal. Coronary angiography revealed no significant narrowing of coronary arteries. Numerous small fistulous communications between the proximal LAD and pulmonary artery were detected. A single small fistula was also detected from the LCX to the pulmonary artery. Right coronary angiography revealed a large fistula originating from the ostium of the RCA and communicating with the pulmonary artery (figure 1). To assess the functional significance of anginal

[1] *Submitted for publication.*

chest pain and coronary abnormalities, the patient underwent bicycle exercise 99-m technetium MIBI SPECT study after stabilization of symptoms with medical treatment. Heart rate increased from 65 to 120 beats/min and the test was terminated because of fatigue without precordial symptoms. Perfusion scintigraphy revealed no significant abnormality. Because of the submaximal heart rate attained with exercise, the patient underwent a high dose dobutamine (up to 40 μg/kg/min) - atropine (0.5 mg) stress echocardiography. Heart rate increased from 66 to 142 beats/min. No significant arrhythmia occurred during the test. The resting echocardiogram was normal. During stress, there was a gradual reduction of motion and thickening of the inferior wall and the basal part of the posterior septum progressing to dyskinesis (figure 2). The test was considered diagnostic of myocardial ischemia in the RCA territory. The diagnosis was made by 2 independent observers unaware of the patient's clinical, angiographic or scintigraphic data who agreed on the presence and localization of abnormalities. The patient continued on medical treatment consisting of beta blockers which resulted in a partial symptomatic relief.

DISCUSSION

The correlation between symptoms of angina and specific markers of myocardial ischemia is important to clarify the functional significance of angina in adult patients with coronary artery fistulae. So far, myocardial ischemia has not been documented in patients with coronary to pulmonary artery fistulae, in absence of concomitant atherosclerotic coronary artery disease. Few reports have described the presence of an objective evidence of myocardial ischemia in the more common type of fistulae communicating to cardiac chambers or coronary veins. Brooks et al. (6) described 2 patients with congenital coronary artery fistulae communication to the left ventricle without concomitant atherosclerotic narrowing who had significant electrocardiographic changes during ischemic episodes. Glynn et al. (7) reported a patient with a fistula communicating between the LAD and coronary vein who had a reversible perfusion defect on exercise thallium scintigraphy. In our study patient, myocardial ischemia was documented by the presence of transient wall motion abnormalities in the RCA territory during dobutamine stress echocardiography. The occurrence of myocardial ischemia confined to the RCA territory can be explained by the smaller size of fistulae of the LAD and the LCX. The lower peak exercise compared to peak dobutamine heart rate may explain the conclusive findings of myocardial ischemia on dobutamine stress echocardiography as opposed to exercise myocardial perfusion scintigraphy. Nevertheless, Said et al. reported that exercise MIBI scintigraphy failed to reveal myocardial ischemia in a 49 year old woman with atypical chest pain and multiple coronary-pulmonary fistulae (8). This may point to the importance of symptomatic status on the occurrence of inducible ischemia in these patients.

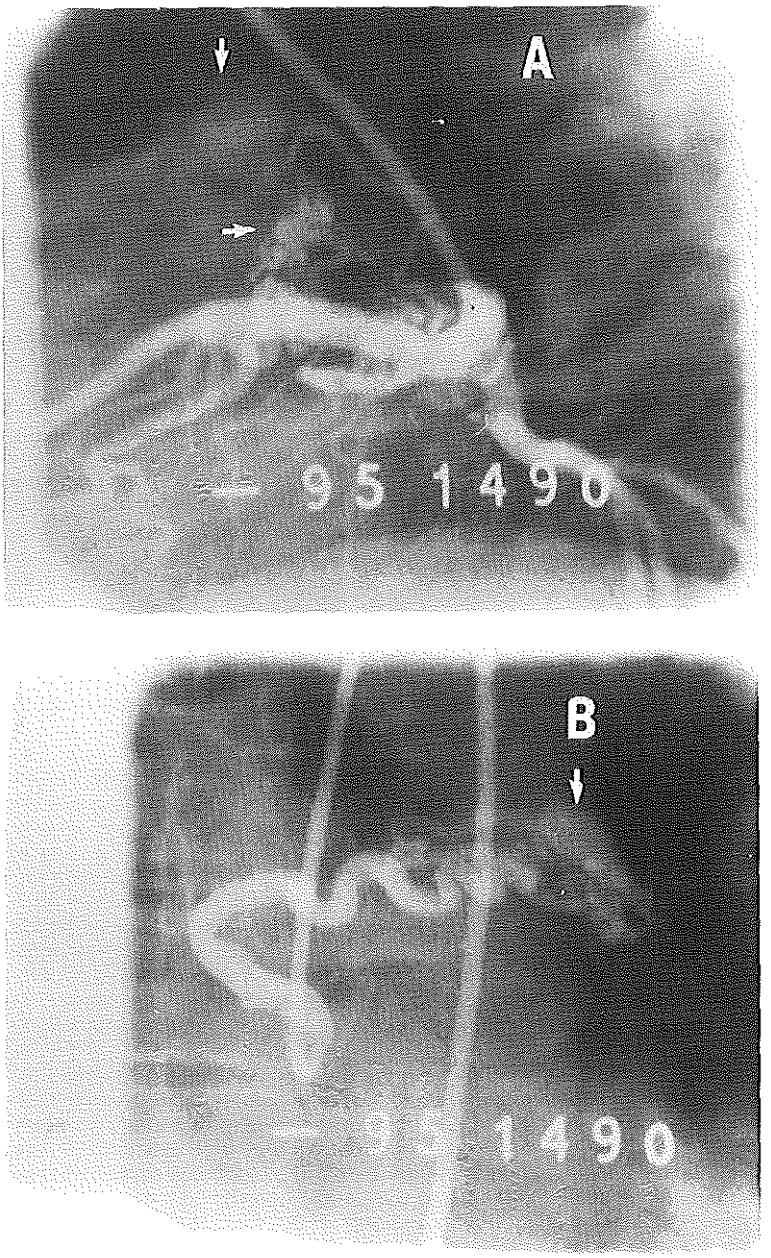

Figure 1 A) Left coronary artery angiogram showing multiple small fistulae originating from the proximal LAD and collecting in a convoluted vascular aggregation (horizontal arrow) which drains into the pulmonary artery (vertical arrow). B) Selective injection of the fistula from the right coronary artery ostium showing opacification of the pulmonary artery (arrow).

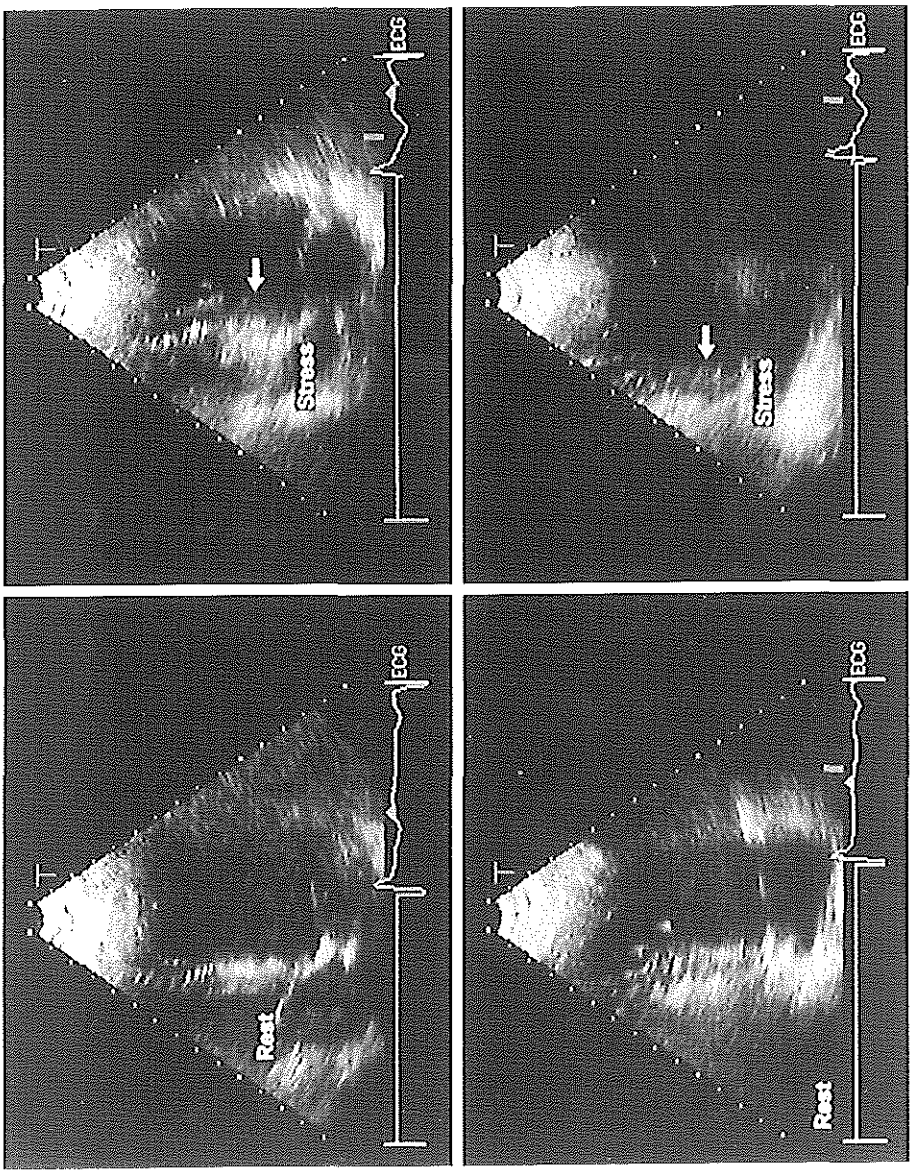

Figure 2. 2-dimensional echocardiographic images at rest and at high dose dobutamine stress from the apical 4 chamber view (top) and apical 2 chamber view (bottom), showing dyskinesis of the basal posterior septum and basal inferior wall at high dose dobutamine stress indicated by arrows.

Myocardial ischemia in patients with coronary fistulae is thought to be due coronary steal (6,7). Although myocardial perfusion scintigraphy is a relatively sensitive method for detecting flow malperfusion as a result of coronary steal, the presence of flow malperfusion may not always imply the occurrence of true ischemia. In contrast, transient mechanical dysfunction mostly implies inadequacy of myocardial supply relative to oxygen demand during stress and represents a highly specific marker of myocardial ischemia (9). For that purpose, in patients with limited exercise capacity, dobutamine stress testing may be preferred to vasodilator stress agents as it produces hemodynamic changes similar to exercise. Therefore with dobutamine, myocardial ischemia is more likely to be provoked under circumstances simulating those occurring during life activity in symptomatic patients.

CONCLUSION

Myocardial ischemia could be documented in an adult patient with bi-coronary to pulmonary artery fistulae who presented with angina. The occurrence of transient wall motion abnormalities during high dose dobutamine stress echocardiography in this patient shows that flow malperfusion may result in true ischemia during stress. Tomographic assessment of myocardial ischemia with dobutamine stress echocardiography may be helpful in the evaluation of anginal symptoms in patients with coronary artery fistulae.

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Part II ASSESSMENT OF MYOCARDIAL VIABILITY

CHAPTER 14

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Prediction of Improvement of Ventricular Function After First Acute Myocardial Infarction Using Low-Dose Dobutamine Stress Echocardiography

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This study was performed to assess the prevalence of spontaneous improvement of regional left ventricular function in patients after acute myocardial infarction, and to evaluate the role of low-dose dobutamine stress echocardiography for its prediction. In 57 patients with a first acute myocardial infarction (thrombolysis, n = 27; Q-wave, n = 49), regional wall motion was evaluated with 2-dimensional echocardiography at rest, during a low-dose dobutamine stress test performed within 1 week after hospital admission, and at 3-month follow-up. Myocardial viability was considered if there was an improvement of ≥1 grade in dyssynergic segments from rest to low-dose dobutamine infusion; recovery of regional function was defined as an improvement of ≥1 grade between rest and follow-up echocardiograms. Wall motion score index decreased from rest to low-dose dobutamine echocardiography (1.46 ± 0.29 to 1.39 ± 0.30, p <0.0001), and this change persisted at follow-up study (1.37 ± 0.30). No differences were found between patients who did and did not undergo thrombolysis, or between those who had Q-wave and non-Q-wave infarction. At baseline echocardiography, 189 of 627 segments were dyssynergic (85 hypokinetic, 104 akinetic). Viability at low-dose dobutamine stress echocardiography was more frequent in hypokinetic than in akinetic segments (30 of 85 vs 12 of 104, odds ratio 4.18, 95% confidence interval [CI] 1.87 to 9.48). Spontaneous recovery was more frequent in hypokinetic than in akinetic segments (30 of 85 vs 20 of 104, odds ratio 2.29, CI 1.13 to 4.68). Sensitivity, specificity, and positive and negative predictive values of low-dose dobutamine stress echocardiography for predicting late recovery of regional function were 66%, 94%, 79%, and 88%, respectively. Sensitivity was lower in akinetic segments than in hypokinetic segments (35%, CI 0.14 to 0.56, vs 87%, CI 0.75 to 0.99). An improvement during low-dose dobutamine stress echocardiography was a strong predictor of reversible postischemic dysfunction (odds ratio 17.1, CI 3.5 to 97.1). In conclusion, in patients after a first, relatively uncomplicated acute myocardial infarction, late spontaneous recovery occurs in 26% of the dyssynergic segments. Low-dose dobutamine stress echocardiography provides very specific information for predicting lack of improvement and has a high sensitivity for predicting improvement in hypokinetic segments, but is not useful in identifying akinetic segments that will spontaneously improve.

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Myocardial stunning is defined as transient prolonged postischemic dysfunction that may occur after the restoration of a normal coronary flow.[1] It has been observed in several clinical conditions, including in patients after acute myocardial infarction treated with thrombolysis.[2–5] The natural history in patients with acute myocardial infarction not treated with thrombolysis includes potential improvement in left ventricular function at follow-up.[6] If this is true, the evaluation of viable myocardium should be desirable in all patients early after an acute myocardial infarction, and could influence the choice between medical treatment or coronary revascularization in selected patients. With the combined analysis of flow and metabolism, positron emission tomography scanning is the reference noninvasive method for assessing the presence of viable myocardium.[7] Recently, myocardial perfusion scintigraphy with different isotopes and with different protocols has been proposed for the same purpose.[8] The administration of dobutamine in conjunction with echocardiographic wall motion analysis has been proposed as a simpler alternative to the more sophisticated and expensive nuclear techniques.[9–12] Despite interest in these findings, little is known about the spontaneous recovery of segmental left ventricular function and the potential role of low-dose dobutamine stress echocardiography for its prediction. Accordingly, the aims of this study were to assess the incidence of late (3 months) spontaneous improvement of regional left ventricular function in an unselected series of patients after a first acute myocardial infarction, and to evaluate the potential role of low-dose dobutamine stress echocardiography (performed within 1 week after myocardial infarction) for its prediction.

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TABLE I Prediction of Recovery of Dyssynergic Segments Using Dobutamine Stress Echocardiography

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
All dyssynergic segments (n = 189)	66% (0.53–0.79)	94% (0.89–0.97)	79% (0.66–0.92)	88% (0.83–0.93)
Akinetic segments (n = 104)	35% (0.14–0.56)	94% (0.89–0.99)	58% (0.30–0.86)	86% (0.79–0.93)
Hypokinetic segments (n = 85)	87% (0.75–0.99)	93% (0.86–1.0)	87% (0.75–0.99)	93% (0.86–1.0)

Values in parentheses are the 95% confidence interval.

METHODS

Patient group: Fifty-seven consecutive patients (48 men and 9 women, mean age 58 ± 10 years, range 25 to 76) were prospectively enrolled in this study. Criteria for recruitment were: (1) admission at our institutions with a diagnosis of first acute myocardial infarction (prolonged chest pain, ≥1 mm ST-segment deviation in ≥2 leads on the initial electrocardiogram, and typical creatine kinase-MB isoenzyme pattern); and (2) wall motion abnormalities on a resting echocardiogram performed within 7 days of admission. Patients with valvular heart disease (n = 2), prior myocardial infarction (n = 4), previous coronary artery bypass graft or percutaneous transluminal coronary angioplasty (n = 3), postinfarction angina requiring revascularization procedures (n = 3), or infarction complicated by severe hemodynamic instability (n = 2) were excluded. No patient was excluded because of inadequate echocardiogram. Twenty-seven patients were treated with thrombolytic agents within 6 hours from the beginning of symptoms, and 30 had contraindications or late presentation to the hospital. Eight patients had a non–Q-wave myocardial infarction, and 2 of them underwent thrombolytic therapy. The site of myocardial infarction was anterior in 30 patients and inferior and/or lateral in 27.

Predischarge dobutamine stress echocardiography and follow-up study: After giving verbal informed consent, all patients underwent dobutamine stress echocardiography within 7 days after hospital admission. Antianginal drugs, digitalis, and other drugs that might alter myocardial contractility were withdrawn 24 to 48 hours before the test. Dobutamine was infused by a volumetric pump at incremental doses according to a protocol based on 2 stages of 5 and 10 μg/kg/min (5 min/dose) and 3-minute stages of 20, 30, and 40 μg/kg/min, plus the addition of atropine (0.25 to 1 mg) in patients not achieving 85% of their age-predicted maximal heart rate who had no symptoms or signs of ischemia. The first 2 stages were considered a "low-dose stress test" and were evaluated for the presence of viable myocardium. Throughout the dobutamine infusion, an electrocardiogram lead was continuously monitored on the echocardiographic monitor. Twelve-lead electrocardiograms and blood pressures were recorded at rest and at the end of each stage. A 2-dimensional echocardiogram was monitored throughout the test and recorded on videotape at rest and during the last minute of each stage. The test was stopped in case of severe new wall motion abnormalities, typical angina, significant cardiac arrhythmias, or any other limiting side effects. At 3-month follow-up, 2-dimensional echocardiograms were obtained at rest in all patients after adequate pharmacologic washout. Echocardiograms were recorded on videotape for subsequent analysis and comparison with the previous examination. All echocardiograms were reviewed on the videotapes and a consensus was achieved by 2 observers unaware of the clinical data. For the purposes of this study, the left ventricular wall was divided into 11 segments.[13] Both inward wall motion and wall thickening were evaluated, and each segment was graded as 1 = normal or hyperkinetic, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. Baseline images before dobutamine infusion were used as references and compared with the corresponding images during low-dose dobutamine infusion. An improvement of ≥1 grade in the dyssynergic segments during dobutamine infusion was considered as a marker of viable myocardium. Thus, hypokinetic segments returning to normal, and systolic myocardial thickening becoming apparent in a segment that was either akinetic or dyskinetic were considered as a positive test for the presence of viable myocardium. Follow-up echocardiograms were compared with the corresponding rest images before dobutamine infusion for comparative segmental analysis. For each segment, a recovery of function was defined as an improvement of ≥1 grade. For each study, a wall motion score index was calculated, dividing the sum of the scores by the number of the segments. Because hyperdynamic left ventricular segments during low-dose dobutamine stress echocardiography were scored as normal (1), wall motion score index was affected only by abnormally contracting segments.

Statistical analysis: Continuous data are expressed as mean ± SD. Continuous variables were analyzed using analysis of variance for repeated measurements and paired *t* test with the Bonferroni correction. An unpaired *t* test was used when appropriate. Sensitivity, specificity, and positive and negative predictive values rely on the standard definition and are reported with the corresponding 95% confidence interval (CI). The difference in late recovery was expressed as the odds ratio with the corresponding CI. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

RESULTS

The median interval from myocardial infarction to dobutamine test was 4 days (range 3 to 7). Atropine was added to dobutamine in 35 patients. No complications occurred during the dobutamine stress test. Heart rate and systolic blood pressure were 80 ± 19 beats/min and

143 ± 38 mm Hg at rest and 82 ± 20 beats/min and 143 ± 38 mm Hg after low-dose dobutamine infusion. Nineteen patients (33%) had a positive low-dose dobutamine stress echocardiogram, and 16 of these (84%) had recovery of at least 1 segment at follow-up, whereas 29 of the 38 patients (76%) with a negative low-dose dobutamine stress echocardiogram had no improvement (n = 28) or even a worsening (n = 1) at follow-up. There was a significant reduction in wall motion score index between rest and both low-dose dobutamine infusion and follow-up echocardiograms (1.46 ± 0.29 vs 1.39 ± 0.30 vs 1.37 ± 0.30, p <0.0001). Patients did not differ according to the type of treatment (thrombolysis vs no thrombolysis) or the type of infarction (Q-wave vs non–Q-wave).

Analysis of segments: At baseline, 189 of 627 segments were dyssynergic (30%). Eighty-five of them were hypokinetic and 104 akinetic. Low-dose dobutamine stress echocardiography revealed the presence of viable myocardium in 42 of 189 segments (22%). At baseline, 30 of these were hypokinetic and 12 were akinetic (7 became hypokinetic, 5 normal). Thus, viability was detected more frequently in hypokinetic than in akinetic segments (35% vs 12%, odds ratio 4.18, CI 1.87 to 9.48). At follow-up, 50 of 189 segments (26%) recovered: 10 from akinetic to normal, 10 from akinetic to hypokinetic, and 30 from hypokinetic to normal. Recovery occurred in 33 of 42 segments (79%) that improved with low-dose dobutamine stress echocardiography, and in only 17 of 147 (12%) that did not improve. Recovery was more frequent in hypokinetic than in akinetic segments (35% vs 19%, odds ratio 2.29, CI 1.13 to 4.68) (Figure 1). When considering only the "viable" segments at low-dose dobutamine stress echocardiography, there was a trend toward more frequent late recovery in the hypokinetic than in the akinetic segments (87% vs 58%, odds ratio 4.64, CI 0.78 to 29.55). Sensitivities, specificities, and predictive values of low-dose dobutamine stress echocardiography for the prediction of spontaneous recovery at follow-up are reported in Table I, both for the overall group and according to the different degrees of dyssynergy.

Predictors of spontaneous recovery: Improvement in wall motion during low-dose dobutamine stress echocardiography (odds ratio 17.1, CI 3.5 to 97.1) and hypokinesia at rest (odds ratio 2.29, CI 1.13 to 4.68) were the only indicators of reversible postischemic dysfunction after acute myocardial infarction.

DISCUSSION

To our knowledge, this is the first study in which patients with a first, relatively uncomplicated acute myocardial infarction were evaluated by dobutamine stress echocardiography and followed up to observe the spontaneous recovery of function, independent of treatment with thrombolytic agents. Moreover, the potential confounding effects of antianginal therapy were avoided. Thus, we attempted to describe the natural history of dyssynergic segments. The main findings of the present study can be summarized as follows: (1) Approximately one fourth of the dyssynergic segments after acute myocardial infarction show a spontaneous recovery at 3-month follow-up. (2) The incidence of the recovery is higher in hypokinetic than in akinetic segments. (3) Low-dose dobutamine stress echocardiography is very specific for predicting the lack of improvement in segmental left ventricular function (94%). (4) The sensitivity is high (87%) in hypokinetic segments, and lowest (35%) in akinetic segments. Among the affected left ventricular segments in our population, the prevalence of akinesia and hypokinesia was similar (55% vs 45%, respectively). However, improvement during the low-dose dobutamine stress test and late spontaneous recovery occurred more frequently in the hypokinetic segments. This is not surprising, since it seems logical to hypothesize that hypokinetic segments contain a mixture of scar, normal, and viable myocardium, whereas in the aki-

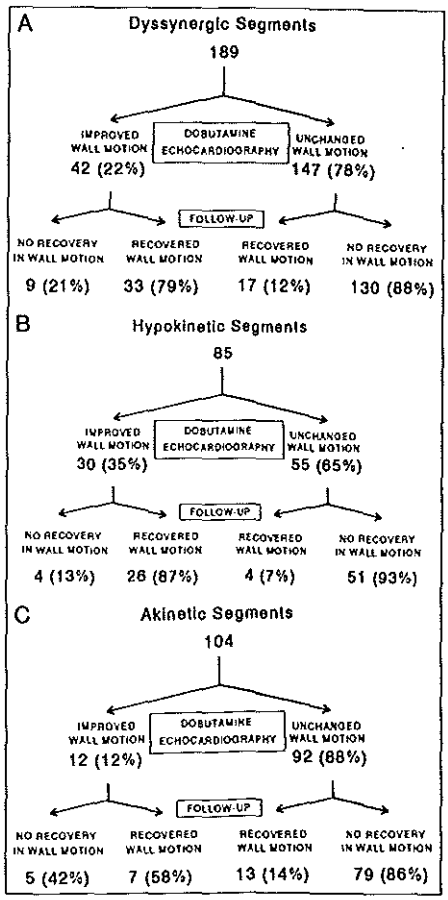

FIGURE 1. Response of the segments to low-dose dobutamine stress echocardiography and the results at follow-up for all the dyssynergic segments (*A*), including only hypokinetic (*B*) or akinetic (*C*) segments.

netic segments the amount of scar is predominant. The time course of recovery of the hypokinetic segments demonstrates that in one third of the cases, the dysfunction was probably based on the presence of myocardial stunning. This phenomenon is less frequent when akinetic segments are considered. Among the segments that were viable during low-dose dobutamine stress echocardiography, there was a clear trend toward less frequent spontaneous recovery in akinetic than in hypokinetic segments (58% vs 87%). It is conceivable that some of these akinetic segments sustain incomplete reperfusion, resulting in a combination of myocardial stunning and hibernation, with less chance of spontaneous recovery. The comparative role of low-dose dobutamine stress echocardiography and positron emission tomography for detecting viable myocardium was first assessed by Pierard et al.[10] Viability was found in 10 patients with acute anterior myocardial infarction, and recovery occurred in 6 of them; patients with no viable myocardium detected by echocardiography had no functional recovery at follow-up. Patients in whom echocardiography revealed viable myocardium but who did not have late functional recovery were characterized by an abnormally high glucose-to-perfusion ratio, suggesting jeopardized myocardium and persistent ischemia. This pattern may explain our finding of absence of recovery in some segments that showed "viability" with low-dose dobutamine stress echocardiography.

The role of low-dose dobutamine stress echocardiography for identifying viable myocardium and predicting improvement after coronary revascularization (either with percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) was assessed by Barilla et al.[12] In this study, 21 patients with anterior non–Q-wave myocardial infarction or post-thrombolytic therapy, or both, were evaluated. Wall motion improved during dobutamine stress echocardiography in all but 1 patient, as indicated by a reduction in wall motion score index. At follow-up, all patients had an improvement in contractility, although the magnitude was greater in the 13 patients who underwent revascularization. Recently, Smart et al[11] investigated the role of different indicators of reversible postischemic dysfunction (wall motion at different doses of dobutamine, non–Q-wave myocardial infarction, peak creatine kinase) in 51 patients after thrombolytic therapy. Low-dose dobutamine stress echocardiography had a sensitivity of 86% and a specificity of 90% for reversible dysfunction, and was sensitive in all infarct locations. Of the other variables not related to stress echocardiography, non–Q-wave myocardial infarction was sensitive only in anterior infarction. However, in that study, 22 patients underwent revascularization before hospital discharge on the basis of angiographic findings alone, and this can affect the real assessment of myocardial stunning. Although these data indicate that low-dose dobutamine–induced wall motion improvement may be sensitive for reversible postischemic dysfunction, all these studies focused on patients after thrombolytic therapy, often limited to anterior myocardial infarction; furthermore, the role of revascularization is difficult to evaluate, and the relative importance of the pattern of dyssynergy at rest has not been considered.

Study limitations: Several limitations of the present study deserve further consideration. Coronary arteriography was not performed in our patients on a routine basis and neither positron emission tomographic scanning for metabolic activity nor thallium scintigraphy was performed. However, we believe that the reference method for stunned myocardium should be spontaneous recovery of wall motion as we have evaluated. Echocardiograms were evaluated qualitatively and digital cine-loop systems were not used. In a previous study using dobutamine stress echocardiography, digital techniques did not offer advantages over analysis on videotapes in terms of diagnosis of myocardial ischemia.[14] Changes in regional wall motion, and particularly hypokinetic segments becoming normal, are subtle and difficult to evaluate. Dobutamine stress echocardiography was performed within 7 days of hospital admission. Thus, some segments could have already recovered, lowering the prevalence of a positive low-dose dobutamine stress echocardiogram. Finally, the results of this study cannot be extrapolated to patients with complicated acute myocardial infarction, who represent the ideal target population and for whom proper identification of myocardial viability is clinically most relevant.

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CHAPTER 15

LOW-DOSE DOBUTAMINE ECHOCARDIOGRAPHY AND REST-REDISTRIBUTION 201-THALLIUM TOMOGRAPHY IN THE ASSESSMENT OF SPONTANEOUS RECOVERY OF LEFT VENTRICULAR FUNCTION AFTER RECENT MYOCARDIAL INFARCTION[1]

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SUMMARY

Spontaneous improvement of contraction and perfusion occurs after acute myocardial infarction. The relative merit of low-dose dobutamine echocardiography (LDDE) and rest-redistribution thallium scintigraphy (RR Tl) in this setting has not been evaluated. We studied 30 patients at 7 $\pm$ 3 days after acute myocardial infarction with LDDE (5-10 μg/kg/min) and RR Tl SPECT. Viability was defined as improvement of wall thickening at LDDE and the presence of redistribution or a defect with uptake $\geq$ 50% of peak activity at RR Tl. Baseline echocardiogram and RR Tl were repeated after 3 months. In 112 dyssynergic segments, viability was detected in 60 (54%) by RR Tl and in 39 (35%) by LDDE ($p<0.005$). Spontaneous improvement of function was detected in 35 (31%) segments. In the same region, Tl uptake increased significantly. The sensitivity, specificity and accuracy of LDDE for the prediction of late improvement of wall motion were 77%, 84% and 82%. Those of RR Tl were 77%, 57% and 63% respectively. Specificity and accuracy of LDDE were higher than RR Tl ($p<0.005$). It is concluded that myocardial viability pattern after acute myocardial infarction is more frequently detected by RR Tl than by LDDE. Both techniques are equally sensitive but LDDE is more specific predictor of spontaneous recovery of regional left ventricular function.

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Key Words: Myocardial viability - thallium SPECT - dobutamine echocardiography

INTRODUCTION

Recent clinical studies have shown that after a recent myocardial infarction, late spontaneous recovery of regional left ventricular function and myocardial perfusion occurs in a substantial percentage of patients (1-7). This finding is consistent with the concept of myocardial stunning (8,9) and may have important clinical implications for an improved risk stratification (10,11) and for a more proper selection of patients for coronary revascularization procedures (12-16). Therefore, the prediction of late functional outcome of left ventricular function would be desirable, if this could be obtained with a noninvasive, simple, accurate, reproducible method. Low-dose dobutamine stress echocardiography (LDDE) and rest-redistribution thallium scintigraphy (RR Tl) have the potential of fulfilling most of these pre-requisites (2-7,10; 17-18). However, the relative value of both techniques in the detection of viable myocardium after a recent myocardial infarction has not been compared in the same patient population. Accordingly, the aim of the present study was threefold: 1) to study the agreement between LDDE and RR Tl on the diagnosis of myocardial viability in patients with a recent myocardial infarction, 2) to describe the spontaneous changes of regional left ventricular function and perfusion at 3 months after myocardial infarction, 3) to assess the relative predictive value of LDDE and RR Tl to predict the late spontaneous improvement of regional left ventricular function.

METHODS

Study population: Thirty two consecutive patients with a recent myocardial infarction and uncomplicated early clinical course were included in the study. The mean age was 61 $\pm$ 11 years (range 37-78) and 21 (70%) were males. The diagnosis of myocardial infarction was based on the presence of at least two of the following criteria: prolonged chest pain ($>$ 30 min), deviation $\geq$ 1 mm in at least two leads on the standard electrocardiogram and significant increase (at least twice the upper normal limit) of serum creatine kinase. The site of the infarction was inferior or infero-postero-lateral in 20 patients, and anterior or anteroseptal in 12. Intravenous thrombolysis was given in 17 patients; the delay in the hospital admission or other clinical conditions were the contraindications in the others. A non-Q wave myocardial infarction was present in 5 patients. Fourteen patients underwent a diagnostic coronary angiography. All patients underwent LDDE at a mean of 7 $\pm$ 3 days (range 5 to 14 days) after the infarction. The anti-anginal therapy was not discontinued before the test and included beta-blockers in 5 patients. RR Tl was performed in all patients at a mean time interval of 1.2 days (range 1-2 days) from LDDE. All patients gave a written consent to participate in the study.

Dobutamine stress-echocardiography

Dobutamine was infused with a volumetric pump at incremental doses (5 - 10 μg/kg/min) with steps of 3 minutes. A 12-lead electrocardiogram and arterial blood pressure were recorded at basal conditions and at the end of each stage. Patients were monitored with 3 ECG leads and two-dimensional echocardiography throughout the test. Echocardiogram (in standard multiple short and long axis views) was recorded on video tape at rest and during dobutamine infusion. The images were also digitized and stored on an optical disk (Vingmed CFM 800) for a display in quad-screen format. A 16-segment model of the left ventricle, according to the recommendations of the American Society of Echocardiography (19) was used for the evaluation of left ventricular wall motion. Both inward wall motion and systolic myocardial thickening were considered for the assessment. Each segment was graded with a 4-point score grading, from 1 to 4 (1 = normal or hyperkinesis; 2 = hypokinesis; 3 = akinesis 4 = dyskinesis). Wall motion score index was calculated dividing the sum of the scores by the number of the segments analyzed. Echocardiographic images were interpreted by two observers blinded to the patients' scintigraphic data. A third observer was asked in cases of disagreement and a majority decision was reached. In our laboratory, the inter-and intraobserver concordance on the response of wall motion during LDDE are 92% (Kappa 0.84) and 94% (Kappa 0.86) respectively (20). The test was considered positive for the presence of viable myocardium if ≥ 1 dyssynergic segment had ≥ 1 decrease of wall motion score compared with resting echocardiogram during dobutamine infusion.

Rest-redistribution thallium SPECT

On fasting, 110 MBq of 201-Tl were injected intravenously at rest, 5 minutes after sublingual adminstration of 1 mg of nitroglycerin. The acquisition of the SPECT images was started within 10 minutes after the injection and repeated 4 hours later. A Picker 3 headed Camera (Prism 3000, Ohio) equipped with low energy, high resolution parallel hole collimators was used. One hundred twenty projections were obtained, over 360 degrees (3 degrees step-wise increment), with an acquisition time of 45 seconds per head. The interpretation of the images was based on 6 short-axis, 3 longitudinal and 3 transverse long-axis slices. The analysis was performed visually with the assistance of quantitative measurements (circumferential profile analysis). Rest and redistribution images were displayed side-by-side for comparison. Analysis was performed by an experienced observer blinded to the results of LDDE. In order to obtain a matched regional assessment of wall motion and Tl uptake, the same 16-segment model used for interpretation of the echocardiogram was applied for the interpretation of the SPECT images. The area falling more than two standard deviations below mean normal values was calculated at each level and the sum of the values was considered as the severity of global Tl uptake

defect. Myocardial viability in dyssynergic segments was considered in the corresponding segment at RR Tl in presence of normal perfusion, a reversible defect or a fixed moderate defect with regional Tl uptake ≥ 50% of maximal (100%) uptake.

Follow-up studies

A rest echocardiogram was performed in all patients at three months. The echocardiographic images were acquired in digital format and stored on the same optical disk used for the pre-discharge study. The images of the baseline and follow-up echocardiogram were visualized side-by-side in a quad-screen format allowing a proper assessment of segmental changes. A regional improvement of left ventricular function was defined as a decrease of wall motion score ≥ 1 grade. A rest-redistribution Tl SPECT was performed in 18 of the 32 patients and the analysis of the results was made as described before. The results were compared with those of the initial study to assess spontaneous changes of myocardial perfusion.

Statistical analysis: Continuous data were expressed as mean ± SD. Baseline and follow-up wall motion score index and Tl defect were compared by paired Student's t-test. Differences were considered significant when $p<0.05$. The diagnostic accuracy of LDDE and RR Tl was evaluated by calculating the sensitivity, specificity, positive and negative predictive value and the corresponding 95% confidence interval. Agreement between the two methods was expressed by the kappa-value. Values between 0.75 and 1 were considered indicative of good, between 0.40 and 0.75 of moderate and between 0 and 0.40 of poor agreement.

RESULTS

No complications occurred during dobutamine infusion. Heart rate and systolic blood pressure at rest were 69 ± 14 beats/min and 120 ± 13 mm Hg respectively and they did not change significantly during dobutamine infusion (73 ± 14 beats/min and 127 ± 18 mm Hg respectively). During follow-up, two patients underwent coronary angioplasty for angina and were excluded from the analysis, while the other 30 had an uncomplicated clinical course up to the repeated tests at three months after the infarction. Eighteen of these 30 remaining patients were studied at follow-up with RR Tl.

Regional myocardial function and perfusion: Twenty segments were excluded from analysis due poor quality. At baseline echocardiogram, 112 of the 460 segments analyzed were dyssynergic and 35 (31%) of them had a late spontaneous improvement (in 14 patients). Viable myocardium was detected in 39 segments by LDDE (35%) and in 60 (54%) by RR Tl (agreement 56%, kappa 0.15; Figure 1). The prevalence of a viability pattern on RR Tl was

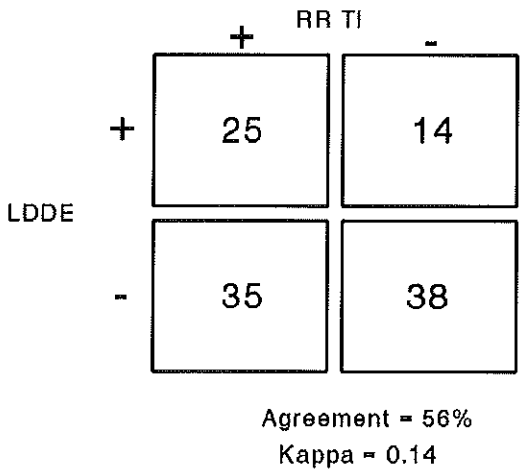

Figure 1. Agreement for the detection of myocardial viability by low-dose dobutamine echocardiography (LDDE) and rest-redistribution thallium SPECT (RR Tl).

significantly higher compared to LDDE ($p<0.005$). Out of the 39 dyssynergic segments with an improvement of wall motion during LDDE, 27 (69%) recovered at the follow-up whereas 8 out of the 73 segments with a negative LDDE (11%) improved at follow-up (Figure 2). A viability pattern on Tl SPECT was present in 60 of the 112 dyssynergic segments (54%). Wall motion at follow-up improved in 27 (45%) of these segments. Fifty two dyssynergic segments (46%) were not viable on RR Tl; 8 of them (15%) showed improvement of contractility at follow-up (Figure 3). Sensitivity, specificity, predictive values and diagnostic accuracy of LDDE and Tl SPECT for the prediction of late improvement of regional wall motion are reported in table I. Sensitivity of both techniques was comparable; whereas specificity and accuracy of LDDE were higher ($p<0.0005$ and <0.005 respectively). Sensitivity, specificity, predictive values, and accuracy of LDDE and RR Tl for the prediction of functional recovery are also shown in table I.

Percentage Tl defect in dyssynergic segments was significantly lower in segments with than without improvement at low-dose dobutamine (34 ± 27 vs 52 ± 22 %, $p<0.0005$) and in segments with than without late functional improvement (38 ± 27 vs 60 ± 14%, $p<0.0001$). Resting wall motion score pindex in the entire study group did not change significantly from baseline echocardiogram to follow-up (1.40 ± 0.29 vs 1.32 ± 0.28).

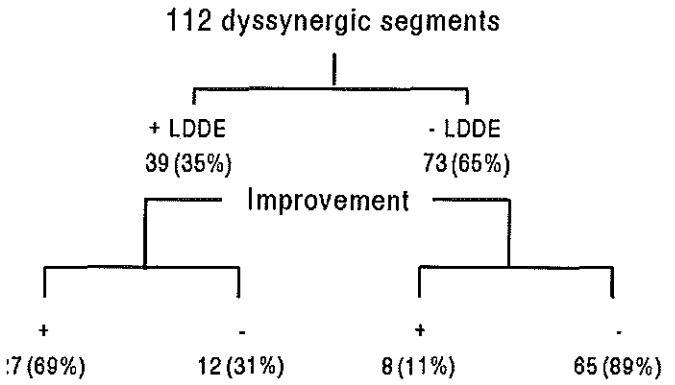

Figure 2. Flow-chart with the results of low-dose dobutamine echocardiography (LDDE) for the detection of myocardial viability in the dyssynergic segments and the improvement of contractility at follow-up.

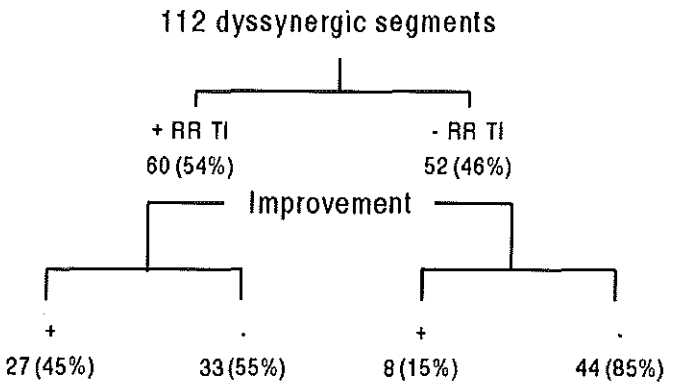

Figure 3. Flow-chart with the results of rest-redistribution thallium SPECT (RR Tl) for the detection of myocardial viability in the dyssynergic segments and the improvement of contractility at follow-up.

Sequential changes of thallium uptake

In the 18 patients in whom RR Tl SPECT at follow-up was performed, the mean value of the quantitative defect in the 66 dyssynergic regions analyzed decreased from 50% ± 19% to 45% ± 18% ($p<0.001$). There was a trend towards a greater reduction of Tl defects in the regions with compared to those without a late recovery of contractility (6.2% ± 14.2% vs 4.9% ± 13.8%, P = NS). The index of severity of total thallium uptake defect decreased in the whole study group from 2137 ± 1321 to 1438 ± 947 ($p<0.05$).

Table I. Diagnostic accuracy with 95% confidence intervals of low-dose dobutamine echocardiography and rest-redistribution thallium SPECT for the prediction of late spontaneous improvement of dyssynergic segments after acute myocardial infarction.

	SENS	SPEC	PPV	NPV	ACC
LDDE	77	84	69	89	82
95% C.I.	69-85	78-91	61-78	83-95	75-89
RR Tl	77	57	45	85	63
95% C.I.	69-85	48-66	36-54	78-91	54-72

ACC = diagnostic accuracy; C.I. = confidence intervals; LDDE = low-dose dobutamine echocardiography; NPV = negative predictive value; PPV = positive predictive value; SENS = sensitivity; SPEC = specificity; RR Tl = rest-redistribution thallium SPECT.

DISCUSSION

Several clinical observations have confirmed the experimental data on the frequent occurrence of a spontaneous recovery of myocardial contractility during the first days after an acute myocardial infarction (21,22), consistent with the presence of a substantial amount of stunned myocardium. However, few clinical studies have been addressed to describe the late functional recovery of the infarcted area that occurs between 1 week and 3 months after the infarction (2-7), if such improvement is accompanied by a concomitant improvement of myocardial perfusion (23), if it is predictable, and by which method.

In the present study, LDDE and quantitative RR Tl SPECT at a mean of 1 week after infarction were used to predict the late spontaneous recovery of regional left ventricular function after 3 months. The main findings of the present study are the following: 1) 31% of dyssynergic segments have a spontaneous improvement; 2) there is an improvement of Tl uptake in the dyssynergic regions, by 10% (5% from 50% defect size) on average; 3) a contractile reserve of the dyssynergic regions detected by LDDE is a powerful predictor of late recovery of regional left ventricular function; 4) a RR Tl

pattern of myocardial viability is equally sensitive but less specific for late spontaneous recovery of contractility.

Spontaneous improvement of left ventricular function and perfusion

Although this study includes a small population, there is no previous clinical study with serial assessment of left ventricular function and Tl uptake from the first week up to 3 months after an acute myocardial infarction. The incidence of functional improvement of the dyssynergic segments of 31% was similar to that reported in other studies (7,8). Global left ventricular function, assessed by wall motion score index showed a trend towards a slight improvement, but did not reach a statistical significance, possibly due to the small size of the study group. Myocardial regional Tl uptake in dyssynergic regions improved significantly at follow-up. In our study, a state-of-the-art method was used to assess myocardial viability, including RR Tl SPECT (10,24), multiple head camera, quantitative assessment of regional uptake and premedication with nitrates (25). The data of our study are consistent to the results recently published by Galli et al with 99m Tc sestamibi (23). This is not surprising, since recent data have demonstrated a great similarity between Tl and sestamibi for the assessment of myocardial viability (26). Spontaneous improvement of perfusion may be attributed to a late resolution of myocardial and vascular stunning (23), the creation of new macro or micro collateral circuits and spontaneous thrombolysis (9). A late resolution of Tl defects has been also described in clinical models of hibernating myocardium, after successful coronary angioplasty (27).

Predictors of improvement of regional left ventricular function

LDDE was a strong predictor of spontaneous improvement of regional wall motion (Table I). These data are aligned with those of previous reports (2-7). In contrast, the assessment of myocardial viability by Tl scintigraphy could only identify segments with low but not those with high probability of spontaneous improvement. The explanations for these discordant results are difficult to find. It can be speculated that the time course of improvement of myocardial perfusion and function might be different, unabling a proper prediction of one parameter from the other. The low specificity of Tl to predict improvement of wall motion can be also partially related to the presence of hibernating myocardium, subtended by severely stenotic coronary lesions which is amenable to improvement after revascularization. However, this assumption entails a limited sensitivity of LDDE for the detection of myocardial viability in a hibernating myocardium, since most of the non-recovered segments with evidence of viability on RR Tl were identified as non-viable by LDDE. Despite the advantage of Tl scintigraphy over echocardiography in term of quantitative assessment of abnormalities, it has inherent technical limitations since it provides relative and not absolute information on myocardial uptake. It can not

be excluded that pre-medication of nitrates may improve the sensitivity of RR Tl at the expense of specificity. Because of the potentials for hypokinesis to occur in normal subjects (28), some hypokinetic segments may not be related to the acute coronary events. Consequently, these segments may show evidence of viability without improvement at follow up and compromise the accuracy of the 2 techniques.

Comparison with previous studies

Lomboy et al. (29) studied 31 patients 2 days after acute myocardial infarction with planar RR Tl. Twenty-two patients underwent radionuclide angiography 3 days after infarction and at variable follow-up period. The presence of viability pattern in the infarct zone was predictive of improvement of ejection fraction and regional function on follow-up radionuclide angiogram as opposed to patients without viability pattern who had worsening of ejection fraction and regional function. These different results compared to our study can be explained by the difference in patient population and methodology. In the study of Lomboy et al., revascularization, performed in 17 patients may have enhanced the accuracy of RR Tl due to recovery of a hibernating myocardium. A limitation of that study is the lack of consistency in the time of obtaining follow-up studies of myocardial function by radionuclide angiography, which ranged from 6 - 270 days, with 64% of the studies performed before discharge (8 ± 2 days after infarction). It has been previously demonstrated that a substantial proportion of myocardial segments may recover spontaneously from 7 days to 2-3 months after acute myocardial infarction (6,7). These segments would be considered as non-viable if the follow-up studies are performed earlier. Despite that radionuclide angiography is a good method for the assessment of global function, its value in the assessment of regional function may be limited by the inability to assess wall thickening. The latter is important in the assessment of myocardial viability because endocardial excursion alone may be passively altered by an adjacent segment. The echocardiographic technique is more useful in the tomographic evaluation of regional wall motion and thickening and consequently provides tomographic abilities equivalent to those of RR Tl SPECT imaging.

The agreement between thallium scintigraphy and low-dose dobutamine echocardiography on the presence of myocardial viability

Two recent studies on patients with chronic left ventricular dysfunction and reduced ejection fraction have shown that a viability pattern is more frequently obtained with stress-reinjection Tl techniques than with LDDE consistent with our findings on RR Tl after acute infarction (20,30). Arnese et al. (20) have recently reported that in patients with chronic left ventricular dysfunction, LDDE and dobutamine stress-reinjection Tl scintigraphy have a comparable sensitivity for the prediction of regional myocardial recovery after

surgical revascularization whereas specificity of LDDE was significantly higher than Tl scintigraphy. Panza et al. (30) reported that a positive inotropic response to dobutamine was directly related to the magnitude of Tl uptake. In our study, thallium uptake in dyssynergic segments was significantly higher in segments with than without improvement at LDDE and in segments with than without late functional improvement. It was suggested that the cellular mechanisms responsible for a positive inotropic response to adrenergic stimulation requires a higher degree of myocyte functional integrity than those responsible for Tl uptake (30). This may explain the lower specificity of Tl scintigraphy in the study of Arnese et al. and in this study by the possibility that only myocytes with a high degree of functional integrity are capable of restoration of function spontaneously or after revascularization.

Limitations of the study

The study group is limited to patients with relatively uncomplicated clinical course and mildly or moderately reduced left ventricular function. The extension of these information to a group of patients with more advanced left ventricular dysfunction would be desirable and clinically more relevant. Coronary arteriography was performed in a minority of patients and therefore the association between angiographic anatomy and the functional outcome could not be performed. It can not be excluded that some of the dyssynergic segments classified as viable by RR Tl, which did not improve at follow-up represent myocardial hibernation due to the presence of significant stenosis of the related coronary artery. Regional function was assessed at baseline and at follow-up studies rather than global function which represent an important determinant of prognosis after acute myocardial infarction (31). However, the occurrence of compensatory hypertrophy after acute infarction tends to preserve the global ejection fraction (8-32). This hypertrophy may resolve when improvement of regional function occurs and thus ejection fraction may not change from baseline to follow-up despite of regional improvement (8). Identification of myocardial segments of interest was based on echocardiographic analysis. This may seem to be in favour of a better accuracy of LDDE. Since echocardiography is an accurate method for the assessment of regional function, we believe that identification of dyssynergic myocardial segments using a baseline echocardiogram is feasible for the selection of myocardial regions of interest. A recent study by Panza et al. (30) used a similar approach.

Conclusions

The prevalence of a viability pattern on RR Tl is higher than on LDDE in dyssynergic segments after acute myocardial infarction. About one third of these segments shows spontaneous improvement of wall motion from day 7 to 3 months and this improvement is paralleled by an improvement of Tl uptake. Our study also demonstrates that both LDDE and RR Tl are equally sensitive

but LDDE is more specific predictor of late spontaneous recovery of regional function.

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CHAPTER 16

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T-Wave Normalization During Dobutamine Echocardiography for Diagnosis of Viable Myocardium

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Low-dose dobutamine stress echocardiography has been proposed as a useful tool for assessing reversible dysfunction after myocardial infarction.[1,2] However, subtle regional wall motion improvement during low-dose dobutamine infusion can be difficult to evaluate, especially in akinetic segments.[3] In our experience with dobutamine stress testing in postinfarction patients, we frequently observed the occurrence of T-wave normalization with low-dose dobutamine without signs of myocardial ischemia. Because we were puzzled by this electrocardiographic (ECG) finding, we wondered whether this pattern could reflect the presence of reversible mechanical dysfunction. In particular, we wanted to test the hypothesis that normalization of the inverted T wave during low-dose dobutamine infusion represents a sign of dysfunctioning but still viable myocardium in patients after recent myocardial infarction.

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With this aim in mind, we enrolled in a prospective study 90 consecutive patients admitted to our institutions who fulfilled the following admission criteria: (1) first Q-wave myocardial infarction (as documented by history, typical isoenzymes curves, and ECG changes); (2) negative T waves in ≥2 infarct-related ECG leads; and (3) segmental wall motion abnormalities on the resting echocardiogram. Patients with overt heart failure and early postinfarction angina requiring revascularization were excluded. Fifty patients were treated with thrombolytic agents. The ECG location of the infarction was anterior in 39 and inferior and/or lateral in 51 patients. Low-dose dobutamine stress echocardiography (5 and 10 μg/kg/min, each stage lasting 5 minutes) was performed within 7 days after hospital admission, with adequate withdrawal of all antianginal and other cardioactive drugs. Regional wall motion was evaluated on an 11-segment 4-grade scale, where 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. Any improvement in wall motion during low-dose dobutamine infusion in ≥1 segment already dyssynergic at rest was considered positive for the presence of viable myocardium. A wall motion score index was derived by dividing the sum of the individual scores by the number of the segments. A 12-lead electrocardiogram was recorded at rest and every minute during the test. T-wave normalization was defined as negative T waves becoming upright in ≥2 infarct-related ECG leads during dobutamine infusion. Both echocardiograms and electrocardiograms were reviewed and a consensus reached by 2 observers unaware of the results of the other test. In 59 patients a rest echocardiogram was obtained after 3 months. During this period, no cardiac events (unstable angina, myocardial infarction, revascularization procedure) occurred. Late spontaneous recovery of function was defined as any improvement of wall motion in the infarct area from predobutamine to follow-up echocar-

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TABLE I Resting Dyssynergies and Improvement in Wall Motion in 29 Patients With Positive Results on Low-Dose Dobutamine Echocardiography

	Group 1 (n = 18)*	Group 2 (n = 11)†
Mean no. of dyssynergic segments (95% CI)	3.1 (1.9–4.3)	3.5 (2.3–4.8)
Mean no. of dyssynergic segments improving with LDD (95% CI)	2.2 (1.6–2.8)	1.7 (1.3–2.2)
% of dyssynergic segments improving with LDD (95% CI)	84 (73–95)	58 (37–78)
Mean WMSI at rest (95% CI)	1.58 (1.34–1.81)	1.71 (1.44–1.99)
Mean WMSI at LDD (95% CI)	1.32 (1.12–1.51)	1.44 (1.18–1.70)
Mean changes in WMSI from rest to LDD (95% CI)	0.26 (0.19–0.33)	0.27 (0.18–0.35)

*Patients with T-wave normalization during low-dose dobutamine infusion.
†Patients with persistent negative T waves during low-dose dobutamine infusion.
CI = confidence interval; LDD = low-dose dobutamine infusion; WMSI = wall motion score index.

diograms. The agreement between echocardiography and electrocardiography was defined as the percentage of concordant diagnosis, and it was also assessed by calculating the κ value and its standard error; κ values between 0.50 and 0.75 were considered indicative of good agreement. Sensitivity, specificity, accuracy, and positive and negative predictive values of both echocardiography and electrocardiography for predicting late spontaneous recovery of function relied on standard definitions, and their values were expressed as percentage with 95% confidence intervals.

All patients completed low-dose dobutamine stress testing without adverse effects. Both heart rate and systolic blood pressure were similar at rest and at low-dose dobutamine infusion (76 ± 18 vs 78 ± 18 beats/min; 140 ± 36 vs 140 ± 36 mm Hg, respectively). Improvement in wall motion in the infarct area during dobutamine infusion occurred in 29 patients (32%), while the T wave normalized in 23 (26%). An example of T-wave normalization during dobutamine infusion is shown in Figure 1. The overall agreement between echocardiography and electrocardiography was 82% (κ = 0.57) (Figure 2). Patients with improvement in wall motion and T-wave normalization (group 1, n = 18) were compared with those with improvement in wall motion but no change in the negative T waves (group 2, n = 11). In these 2 subgroups, both the number of dyssynergic segments at rest and the changes in wall motion score index during low-dose dobutamine infusion were similar. However, the percentage of resting dyssynergic segments that improved during low-dose dobutamine infusion was higher in patients with T-wave normalization (Table I). At follow-up, spontaneous recovery in the infarct area was present in 21 of 59 patients (36%). In these 21 patients, agreement between echocardiography and electrocardiography was 62%. Echocardiography and electrocardiography had similar values of sensitivity, specificity, accuracy, and positive and negative predictive values for predicting late spontaneous recovery of function. When either improvement in wall motion or T-wave normalization was considered, there was a trend toward higher sensitivity, without loss of specificity (Table II).

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In recent years there has been an increasing interest in the detection of viable myocardium. Inotropic challenge with low-dose dobutamine infusion has the potential to recruit the contractile reserve of dysfunctioning but still viable myocardium which can be recognized by 2-dimensional echocardiography. The results of this approach are encouraging, both for stunned and hibernating myocardium. However, the prevalence of this phenomenon as evaluated in previous studies by low-dose dobutamine stress echocardiography is different.[1–4] This may be due to the difficult and subjective evaluation of subtle changes in segmental wall motion and thickening during dobutamine infusion. Furthermore, wall motion can also be affected by factors not primarily related to the inotropic state. Thus, evaluation of other nonechocardiographic parameters may be helpful for identifying viable myocardium during low-dose dobutamine infusion.

The underlying pathophysiology of negative T waves in ischemic heart disease is not completely understood. There is clinical evidence that T-wave inversion is associated with viable myocardium in patients with unstable angina, being an electrophysiologic correlate of myocardial stunning.[5] In this clinical setting, negative T waves reflect primary changes due to an abnormal pathway of electrical repolarization. In Q-wave myocardial infarction, negative T waves in the infarct ECG leads may result from change in the order of repolarization secondary to alterations of the sequence of depolarization. However, experimental and clinical data indicate that sympathetic denervation of viable myocardium distal to the area of necrosis also may delay repolarization and result in primary negative T waves.[6] In patients with recent myocardial infarction, inotropic stimulation with low-dose dobutamine may have the potential to normalize primary T-wave changes (unmasking the presence of viable myocardium), while secondary T-wave changes are not affected.

TABLE II Relative Value of Echocardiography and Electrocardiography During Dobutamine Stress Testing for Predicting Late Spontaneous Recovery of Function After Acute Myocardial Infarction

	Sens.	Spec.	Acc.	PPV	NPV
Echo*	57 (34–78)	89 (75–97)	78 (65–87)	75 (47–92)	79 (64–90)
ECG†	47 (25–70)	92 (78–98)	76 (63–86)	76 (46–95)	76 (61–87)
Echo and/or ECG	71 (45–88)	89 (75–97)	83 (71–91)	79 (54–94)	85 (70–94)

*Improvement in contractility during low-dose dobutamine stress testing.
†Normalization of negative T waves during low-dose dobutamine stress testing.
Values are expressed as percentage with corresponding 95% confidence intervals.
Acc. = accuracy; Echo = echocardiography; ECG = electrocardiography; NPV = negative predictive value; PPV = positive predictive value; Sens. = sensitivity, Spec. = specificity.

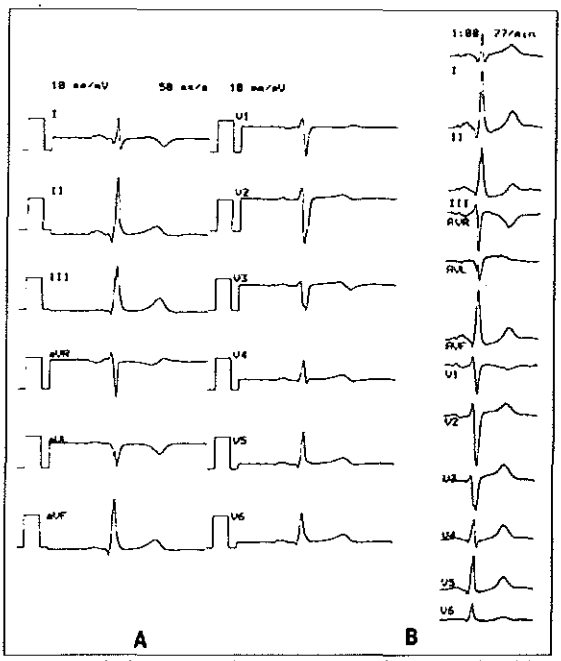

FIGURE 1. Twelve-lead electrocardiogram at rest (A) and during low-dose dobutamine infusion (B) in a patient with lateral Q-wave myocardial infarction. Negative T waves at rest in leads I and aVL normalize during inotropic stimulation.

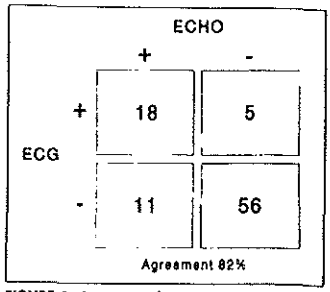

FIGURE 2. Agreement between improvement in contractility (ECHO +) and T-wave normalization (ECG +) during low-dose dobutamine stress testing in the original group of 90 patients. ECG = electrocardiography; ECHO = echocardiography.

The results of the present study indicate a good agreement between improvement in wall motion and normalization of negative T waves during low-dose dobutamine infusion. We have also found that, conditional to patients with positive results on low-dose dobutamine stress echocardiography, the percentage of dyssynergic segments improving during dobutamine infusion was higher in those with a concomitant T-wave normalization. However, and most interesting, 5 patients with negative results on low-dose dobutamine echocardiography had T-wave normalization as well, with late spontaneous improvement in wall motion in all 3 who were evaluated at follow-up. Thus, the main finding of the present study is the additional value of this ECG pattern for predicting late spontaneous recovery of segmental wall motion. The higher sensitivity of electrocardiography added to echocardiography compared with that of echocardiography alone was not corroborated by a clear separation of the corresponding 95% confidence intervals. However, from this figure we estimated that ≈1,000 patients should be needed to reach a statistical significance. The results of the present study may also explain the low specificity for myocardial ischemia of normalization of negative T waves during exercise reported in previous studies.[7] This finding may represent viable myocardium not at risk. Finally, the relatively low sensitivity for predicting recovery with low-dose dobutamine echocardiography in our study compared with available data[1] can be explained by several factors: the different patients selected, the different echocardiographic left ventricular model and definition of improved wall motion and reversible dysfunction, and the prevalence of akinetic segments at rest, which has been shown to lower sensitivity of the test.[3]

These preliminary data indicate that T-wave normalization during low-dose dobutamine stress testing is an ancillary sign of viable myocardium after acute myocardial infarction and increases the sensitivity of echocardiography for predicting late spontaneous recovery of function.

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CHAPTER 17

RELATIONSHIP BETWEEN ST-SEGMENT ELEVATION DURING DOBUTAMINE STRESS TEST AND MYOCARDIAL VIABILITY AFTER A RECENT MYOCARDIAL INFARCTION[1]

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ABSTRACT

Though exercise-induced ST-segment elevation (STE) in patients with recent myocardial infarction has been related to residual myocardial viability, the relation between this pattern and late improvement of function has not been evaluated. Aim of the study was to assess the relation between STE during dobutamine stress test and late improvement of function after acute Q-wave myocardial infarction. Seventy patients were studied 8 ± 3 days after acute myocardial infarction with high dose dobutamine stress echocardiography (up to 40 μg/kg/min) and a follow-up echocardiogram at 85 ± 10 days. A 16 segments-4 grade score model was used to assess left ventricular function. Functional improvement was defined as a reduction of wall motion score ≥1 in ≥1 segments at follow-up. Myocardial revascularization was performed in 23 patients (33%) before follow-up studies. STE occurred in 40 patients (57%). Late functional improvement occurred in 35 patients (50%). Patients with STE had a higher prevalence of functional improvement (68% vs 30%, $p<0.005$) and a higher number of improved segments at follow-up (1.9 ± 2.2 vs 0.5 ± 1.1, $p<0.005$). Wall motion score decreased from baseline to follow-up in patients with STE (24.7 ± 8 vs 23.6 ± 6.9, $p<0.05$) but not in patients without STE (22.3 ± 9.7 vs 23.2 ± 7.5). The accuracy of STE for the prediction of functional improvement was similar to that of low-dose dobutamine echocardiography in patients with anterior infarction (80% vs 83%) and in patients who underwent revascularization (78% vs 83% respectively). It is concluded that in patients with a recent Q wave myocardial infarction, dobutamine-induced STE is a valuable marker of myocardial viability

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particularly when the test is performed without or with suboptimal echocardiographic imaging.

Key words: Dobutamine stress test, ST-segment elevation, myocardial viability

INTRODUCTION

The detection of myocardial viability after myocardial infarction is important for the proper selection of patients in whom myocardial function is more likely to improve after revascularization (1-3). Thallium scintigraphy, positron emission tomography and low-dose dobutamine (LDD) echocardiography are useful methods for that purpose (1-7). In a recent study, exercise-induced ST-segment elevation (STE) was reported as a specific marker of residual viability (8). However, these results have not yet been confirmed by other studies. Dobutamine stress test (DST) is an exercise simulating stress modality which is increasingly used for the functional assessment of patients after myocardial infarction (9-11). We have previously reported that normalization of negative T-waves in the electrocardiogram during LDD infusion in patients with a recent myocardial infarction is a marker of myocardial viability and a predictor of late improvement of function (12). STE is a common finding in this population during DST (9). However the relationship between this pattern and late functional improvement has not been studied. Consequently, the aims of the study were: 1) to find the relationship between STE during DST after a recent myocardial infarction and myocardial viability assessed by LDD echocardiography. 2) to compare the value of STE and LDD echocardiography in the prediction of late improvement of left ventricular function.

METHODS

Patient selection

The study comprised 70 consecutive patients with a recent myocardial infarction who were studied by DST for the diagnosis of residual myocardial viability and ischemia. All patients fulfilled the following criteria: 1) A recent myocardial infarction ≤ 2 weeks diagnosed by standard criteria of chest pain, a diagnostic rise and fall of the serum creatine kinase and electrocardiographic changes. 2) The absence of severe heart failure, hypotension, high grade ventricular arrhythmias or chest pain not responding to medical therapy. 3) The presence of pathological Q waves and wall motion abnormalities in the corresponding segments at the day of the study. 4) Absence of myocardial aneurysm, left ventricular hypertrophy or bundle branch block. All patients gave a consent to participate in the study. There were 49 men (70%) and 21 women (30%). Mean age was 58 $\pm$ 11 years. Thirty one patients (44%) were receiving oral nitrates and/or calcium channel blockers. If administered, beta blocking agents were stopped 1 day before the test.

Dobutamine stress test: DST was performed 8 ± 3 days after infarction (range = 6-14 days). Dobutamine was infused through an antecubital vein starting at a dose of 5 μg/kg/min for 3 minutes, 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age predicted maximal heart rate (13). The electrocardiogram (3 leads) was monitored and a 12-lead electrocardiogram was recorded each minute. The level of ST-segment was calculated, after signal averaging by a computer-assisted system (Cardiovet CSG/12, Schiller). Cuff blood pressure was measured every 3 minutes. The electrocardiograms were reviewed by 2 cardiologists unaware of the echocardiographic data. STE was defined as new or additional ≥ 0.1mV elevation of the J point with a horizontal or upsloping ST-segment lasting 80 ms during stress in 2 or more leads with Q waves considering the PQ segment as the isoelectric line (14). ST-segment depression was defined as ≥ 0.1mV horizontal or downsloping depression 80 ms after the J point, below baseline level. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test.

Stress echocardiography: The echocardiogram was performed and recorded on video tape at rest and during stress. Rest, LDD and peak stress images were also digitized and stored on an optical disk (Vingmed CFM 800) for a display in quad-screen format. A 16-segment model was used to assess left ventricular function (15) was used. Both inward endocardial motion and myocardial thickening were considered for analysis. Each segment was graded with a 4-point score grading (1 = normal or hyperkinesis; 2 = hypokinesis; 3 = akinesis; 4 = dyskinesis). Wall motion score was derived by the summation of the score of the 16 segments. The test was considered positive for the viability if ≥1 dyssynergic segment had ≥1 decrease of wall motion score during LDD (5-10 μg/kg/min). Viability index was defined as the number of dyssynergic segments with improvement at LDD divided by the total number of dyssynergic segments. The diagnosis of ischemia was based on the occurrence of new or worsening wall motion abnormalities in one or more segments. As previously reported, ischemia was not considered when akinetic segments at rest became dyskinetic without improvement at LDD (16). Assessment of images was performed by 2 experienced investigators without knowledge of the patients' electrocardiographic data. In case of disagreement, a majority decision was achieved by a third investigator. In our center, the inter- and intra-observer variability for the interpretation of dobutamine stress echocardiographic studies are 92% and 94% respectively (3).

Follow-up studies: A rest echocardiogram was performed in all patients 85 ± 10 days after infarction (range 71-98 days). The images of the baseline, LDD

and follow-up were compared side-by-side in a quad-screen format. Regional improvement of function was defined as a decrease of wall motion score ≥ 1 grade in ≥ 1 segments. Improvement index was derived by dividing the number of improved segments at follow-up by the total number of dyssynergic segments in the initial study.

Coronary angiography: Coronary angiography was performed using the Judkins technique, within 1 month after infarction in 34 patients (49%). Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$ in one or more major epicardial arteries.

Assignment of the electrocardiogram to myocardial segments and coronary arteries: Two electrocardiographic segments were identified: 1) the anterior segment which included leads V1-V4 and was assigned to the anterior wall, the interventricular septum and the apical anterior and apical septal segments, and to the left anterior descending coronary artery at angiography. 2) the inferolateral segment which included leads II, III, aVF, I, aVL, V5, V6 and was assigned to the inferior and posterolateral wall and to the left circumflex and/or the right coronary artery at angiography. The apical lateral and apical inferior segments were considered as overlap segments between the anterior and inferolateral locations and were assigned to the segments with concomitant abnormalities. Regional wall motion score was derived by the summation of the score of the segments in the corresponding location of Q waves at rest, LDD and follow-up. Regional viability and improvement indices were derived in each location as previously mentioned.

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. The Student t test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant. Sensitivity, specificity, predictive value and accuracy were derived according to the standard definition and were presented with the corresponding 95% confidence intervals (CI).

RESULTS

Dobutamine stress test

There was a significant increase of heart rate, systolic blood pressure and rate pressure product from rest to peak stress (71 $\pm$ 13 vs 136 $\pm$ 18 beats/minute; $p < 0.001$, 121 $\pm$ 27 vs 137 $\pm$ 30 mm Hg; $p < 0.01$ and 8,631 $\pm$ 1,543 vs 18,619 $\pm$ 4,325; $p < 0.0001$ respectively).

Stress echocardiography: All patients had wall motion abnormalities at rest. Among 377 dyssynergic segments in regions corresponding to Q waves, 106 segments (28%) improved at LDD. Wall motion score decreased significantly

from rest to LDD (23.8 ± 5.3 vs 22.3 ± 5.7, $p<0.0001$). Ischemia was detected in 32 patients (46%).

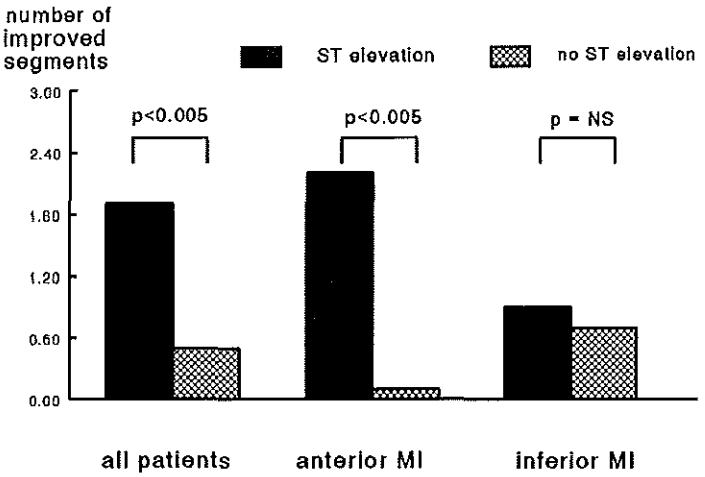

Figure 1 The number of dyssynergic segments with late functional improvement in patients with recent Q wave myocardial infarction (MI) with and without ST-segment elevation during dobutamine stress test.

Rate pressure product did not change significantly from rest to LDD. In 9 patients (13%), the test was interrupted prematurely. Reasons for premature termination were angina in 7 patients, ST-segment depression in 1 patient and hypotension in 1 patient. One patient had atrial fibrillation at peak dobutamine dose. He was successfully treated by pharmacological cardioversion. Ventricular premature beats occurred in 24 patients. Two patients had a short ventricular tachycardia (< 10 complexes). Fifty four patients (77%) achieved 85% of the maximal heart rate predicted for age and sex. Atropine was administered in 22 patients (31%). Angina occurred in 15 patients (21%) and ST-segment depression in 29 patients (41%). STE was present in 24 patients (34%) at rest. New or additional STE in Q leads occurred in 40 patients (57%) during stress (group A). The remaining 30 patients (43%) constituted group B including 5 patients with STE at rest who had no further elevation during stress. The mean heart rate at STE was 109 ± 24 beats/min ($p<0.01$ vs resting heart rate) and mean dobutamine dose was 31 ± 11 μg/kg/min.

Echocardiographic data (table II): There was a trend to a higher resting wall motion score and a higher number of dyssynergic segments in group A. There

was no significant difference between both groups with respect to prevalence of ischemia. Group A patients had a higher prevalence of viability pattern at LDD. At follow-up patients of group A had a higher prevalence of regional improvement and a higher number of improved segments. Wall motion score decreased from baseline to follow-up in group A (24.7 ± 8 vs 23.6 ± 6.9, $p<0.05$) but not in group B (22.3 ± 9.7 vs 23.2 ± 7.5).

In patients of group A, there was no significant difference between patients with and without late functional improvement with respect to heart rate at STE (108 ± 25 vs 112 ± 22 beats/min) or dobutamine dose at STE (31 ± 11 vs 31 ± 11 μg/kg/min).

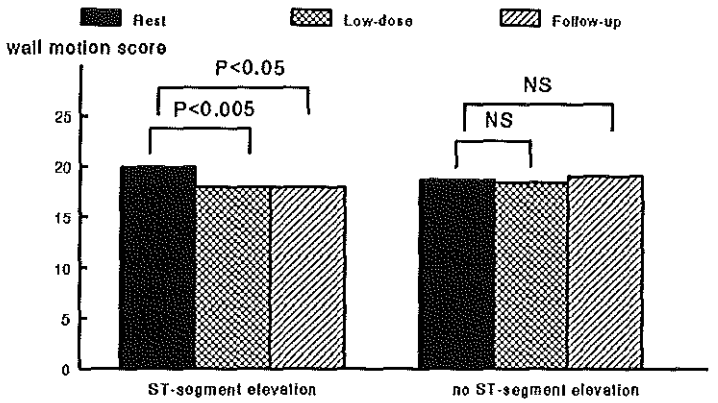

Figure 2 Regional wall motion score at baseline, low-dose dobutamine and follow-up in patients with recent anterior infarction with and without ST-segment elevation.

Follow-up echocardiography: Twenty three patients (33%) underwent revascularization of the infarct related artery before follow-up (15 with anterior and 8 with inferior infarction) which was performed before DST in 11 patients. At follow-up, improvement of thickening occurred in 95 of the 377 dyssynergic segments (25%; in 35 patients).

Comparison of patients with (group A) and without (group B) ST segment elevation

Clinical and hemodynamic data (table I): There was no significant difference

between group A and B with respect to thrombolytic therapy, angina during stress, peak systolic blood pressure, peak rate pressure product and percentage of patients achieving 85% of the target heart rate. Patients of group A had a higher peak heart rate and a higher prevalence of ST-segment depression.

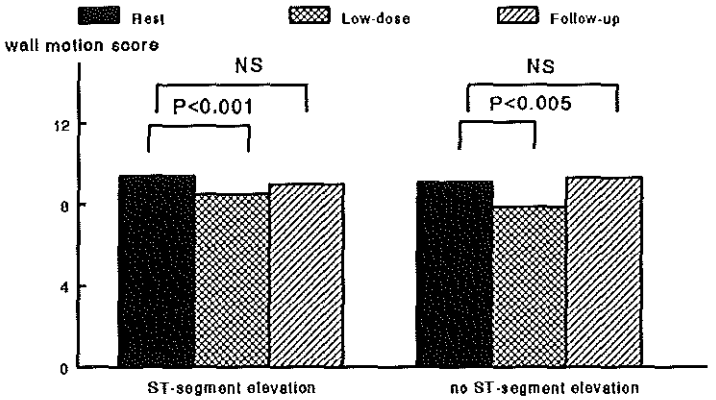

Figure 3. Regional wall motion score at baseline, low-dose dobutamine and follow-up in patients with recent inferior infarction with and without ST-segment elevation.

Anterior versus inferior myocardial infarction: In patients with anterior infarction (table III), there was a trend to a higher regional wall motion score at rest and a higher number of dyssynergic segments in group A. Prevalence of viability pattern and number of viable segments at LDD were higher in group A. At follow up, the prevalence of functional improvement, number of improved segments (figure 1) and improvement index were higher in group A. Wall motion score decreased from baseline to follow-up studies (figure 2) in group A (19.9 $\pm$ 4.3 vs 17.9 $\pm$ 5.9, $p<0.05$) and showed a slight non significant increase in group B (18.6 $\pm$ 6.6 vs 19.0 $\pm$ 7.3).

In patients with inferior infarction (table IV, including 4 patients with STE in anterior leads as well), none of these previous variables was different in both groups. There was a slight, non significant decrease of wall motion score (figure 3) from rest to follow-up in group A (9.4 vs 9.0) and a slight non significant increase in group B (9.1 vs 9.3). The prevalence of overall, homozonal or remote ischemia was not significantly different between group A and B regardless of the site of infarction. The sensitivity, specificity and accuracy of STE and LDD echocardiography for late functional improvement

in the whole population and in the subgroups with anterior and inferior infarction are shown in table V. Accuracy of STE was higher in patients with anterior versus inferior infarction (80% vs 57%, $p < 0.05$). In patients with anterior infarction, accuracy of LDD echocardiography was similar to that of STE (83% vs 80%); whereas in patients with inferior infarction, accuracy of LDD echocardiography was higher than STE (77% vs 57%, $p < 0.05$).

Table I: Clinical features and hemodynamic data in patients with recent Q wave myocardial infarction with (group A) and without (group B) ST-segment elevation.

	Group A N = 40	Group B N = 30
Age (years)	57 ± 11	61 ± 11
Male gender	31 (78%)	18 (60%)
Anterior infarction	18 (45%)	12 (40%)
Inferior infarction	26 (65%)#	18 (60%)
Thrombolysis	21 (53%)	13 (43%)
Peak HR	141 ± 18	130 ± 18*
Peak SBP	134 ± 25	142 ± 36
Peak rate-pressure product	18,775 ± 3,806	18,384 ± 5,129
85% of target HR achieved	32 (80%)	22 (73%)
Maximal dobutamine dose	38.8 ± 4.0	37.0 ± 7.7
Angina during the test	7 (18%)	8 (27%)
ST-segment depression	22 (55%)	7 (23%)*

SBP = systolic blood pressure (mm Hg), HR = heart rate (beats/min), WMA = wall motion abnormalities, * $p < 0.01$, # 4 patients had ST-segment elevation in anterior leads as well.

Figure 4 demonstrates the distribution of functional recovery in various combinations of STE and viability pattern at LDD echocardiography in patients with anterior myocardial infarction. It shows that in the 14 patients with ST-elevation and viability pattern at LDD echocardiography, late improvement of function occurred in 12 patients (positive predictive value of the combination = 86%), whereas no improvement occurred in any of the 9 patients without STE or viability at LDD echocardiography (negative predictive value = 100%).

Table II. Echocardiographic data of dobutamine stress test and follow-up in patients with Q wave myocardial infarction with (group A) and without (group B) ST-segment elevation.

	Group A N = 40	Group B N = 30
Dyssynergic segments, nr	5.9 ± 3.8	4.7 ± 3.9
Resting WMS	24.7 ± 8.0	22.3 ± 9.7
LDD WMS	17.9 ± 4.8	18.4 ± 6.8
Follow-up WMS	23.6 ± 6.9	23.2 ± 7.5
Viability at LDD, pts	27 (68%)	12 (40%)*
Viable segments at LDD	1.8 ± 2.2	1.1 ± 1.6
LDD viability index	0.34 ± 0.36	0.33 ± 0.42
Improvement at follow-up, pts	26 (68%)	9 (30%)#
Improved segments, nr	1.9 ± 2.2	0.5 ± 1.1 #
Improvement index	0.38 ± 0.36	0.22 ± 0.40
Ischemia at high-dose, pts	20 (50%)	12 (40%)

LDD = low-dose dobutamine echocardiography, WMS = wall motion score, pts = patients.* $p<0.05$, # $P<0.005$.

Coronary angiography and revascularization procedures

Coronary angiography was performed in 19 patients of group A and in 15 of group B. Coronary angioplasty of the infarct related artery was successfully performed before DST in 6 patients in group A and 5 patient in group B. There was no significant difference between both groups with respect to prevalence of multivessel disease (42% vs 33%) or significant stenosis of infarct related artery (68% vs 67%). Twelve patients underwent a revascularization a procedure 15 ± 8 days after DST. In these patients, the interval between intervention and follow-up ranged from 35 to 83 days (mean 72 days). Intervention included coronary angioplasty (3 patients of group A and 3 patients of group B) and coronary artery bypass graft (4 patients of group A and of 2 patients of group B). In the 34 patients in whom coronary angiography was performed, functional improvement occurred in 12 of 23 patients (52%) with and in 5 of 11 patients (45%) without revascularization (p = NS). In patients who underwent revascularization, the accuracy of STE for the prediction of late functional improvement was comparable to that of LDD

echocardiography (78% vs 83% respectively; table V).

Table III. Regional echocardiographic data of dobutamine stress test and follow-up in patients with anterior Q wave myocardial infarction with (group A) and without (group B) ST-segment elevation.

	Group A N = 18	Group B N = 12
Dyssynergic segments, nr	6.3 ± 2.4	4.7 ± 3.1
Resting WMS	19.9 ± 4.3	18.6 ± 6.6
LDD WMS	17.9 ± 4.8	18.4 ± 6.8
Follow-up WMS	17.9 ± 5.9	19.0 ± 7.3
Viability at LDD, pts	14 (78%)	3 (25%)*
Viable segments at LDD	1.7 ± 2.2	0.2 ± 0.4**
LDD viability index	28.8 ± 34.8	12.2 ± 33.1
Improvement at follow-up, pts	15 (83%)	3 (25%)*
Improved segments, nr	2.2 ± 2.2	0.1 ± 0.3**
Improvement index	0.40 ± 0.37	0.11 ± 0.33#
Homozonal ischemia, pts	5 (28%)	4 (25%)

LDD = low-dose dobutamine echocardiography, WMS = wall motion score, pts = patients, * $p<0.005$, ** $p<0.0001$, # $p<0.05$.

DISCUSSION

The functional evaluation of patients with recent myocardial infarction before hospital discharge aims at the detection of peri-infarction and remote ischemia, the assessment of baseline ventricular function and the identification of viable myocardium in the infarct region. Recent studies have inferred the value of dobutamine stress echocardiography in that clinical setting (5-7,10-12). Some recent observations pointed out that electrocardiographic changes during stress testing may also provide useful information on myocardial viability. We have recently shown that normalization of inverted T-waves in patients with a recent myocardial infarction during LDD infusion is a marker of myocardial viability as well as a predictor of functional improvement (12). Margonato et al. reported that exercise-induced STE is a specific marker of myocardial viability assessed by positron emission tomography (8).

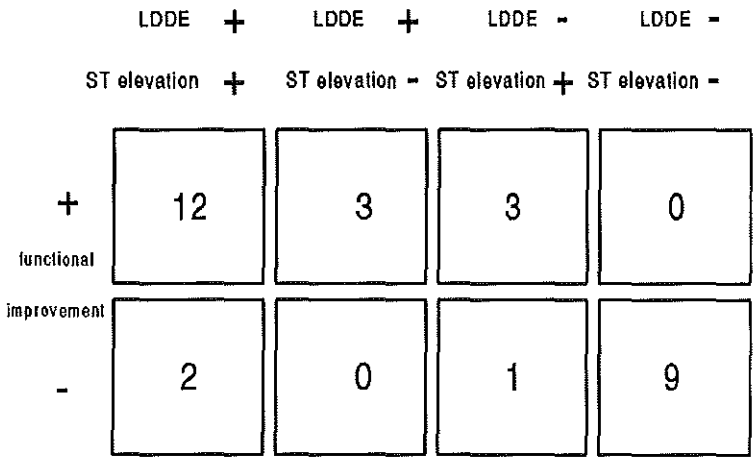

Figure 4. Distribution of late functional recovery in patients with anterior myocardial infarction in various combinations of ST-segment elevation and viability at low-dose dobutamine echo (LDDE).

Our study is the first which evaluates the relation between stress-induced STE and improvement of function after a recent myocardial infarction. The results of our study show that in patients studied 8 days after a recent Q-wave myocardial infarction, dobutamine-induced STE is associated with a higher prevalence of late functional improvement of dyssynergic segments 2-3 months after infarction as well as a higher number of improved segments compared to patients without STE. This difference was remarkable in anterior compared to inferior infarction. The accuracy of STE for the prediction of functional improvement was comparable to that of LDD echocardiography in patients with anterior infarction and in those who underwent revascularization. Despite that patients with STE had a relatively more extensive regional wall motion abnormalities, they had a higher prevalence of functional improvement. Since revascularization was performed only in 33% of patients, it can be postulated that in patients with more extensive wall motion abnormalities who developed STE, myocardial stunning was more severe and required a longer time to functional improvement (17). Consequently these patients had more extensive wall motion abnormalities 1-2 weeks after infarction and a higher rate of late functional improvement compared to patients without STE in whom myocardial stunning is presumed to be less severe and might have completely or partially resolved before DST.

The heart rate and dobutamine dose at ST-segment elevation

STE was associated with a significant increase of heart rate and occurred mostly at doses higher than 10 μg/kg/min. This is not surprising, since the heart rate does not increase significantly at LDD (7). Previous studies have shown the importance of heart rate increment for the occurrence of STE during exercise (18). In our study the mean heart rate and mean dobutamine dose at STE were not different in patients with or without functional improvement.

Table IV. Regional echocardiographic data during dobutamine stress test and follow-up in patients with inferior Q wave myocardial infarction with (group A) and without (group B) ST-segment elevation.

	Group A (N = 26)	Group B (N = 18)
Dyssynergic segments, nr	2.5 ± 1.6	2.7 ± 1.5
Resting WMS	9.4 ± 2.2	9.1 ± 1.6
LDD WMS	8.5 ± 2.4	7.9 ± 2.1
Follow-up WMS	9.0 ± 2.6	9.3 ± 2.8
Viability at LDD, pts	15 (58%)	10 (56%)
Viable segments at LDD	1.0 ± 1.1	1.0 ± 1.3
LDD viability index	38.1 ± 39.2	48.2 ± 49.1
Improvement at follow-up, pts	13 (50%)	6 (33%)
Improved segments, nr	0.9 ± 1.2	0.7 ± 1.1
Improvement index	0.32 ± 0.39	0.31 ± 0.46
Homozonal ischemia, pts	10 (38%)	5 (28%)

LDD = low-dose dobutamine echocardiography, WMS = wall motion score, pts = patients.

Prevalence of stress-induced ST-segment elevation after acute myocardial infarction

Exercise-induced STE has been reported to occur more frequently in patients with recent than with old myocardial infarction (8). The difference may be explained by a high prevalence of myocardial viability in patients with recent infarction. This viable myocardium may improve (spontaneously or after revascularization), undergo necrosis or continue as an ischemic hibernating myocardium. In the first two situations, viable myocardium will no longer exist and consequently the prevalence of STE will decrease as the infarct gets older.

This theory is supported by a previous study which has shown that the majority of recently infarcted myocardial regions retain residual metabolic activity, the extent of which was inversely related to the time elapsed from the occurrence of acute event. Exercise-induced STE was more common in patients with than without flourodeoxyglucose uptake in the underperfused regions (19).

Table V. Diagnostic accuracy (%) with 95% confidence intervals of low-dose dobutamine echocardiography and ST-segment elevation during dobutamine stress test (overall and regional) for the prediction of late improvement of left ventricular function after a recent myocardial infarction.

	SENS	SPEC	PPV	NPV	ACC
LDDE overall	83	71	74	81	77
95% C.I.	74-92	61-82	64-85	71-90	67-87
LDDE anterior	83	83	88	77	83
95% C.I.	70-97	70-97	77-100	62-92	70-97
LDDE inferior	89	68	68	89	77
95% C.I.	80-99	54-82	54-82	80-99	65-90
STE overall	74	60	65	70	67
95% C.I.	64-85	49-71	54-76	59-81	56-78
STE anterior	83	75	83	75	80
95% C.I.	70-97	60-90	70-97	60-90	66-94
STE inferior	68	48	50	67	57
95% C.I.	55-82	33-63	35-65	53-81	42-71
LDDE (revasc)	83	82	83	82	83
95% C.I.	68-99	66-98	68-99	66-98	67-98
STE (revasc)	83	73	77	80	78
95% C.I.	68-99	54-91	60-94	64-96	61-95

ACC = diagnostic accuracy; C.I. = confidence intervals; LDDE = low-dose dobutamine echocardiography; NPV = negative predictive value; PPV = positive predictive value; SENS = sensitivity; SPEC = specificity; STE = ST-segment elevation, Revasc = revascularized patients (N = 23).

Relationship between ST-segment elevation and myocardial ischemia

In our study, there was no significant difference between patients with or without STE during DST with regard to prevalence of homozonal or remote ischemia on echocardiography. We have previously shown that dobutamine-induced STE in patients with recent or old myocardial infarction is compatible but not specific for ischemia on simultaneous myocardial perfusion SPECT

imaging (20). The higher prevalence of ST-segment depression in patients with than without STE can be explained by the occurrence of reciprocal changes without true ischemia (21).

Similar findings have been reported by Coma-Canella et al. (22). They reported a poor response of regional ejection fraction in patients with recent myocardial infarction and STE during DST. These findings do not preclude myocardial viability, since imaging was performed at high dose dobutamine which may lack the sensitivity for eliciting a contractile reserve and may provoke ischemic dysfunction. Furthermore, radionuclide angiography is not the method of choice for the assessment of regional function due to the limited tomographic views and inability to assess myocardial thickening.

Many other authors have reported that exercise induced STE is not specific for ischemia in patients with myocardial infarction (18, 23,24). In contrast, Shimonagata et al.(25) and Margonato et al.(26) reported that exercise-induced STE after a recent myocardial infarction is specific for ischemia on thallium scintigraphy.

Exercise-induced ST-segment elevation as a marker of viability

Margonato et al. (8) reported that exercise-induced STE in patients with previous myocardial infarction is highly specific for viability assessed by positron emission tomography. The accuracy of STE was higher in anterior versus inferior infarction. However, there are some limitations of that study including the heterogeneity of population with respect to the time from infarction. Myocardial regions of interest were defined as those with perfusion defects on rest sestamibi SPECT. This approach does not consider dyssynergic segments with normal perfusion. These segments are likely to be viable and if included, the prevalence of viable myocardium may increase in patients without STE who had less severe coronary stenosis and possibly normal perfusion in dyssynergic segments at rest. The low accuracy of STE in inferior versus anterior infarction in our study and in the study of Margonato et al. (8) may be explained by the need of a critical mass of dyssynergic myocardium for the occurrence of STE which is more available in anterior compared to inferior infarction. The similar accuracy of LDD echocardiography and STE for the prediction of functional recovery in patients with revascularization in our study may be related to the relatively higher prevalence of anterior infarction in the latter group.

Mechanism of ST-segment elevation

STE was believed to result from an electric gradient created between normal and ischemic or necrotic myocardium that can be aggravated by exercise (23). It may be postulated that in patients with viable myocardium, sympathetic stimulation as occurs during exercise or dobutamine infusion creates heterogeneity of contraction in the infarct zone between the viable segments that

improve and the non-viable segments that do not improve or move paradoxically. This heterogeneity of contraction may be the underlying mechanism of STE in patients with viable myocardium.

Limitations of the study: The anatomy of infarct related artery was not delineated in all patients. The majority of patients did not undergo a revascularization procedure. It can not be excluded that some of the persistently dyssynergic segments may improve after revascularization. However, there was no rationale to catheterize asymptomatic patients with uncomplicated clinical course. Late functional improvement was spontaneous in most of patients consistent with myocardial stunning. The value of dobutamine-induced STE in the setting of myocardial hibernation has to be expanded in a large number of patients. It is to be noted that in patients with recent myocardial infarction, improvement of function after early revascularization does not rule out myocardial stunning as a mechanism of reversible dysfunction since we have previously shown that about one third of dyssynergic segments detected at a mean of 1 week from the onset of infarction recover spontaneously after 3 months (7).

Clinical implications: In patients with recent myocardial infarction undergoing pre-discharge high-dose DST, STE in Q leads during the test occurs in patients with a higher prevalence of viable myocardium identified at LDD echocardiography and a higher prevalence and extent of late functional improvement than patients without STE. The accuracy of STE for the prediction of functional improvement is comparable to that of LDD echocardiography in patients with anterior infarction and in those with myocardial revascularization. Although some authors discourage the use of electrocardiographic recording during dobutamine stress echocardiography (27), we recommend that more attention should be given for the proper positioning of electrocardiographic leads and obtaining high quality tracings, particularly when the test is performed without or with suboptimal echocardiographic imaging.

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CHAPTER 18

STRESS-INDUCED ST-SEGMENT ELEVATION AFTER A RECENT MYOCARDIAL INFARCTION: MYOCARDIAL NECROSIS, VIABILITY OR BOTH?[1]

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INTRODUCTION

The assessment of residual myocardial ischemia and viability is important for the management of patients after acute myocardial infarction. Recent data have inferred the value of dobutamine stress echocardiography for that purpose (1,2). ST-segment elevation is frequently induced by dobutamine or exercise stress testing in these patients. Therefore, it is important to evaluate the functional significance of this electrocardiographic finding and its relation to the presence of jeopardized myocardium in the infarct region.

Relationship between stress-induced ST-segment elevation and myocardial ischemia

While available data agree on the specificity of stress-induced ST-segment elevation for ischemia in patients without previous myocardial infarction (3,4), the significance of this findings in patients with myocardial infarction is controversial (4-8). Margonato et al. (7) found reversible defects on exercise thallium scintigraphy in 16 of 17 patients with exercise-induced ST-segment elevation after acute myocardial infarction. However, there was no control group without ST-segment elevation to exclude that the high predictive value of ST-segment elevation for ischemia is related to the selection of patients with high likelihood of manifesting peri-infarction ischemia. Fox et al. (8) reported that in patients with myocardial infarction, exercise-induced ST-segment elevation could by abolished in 11 patients after coronary artery bypass grafting even in absence of improvement of global left ventricular function after surgery suggesting that ST-segment elevation was related to myocardial ischemia.

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[1] *Eur Heart J; in press.*

In contrast, Elhendy et al. (4) reported a specificity of ST-segment elevation during dobutamine stress test of 56% and 50% for myocardial ischemia assessed by myocardial perfusion scintigraphy and echocardiography respectively in 34 patients with recent myocardial infarction. Similarly, Lanzarini et al. (5) reported a specificity of 50% of ST-segment elevation for myocardial ischemia assessed by echocardiography in 42 patients. In these 2 studies, the prevalence of ischemia was not different with or without ST-segment elevation, whereas patients with ST-segment elevation had more severe resting left ventricular dysfunction. Similar findings were reported by Coma-Canella et al. (6) in 88 patients with recent myocardial infarction undergoing dobutamine thallium scintigraphy.

The apparently discordant conclusions regarding the significance of stress-induced ST-segment elevation in patients with previous myocardial infarction may reflect differences in patient population or methodological deficiencies. Most of the clinical studies which investigate the significance of ST-segment elevation are performed in patients with high pretest likelihood of manifesting inducible ischemia, a finding that may damp a significant difference in the prevalence of homozonal ischemia between patients with or without ST-segment elevation. Despite the reasonable overall sensitivity of the currently used methods for the assessment of ischemia, mainly echocardiography and perfusion scintigraphy, the sensitivity for detecting ischemia in individual vascular territories is not actually high. In a study by Marwick et al., (9) the sensitivity of dobutamine MIBI SPECT and echocardiography in patients with single vessel disease ranged between 62 and 76% in different vascular territories. Sensitivity for individual vessel stenosis may be further reduced in presence of multivessel disease due to different ischemic threshold and in the presence of resting wall motion and perfusion abnormalities, almost always encountered in patients with ST-segment elevation in the peri-infarction leads (4). This contention is supported by the high predictive value of ST-segment elevation for significant, mostly severe stenosis of the related coronary artery as shown in different studies (4-7). Despite that resting wall motion abnormalities are more severe in patients with ST-segment elevation, these abnormalities seldom involve the entire vascular territory particularly in the LAD related infarction, a findings that heralds a high prevalence of jeopardized myocardium. Animal studies have shown that acute ischemia adjacent to a chronic infarction induces ST-segment elevation at the surface of the scar despite the virtual absence of viable tissue within the infarction, suggesting a passive ST-segment potential transmission through the infarction (10). Whether the absence of inducible ischemia on the standard techniques denotes the absence of functional significance of coronary stenosis, or underestimation of dysfunction, cannot be determined due to the lack of golden standard in the peri-infarction area.

Relationship between ST-segment elevation and myocardial viability

In the study of Lanzarini et al. (5), the prevalence of myocardial viability pattern at low-dose dobutamine was not different with or without ST-segment elevation (1). Conversely, Margonato et al. (11) reported that in 34 patients with previous myocardial infarction, myocardial viability assessed by positron emission tomography was more frequently encountered in patients with than without exercise-induced ST-segment elevation. In 21 patients with anterior myocardial infarction, the sensitivity, specificity and accuracy of exercise-induced ST-segment elevation for detection of residual viability were 82%, 100% and 86% respectively. The difference in the methods and patient population may again play a role in these controversial conclusions. Despite the similar prevalence of viability pattern found by Lanzarini et al. with or without ST-segment elevation, myocardial viability was highly prevalent with ST-segment elevation (87%). If ST-segment elevation reflects myocardial viability, a more sensitive technique, like positron emission tomography may further detect viability in the remaining 13% of patients. As we have previously shown (1), the sensitivity of low-dose dobutamine echocardiography in the detection of stunned myocardium after a recent myocardial infarction is relatively low in akinetic segments. Furthermore, the presence of more extensive akinesis as in patients with ST-segment elevation may hinder the development of systolic thickening at low-dose dobutamine by tethering of a necrotic segment on the adjacent akinetic but viable segments. Additionally, it cannot be excluded that in presence of severe coronary stenosis as in case of patients with ST-segment elevation, ischemia may develop at low-dose dobutamine preventing the occurrence of a contractile response in dyssynergic segments.

The relation between exercise-induced ST-segment elevation and myocardial viability reported by Margonato et al. is supported by their previous study (12) in which they found that the majority of recently infarcted myocardial regions retain residual metabolic activity, the extent of which was inversely related to the time elapsed from the occurrence of acute event. Exercise-induced ST-segment elevation was more common in patients with than without flourodeoxyglucose uptake in the underperfused regions (12). However, exclusion of dyssynergic segments with normal perfusion in that study (11) may underestimate myocardial viability in patients without ST-segment elevation who had less severe coronary stenosis and are likely to have normal resting myocardial perfusion in dyssynergic segments. Myocardial stunning may represent the underlying pathophysiology of ST-segment elevation after myocardial infarction. Resolution of myocardial stunning may be a factor contributing to the lower prevalence of ST-segment elevation in patients with old infarction (11). In this situation, the presence of myocardial viability in dyssynergic regions with ST-segment elevation in the related leads may represent myocardial viability without ischemia.

Coma-Canella et al. (6) reported an inverse linear correlation between ST-segment elevation and increase of regional ejection fraction assessed by dobutamine radionuclide angiography after a recent myocardial infarction. This finding cannot preclude the presence of myocardial viability in regions corresponding to ST-segment elevation because imaging was acquired at high dose dobutamine, which may be insensitive for eliciting contractile reserve in viable segments and may induce ischemic dysfunction. Furthermore, radionuclide angiography cannot assess regional myocardial thickening which is required for the diagnosis of myocardial viability.

While the previous studies aimed at the assessment of the relation between ST-segment elevation and myocardial viability (5,11), these studies are limited by the small number of patients included and inability to assess the prevalence and extent of spontaneous or post-revascularization improvement of left ventricular function with or without ST-segment elevation, which is more clinically relevant than a correlative study with markers of viability.

SUMMARY AND CONCLUSIONS

Stress-induced ST-segment elevation after acute myocardial infarction cannot identify patients with a higher prevalence of peri-infarction ischemia based on reversible wall motion or perfusion abnormalities. Whether this finding reflects poor sensitivity and specificity of ST-segment elevation for ischemia or methodological problems in the selection of patients or the techniques of assessment of peri-infarction ischemia cannot be precisely concluded. Because of the high prevalence of severe coronary stenosis in patients with ST-segment elevation, a large prospective study before and after revascularization would help in a better understanding of its significance. Despite the high prevalence of viability pattern in patients with ST-segment elevation after a recent myocardial infarction, the relationship between this pattern and late functional improvement has not been evaluated. Therefore, a large study is needed to assess the prevalence and extent of late improvement of left ventricular function in patients with or without stress-induced ST-segment elevation after acute myocardial infarction.

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CHAPTER 19

AKINESIS BECOMING DYSKINESIS DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY: A PREDICTOR OF POOR FUNCTIONAL RECOVERY AFTER SURGICAL REVASCULARIZATION[1]

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ABSTRACT

Background. Akinesis becoming dyskinesis at high dose dobutamine stress echocardiography (DSE) has been disregarded as a marker of myocardial ischemia. However, the relationship between this pattern and myocardial viability has not been assessed.

Methods. We studied 42 patients with myocardial infarction who underwent DSE (up to 40 μg/kg/min) before coronary artery bypass surgery, and resting echocardiogram 3 months after surgery. Viability in akinetic segments was considered if systolic thickening occurred at low-dose dobutamine (LDD).

Results. During high dose DSE, dyskinesis occurred in 35 of the 164 akinetic segments (group A). The remaining 129 segments comprised group B. Segments of group B had a higher prevalence of viability pattern at LDD (18% vs 0%, $p<0.01$) and a higher prevalence of functional improvement (20% vs 0%, $p<0.005$) compared to group A. In absence of viability pattern at LDD, postoperative improvement occurred in 10% of segments in group B and in none of segments in group A, resulting in a higher negative predictive value of LDD in group A versus B (100% vs 90%, $p<0.05$).

Conclusion. The phenomenon of akinesis becoming dyskinesis at high dose DSE is associated with absence of viability pattern at LDD and poor functional outcome after surgical revascularization. Observation of this pattern provides additional data to those obtained only at LDD echocardiography.

Key words: Dobutamine stress echocardiography - Myocardial viability - coronary artery bypass surgery.

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INTRODUCTION

In patients with coronary artery disease and left ventricular dysfunction, the detection of myocardial viability is important for the proper identification of patients in whom left ventricular function may improve after revascularization (1,2). Recent studies have demonstrated the value of dobutamine stress echocardiography for the detection of myocardial viability at low-dose (2,3) and ischemia at high dose (4,5). We have recently reported that akinetic segments at baseline echocardiogram, developing dyskinesis at high dose dobutamine, without improvement at low-dose dobutamine (LDD) represent a mechanical phenomenon unrelated to myocardial ischemia assessed by simultaneous perfusion scintigraphy (6). However, the relationship between this pattern and functional improvement after revascularization has not been studied. Therefore, the aims of this study were: 1) to assess the relationship between the pattern of akinesis becoming dyskinesis at high dose dobutamine stress echocardiography and functional improvement after surgical revascularization. 2) to find if observation of this phenomenon improves the value of LDD echocardiography for the prediction of postoperative functional improvement.

METHODS

Study population

Study population comprised 42 patients with coronary artery disease and left ventricular dysfunction, undergoing coronary artery bypass surgery who fulfilled the study inclusion criteria:

- history of previous (> 3 months old) myocardial infarction.
- two or more akinetic segments on preoperative resting echocardiography.
- Absence of unstable angina, severe heart failure, or significant valvular disease.
- Absence of perioperative myocardial infarction. Mean age was 59 $\pm$ 9 years. There were 33 males and 9 females. Thirty nine patients had typical angina and 9 patients had exertional dyspnea before the test. Single vessel disease, defined as diameter stenosis of a major coronary artery >50%, was present in 6 patients, 2 vessel disease in 15 patients and 3 vessel disease in 21 patients. The mean ejection fraction determined by angiography was 39 $\pm$ 14%. Thirty nine patients were receiving antianginal therapy. In patients receiving beta blocking agents, the latter were withdrawn 2 days before stress testing.

Dobutamine stress test

The test was performed according to a previously described protocol (2). Dobutamine was infused through an antecubital vein starting at a dose of 5 μg/kg/min for 3 minutes, 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age predicted maximal heart rate (7). The electrocardiogram was monitored throughout dobutamine

infusion and recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted prematurely if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test.

Stress echocardiography

As previously described (2), the echocardiogram in standard views was performed and recorded on video tape at rest and during stress. Rest, low-dose and peak stress images were also digitized and stored on an optical disk (Vingmed CFM 800) for a display in quad-screen format. Left ventricular function was assessed using a 16-segment model. Both inward endocardial motion and myocardial thickening were considered for analysis. Each segment was graded with a 4-point score grading (1 = normal or hyperkinesis; 2 = hypokinesis; 3 = akinesis 4 = dyskinesis). Akinesis was considered in the absence of systolic wall motion and thickening. Dyskinesis was defined as absence of systolic thickening with outward bulging away from the center of left ventricular cavity in systole. To reduce the confounding effect of tethering, segmental wall thickening was analyzed frame by frame during the first half of systole. Wall motion score index was derived by dividing the summation of the 16 segments by 16. Viability in akinetic segments was considered if myocardial thickening was observed during LDD infusion (5-10 μg/kg/min). Ischemia was defined as the appearance of new wall motion abnormalities or worsening of a hypokinetic segment. 2 experienced investigators assessed the images. In case of disagreement, a third investigator viewed the images and a majority decision was achieved. We have previously reported a good inter- and intra-observer agreement on the assessment of rest and stress echocardiographic images in our laboratory (2,8).

Follow-up studies

A rest echocardiogram was performed in all patients, 3 months after surgery. An improvement of akinetic segments was considered if systolic thickening occurs postoperatively. Absence of improvement was considered in case of surgical excision of the segment or absence of systolic thickening at follow-up. Myocardial segments which were not revascularized were not included in analysis.

Statistical analysis

Continuous data are expressed as mean $\pm$ standard deviation. Univariate analysis for categorial variables was performed using the chi-square test with Yate's correction or Fisher's exact test. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. Sensitivity, specificity and positive and negative predictive values were based upon their standard definitions and are reported with the corresponding 95%

confidence intervals (C.I.).

RESULTS

Dobutamine stress test

Heart rate increased from 71 ± 12 at rest to 139 ± 13 beats /min at peak stress ($p < 0.001$) and rate pressure product from 9112 ± 2744 to 16776 ± 4126 ($p < 0.001$). Rate pressure product did not change significantly at LDD (10 μg/kg/min). Angina occurred in 29 patients (59%). In 10 patients (24%), the test was interrupted prematurely before reaching the maximal dose or the target heart rate. Reasons for premature termination of the test were angina (3 patients), ST-segment depression (1 patient) and hypotension (6 patients).

Low-dose dobutamine echocardiography

Wall motion score index decreased significantly from rest to LDD (1.82 ± 0.4 to 1.57 ± 0.38, $p < 0.01$). Among 164 akinetic segments at baseline echocardiogram which were revascularized, improvement at LDD was observed in 23 segments (14%).

Table 1. Diagnostic accuracy of low-dose dobutamine echocardiography for the prediction of functional improvement of akinetic segments after surgical revascularization.

	SENS	SPEC	PPV	NPV	ACC
%	58	94	65	92	88
95% C.I.	50-65	91-98	58-73	88-96	83-93

ACC = diagnostic accuracy; C.I. = confidence intervals; NPV = negative predictive value; PPV = positive predictive value; SENS = sensitivity; SPEC = specificity.

High dose dobutamine echocardiography

Ischemia (new or worsened wall motion abnormalities) was detected in 38 patients (90%). Dyskinesis a peak stress developed in 35 of the 164 akinetic segments (group A). This pattern was observed in 12 patients. The remaining 129 akinetic segments constituted group B. Systolic thickening at LDD was observed in 23 segments of group B (18%) and in none of segments in group A ($p < < 0.01$). There was no significant difference between both groups with regard to the corresponding rate pressure product at rest, LDD or peak stress. Baseline wall motion score index was not different between patients with or without akinesis becoming dyskinesis in one or more segments (1.84 ± 0.41 vs 1.81 ± 0.40 respectively).

Postoperative results

A significant improvement of symptoms occurred after surgery. At follow up echocardiography, improvement occurred in 26 of the 164 akinetic segments (16%). Improvement occurred in 26 segments in group B (20%) and none of segments in group A ($P < 0.005$). Eight segments in group A (23%) and 12 segments in group B (9%) were excised due to the presence of gross pathology identified during surgery ($p < 0.05$). Functional improvement occurred in 15 of 23 segments with and in 11 of 141 segments without viability pattern at LDD echocardiography. The sensitivity, specificity, predictive value and accuracy of low dose dobutamine echocardiography for the prediction of postoperative functional improvement in akinetic segments are shown in table 1. The negative predictive value was significantly higher in group B compared to group A (100% vs 90%, $p < 0.05$; figure 1).

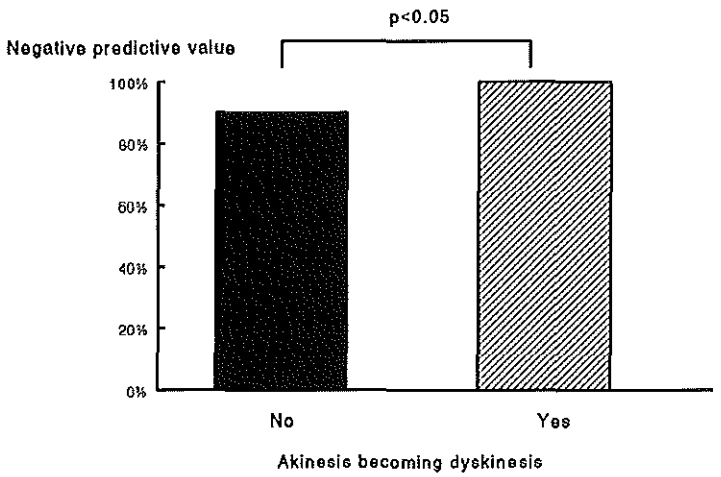

Figure 1. Figure 1. The negative predictive value of low dose dobutamine echocardiography for postoperative functional improvement in akinetic segments with and without dyskinesis at high dose dobutamine.

Coronary angiography

Coronary angiography was performed in 15 patients (5 patients with and 10 patients without akinesis becoming dyskinesis) after surgery and revealed patency of grafts to analyzed segments in all patients.

DISCUSSION

In symptomatic patients with coronary artery disease and left ventricular dysfunction, myocardial revascularization aims at improvement of baseline

function, amelioration of symptoms, and improvement of prognosis (9). For that reason, the non invasive assessment of myocardial viability and ischemia before revascularization is important for the selection of patients who will benefit from the procedure. Dobutamine stress echocardiography is increasingly used for the functional assessment of patients with ischemic left ventricular dysfunction (2-5). The diagnosis of myocardial viability relies upon the occurrence of a contractile response of dyssynergic segments during LDD infusion (2,3). Myocardial ischemia is considered when new or worsening of wall motion abnormalities occur during the test (4,5,7). We have previously reported that akinetic segments which do not respond to LDD meanwhile develop dyskinesis at high dose are associated with absence of perfusion scintigraphic evidence of ischemia (6). In the previous study, we could not identify any segment showing the pattern of akinesis becoming dyskinesis with improvement at LDD. Consequently, the question remains whether this pattern is compatible with the presence of myocardial viability or not and awaits extension of the previous study. Furthermore, the detection of reversible perfusion defects in presence of severe resting hypoperfusion represent a technical challenge (10). Therefore, we assessed, in a new series of patients, the relationship between the pattern of akinesis becoming dyskinesis and myocardial viability at LDD and we studied the more relevant issue of post revascularization outcome of these segments.

Our data show that in symptomatic patients with coronary artery disease, the phenomenon of akinesis becoming dyskinesis at high dose dobutamine stress test is consistently associated with absence of viability pattern at LDD as well as absence of functional improvement after surgical revascularization. Some of these segments were excised due to gross pathology identified at surgery and the remaining segments failed to exhibit systolic thickening 3 months after surgery. Furthermore, the observation of this pattern at high dose gave additional information to those obtained only at LDD. In absence of this pattern, 10% of akinetic segments identified at LDD as non viable showed functional improvement after surgery. Thus the negative predictive value of dobutamine stress echocardiography for postoperative improvement was significantly higher in association with this pattern (100% vs 90%).

The steady increase of myocardial contractility in normal segments (11,12), and possibly in viable dyssynergic segments during dobutamine infusion may cause flappy akinetic segments with severe necrosis to bulg paradoxically in systole. Therefore, akinetic segments showing this pattern failed to demonstrate systolic thickening at LDD or after revascularization. Despite that myocardial ischemia is considered when a normal or hypokinetic segment at rest become dyskinetic at peak stress, this condition did not seem to apply to akinetic segments. It can be postulated that dyskinesis developing in a normal or hypokinetic segment represents severe ischemia, which in turn requires a substantial mass of preserved myocardium that may not be available in akinetic

segments.

We have previously reported the value of LDD echocardiography for the prediction of recovery of regional function after recent myocardial infarction (3) and after coronary artery bypass surgery in patients with chronic left ventricular dysfunction (2). The results of this study demonstrate an additional value of observation of worsening of akinetic segments at high dose dobutamine for the prediction of functional recovery.

Limitations of the study

Coronary angiography was performed only in 36% of patients after surgery. However, in all of these patients, sustained patency of the grafts to the analyzed segments was demonstrated. Additionally, symptomatic improvement occurred in all patients after surgery denoting successful revascularization.

Summary and conclusion

In symptomatic patients with coronary artery disease and left ventricular dysfunction, the phenomenon of akinesis becoming dyskinesis at high dose dobutamine stress test is associated with absence of viability pattern at LDD echocardiography and lack of functional improvement after surgical revascularization. Observation of this pattern at high dose provides additional data to those obtained at LDD and improves the negative predictive value of dobutamine stress echocardiography for postoperative functional improvement of akinetic segments.

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CHAPTER 20

THE EFFECT OF SEVERITY OF CORONARY ARTERY STENOSIS AND THE COLLATERAL CIRCULATION ON THE FUNCTIONAL OUTCOME OF DYSSYNERGIC MYOCARDIUM AFTER REVASCULARIZATION IN PATIENTS WITH CHRONIC LEFT VENTRICULAR DYSFUNCTION[1]

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ABSTRACT

Background. Patency of the infarct related artery and the presence of high grade collateral circulation have been associated with more myocardial preservation early after acute myocardial infarction. However, the influence of these angiographic parameters on the extent of functional improvement of dyssynergic myocardium after revascularization in patients with chronic left ventricular dysfunction has not yet been evaluated. Therefore, we assessed the influence of these parameters on myocardial viability in patients with chronic left ventricular dysfunction undergoing dobutamine stress echocardiography before elective coronary artery bypass grafting.

Methods. Forty patients (mean age $=59 \pm 8$ years, 30 males) with old myocardial infarction and coronary artery stenosis ($\geq 50\%$ diameter stenosis) subtending severely dyssynergic segments were studied by dobutamine stress echocardiography before coronary artery bypass grafting. Left ventricular function was assessed using a 16 segments-5 grade score model. Viability was defined as improvement of thickening of severely dyssynergic segments at low-dose dobutamine. Functional recovery was defined as improvement of thickening at echocardiography obtained 3 months after surgery.

Results. There were 56 stenotic coronary arteries subtending severely dyssynergic myocardial segments, of which 38 were occluded. Among 186 severely dyssynergic segments postoperative functional recovery occurred in 42 (23%). There was no significant difference between myocardial regions with patent or occluded coronary arteries with respect to prevalence of viability or

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functional recovery, number of viable or recovered segments, and percentage of viable or recovered segments relative to the total number of dyssynergic segments in the same region. In patients with total occlusion, the previous parameters were not different between regions with different grades of collateral circulation. Sensitivity, specificity and accuracy of low dose dobutamine echocardiography for predicting postoperative functional improvement of severely dyssynergic segments were 71% (CI. 65-78), 90% (CI. 86-95) and 86% (CI. 81-91) respectively.
Conclusion. In patients with chronic left ventricular dysfunction following myocardial infarction, the presence of total occlusion of coronary arteries supplying severely dyssynergic regions does not imply a lower prevalence or extent of functional recovery following revascularization regardless of the grade of angiographically visualised collateral circulation. The benefit of revascularization of these segments is equivalent to that of segments with patent coronary arteries. Independent on the severity of coronary stenosis in these patients, noninvasive evaluation of myocardial viability using techniques like low-dose dobutamine echocardiography is required to identify myocardial regions with high probability of functional improvement following revascularization.

Key Words: Myocardial viability. Dobutamine stress echocardiography. Coronary artery bypass grafting.

INTRODUCTION

Previous studies have demonstrated the value of coronary artery bypass grafting in amelioration of symptoms, improvement of left ventricular function and prolongation of survival in patients with chronic ischemic left ventricular dysfunction (1,2). The assessment of myocardial viability is important to predict the occurrence of functional improvement of dyssynergic segments after revascularization (3,4). The clinical utility of various techniques in this clinical setting has been established. These include positron emission tomographic assessment of myocardial perfusion and metabolism, 201-thallium myocardial perfusion scintigraphy and low-dose dobutamine echocardiography (2-4). Few studies have been addressed to a assess the relationship between coronary angiographic findings and myocardial viability in severely dyssynergic regions in patients with chronic left ventricular dysfunction (5,6). The value of angiographically visualised collateral vessels to occluded coronary arteries in maintaining myocardial viability in the related dyssynergic segments is controversial (5,6). Furthermore, angiographic findings have been correlated with metabolic markers of viability without studying the impact on functional outcome of dyssynergic segments after revascularization, which is the ultimate target of the identification of viable myocardium. Therefore, the aim of this study was to assess the relationship between the severity of coronary artery

stenosis in patients with chronic left ventricular dysfunction and myocardial viability at low-dose dobutamine echocardiography and to determine the impact of the severity of coronary stenosis and collateral circulation in occluded coronary arteries on the prevalence and magnitude of functional improvement of dyssynergic segments following revascularization.

METHODS

Study patients: The study population was derived from a consecutive series of patients with left ventricular dysfunction and significant coronary artery stenosis who underwent dobutamine stress echocardiography for the diagnosis of myocardial ischemia and viability before coronary artery bypass grafting. Patients were included if they fulfilled the following criteria: 1) the presence of proximal or mid coronary artery stenosis ($\geq 50\%$ luminal diameter stenosis) of ≥ 1 major coronary artery subtending a myocardial region with akinesis or severe hypokinesis on resting echocardiogram. 2) coronary artery bypass grafting of arteries supplying the dyssynergic regions within 1 month after dobutamine stress test without concomitant myocardial resection. 3) absence of perioperative infarction. Forty patients fulfilled these criteria and all gave an informed consent to undergo dobutamine stress echocardiography before and after surgery. There were 30 males and 10 females. Mean age was 59 $\pm$ 8 years. Symptoms before surgery included angina in 37 patients and dyspnea in 8 patients. Beta blocking agents were stopped 2 days before dobutamine stress test. Medications at the day of the test included calcium chancel blockers in 20 patients, nitrates in 29 patients and angiotensin converting enzyme inhibitors in 24 patients. All patients had previous myocardial infarction diagnosed by the standard criteria of chest pain, diagnostic rise of cardiac enzymes and serial electrocardiographic changes. The mean time from the infarction was 4 $\pm$ 5.3 years (range 6 months to 25 years). The infarction was anterior (or anterolateral) in 19 patients, inferior (or infero-posterolateral) in 12 patients and in both locations in 9 patients.

Dobutamine stress test: Dobutamine was infused through an antecubital vein starting at a dose of 5 followed by 10 μg/kg/min (3 minutes stages), increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age predicted maximal heart rate at the maximal dobutamine dose. The ECG was monitored throughout dobutamine infusion and was recorded each minute. Cuff blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia or systolic blood pressure fall of >40 mm Hg occurred during the test.

Stress echocardiography: Echocardiographic images were acquired at rest and

during stress and recovery. The echocardiograms were recorded on video tapes and were also digitized on optical disk and displayed side by side in quad-screen format (Vingmed CFM 800) to facilitate the comparison of rest, low-dose and maximal stress images. Left ventricular wall was divided into 16 segments and scored using a 5-point scale, where 1=normal, 2=mild hypokinesis, 3= severe hypokinesis, 4 = akinesis, 5 = dyskinesis (4). The interpretation of images was performed by 2 experienced observers without the knowledge of the patients' angiographic data. In case of disagreement, a majority decision was achieved by a third reviewer. In our laboratory, inter-and intra-observer agreement for stress echocardiographic assessment are 92% and 94% respectively (7). Both wall motion and thickening were considered for analysis. The diagnosis of ischemia was based on the occurrence of new or worsening wall motion abnormalities in one or more segments. As previously reported, ischemia was not considered when akinetic segments at rest became dyskinetic without improvement at low-dose (8). Myocardial viability in akinetic or severely hypokinetic segments was considered as ≥ 1 decrease of wall motion score during low-dose dobutamine (5-10 μg/kg/min).

Follow-up studies: A rest echocardiogram was performed in all patients, 3 months after surgery. The echocardiographic images were stored on the same optical disk used for the preoperative study. The resting pre and postoperative images were visualized side-by-side in a quad-screen format allowing a proper assessment of segmental changes. An improvement of akinetic or severely hypokinetic segments was considered as a reduction of wall motion score ≥ 1. At the day of performing the follow-up echocardiograms, dobutamine stress echocardiography was repeated in 28 patients, using the previously described method. The remaining 12 patients did not agree to undergo dobutamine stress test.

Coronary angiography: Coronary angiography was performed, using the Judkins technique, within 1 month in all patients. Coronary stenosis was quantified using a previously described method from our center (9). All 35-mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical). Measurements were performed from end-diastolic frames with optimal vessel opacification. For edge detection, a region of interest of 512 x 512 pixels was selected and digitized using a high fidelity charge coupled device video camera. The lumen edges were detected on the basis of the weighted sum of the first and second derivative function of the brightness profile of each scan line perpendicular to the vessel centerline. The vessel diameter function was determined by computing the shortest distance between the right and left contours. Calibration of these measurements to absolute values was achieved by using a catheter tip as a scaling device. A computer derived estimation of the original arterial dimension at the site of obstruction was used to calculate the

interpolated reference diameter. This technique is based on a computer derived estimation of original values over the analyses region. The calculation is based on a first degree polynomial computed through the diameter values of the proximal and distal portion of the arterial segment, followed by a translation to the 80th percentile level. Significant coronary artery disease was defined as a diameter stenosis $\geq 50\%$. Collateral channels to completely occluded coronary arteries were assessed by observing the degree of opacification distal to the occlusion and was graded using the TIMI classification (5,10): Grade 1: absent filling to the distal vessel, grade 2: minimal, in case of faint opacification of the distal vessel or visualisation of a small vessel, grade 3: well developed collaterals with visualization and dense opacification of the entire distal vessel. Coronary arteries were assigned to particular myocardial segments as previously described (11). 2 experienced observers who were unaware of the results of dobutamine stress test reviewed the angiograms. In case of disagreement, a consensus was reached by a third observer. For stenotic coronary arteries subtending severely dyssynergic regions, the following regional echocardiographic parameters were studied in the corresponding area: wall motion score index (derived by dividing the summation of the score of individual segments in the related region by the total umber of segments subtended by the related artery), prevalence of ischemia, prevalence of viability in severely dyssynergic segments at low dose dobutamine, viability index (derived by dividing the number of severely dyssynergic segments with improvement at low-dose dobutamine by the total number of severely dyssynergic segments in the same region), prevalence of functional recovery of severely dyssynergic segments after surgery and recovery index (derived by dividing the number of recovered segments by the total number of severely dyssynergic segments in the same region).

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. The Student *t* test was used for analysis of continuous data. A $p < 0.05$ was considered statistically significant. Sensitivity, specificity, predictive value and accuracy were derived according to standard definition and presented with their corresponding 95% confidence interval (CI).

RESULTS

Coronary angiography: There were 56 arteries supplying severely dyssynergic myocardial regions. The involved arteries were: the left anterior descending (28 territories), left circumflex (11 territories) and the right coronary artery (17 territories). Of these arteries, 38 (68%) were occluded. Coronary collaterals grade 1 were observed in 7 arteries (18%), grade 2 in 10 arteries (26%) and grade 3 in 21 arteries (55%). Eighteen arteries were patent with a diameter stenosis $\geq 50\%$ (mean of $65 \pm 8\%$). Of the 40 patients, 7 had single vessel

disease (18%), 13 had 2 vessel disease (33%) and 20 (50%) had 3 vessel disease.The angiographic ejection fraction in the whole population was 41 ± 13%.

Hemodynamics: Dobutamine stress test was performed without serious complications in any patient. Heart rate increase significantly from rest to peak stress (72 ± 13 vs 141 ± 15 beats/min, $p<0.0001$); whereas systolic blood pressure did not change significantly (126 ± 23 vs 122 ± 25 mm Hg). Angina occurred in 28 patients (70%) and ST-segment depression in 15 patients (38%).

Dobutamine stress echocardiography: At baseline, a total of 186 severely dyssynergic segments were detected in the 56 coronary artery regions. The mean number of severely dyssynergic segments per region was 3.3 ± 2.3 (range = 2 - 9 segments). Systolic thickening at low dose dobutamine occurred in 25 of 134 akinetic segments (19%) and improved in 19 of 52 severely hypokinetic segments (37%, $p = 0.01$). The viability pattern was observed in 21 of the 56 vascular territories (38%) in 17 of the 40 patients (43%). In the entire population, wall motion score index decreased significantly from rest to low dose dobutamine (1.96 ± 0.37 vs 1.7 ± 0.35, $p<0.001$) and increased significantly at high dose (2.24 ± 0.37, $p<0.0001$ vs resting value). Ischemia was detected in 27 of the 56 vascular territories (48%).

Table 1. Diagnostic accuracy of low-dose dobutamine echocardiography for the prediction of functional recovery of severely dyssynergic segments after coronary artery bypass grafting.

	SENS	SPEC	PPV	NPV	ACC
%	71	90	68	92	86
95% C.I.	65-78	86-95	61-75	88-96	81-91

ACC = diagnostic accuracy; C.I. = confidence intervals; NPV = negative predictive value; PPV = positive predictive value; SENS = sensitivity; SPEC = specificity.

Follow-up data: Symptoms of angina improved in all patients after revascularization. Regional improvement of ventricular function occurred in 42 of the 186 severely dyssynergic segments (23%). This was more frequent in severely hypokinetic compared to akinetic segments: 18/52 (35%) vs 24/134 (18%), $p = 0.01$. Improvement occurred in 25 vascular territories (45%) in 21 patients (53%). The distribution of viability pattern at low-dose dobutamine echocardiography and functional improvement of severely dyssynergic segments after revascularization is shown in figure 1. Sensitivity, specificity, predictive

value and accuracy of low-dose dobutamine stress echocardiography in the prediction of post-revascularization improvement of severely dyssynergic segments are given in table 1. In 28 patients who underwent high dose dobutamine echocardiography after surgery, angina occurred only in 2 patients. No patient developed ischemia at high dose dobutamine echocardiography in the studied vascular territories. Coronary angiography was performed in 13 patients (33%) after surgery and revealed no significant graft stenosis in the studied regions in all patients.

Table 2. Regional echocardiographic data in myocardial areas with severe dyssynergy in presence of occlusion or patency of the related coronary artery.

	Occluded arteries (N = 38)	Patent arteries (N = 18)	p value
WMSI at rest	2.74 ± 0.39	2.72 ± 0.39	0.9
WMSI at low-dose dobutamine	2.51 ± 0.46	2.49 ± 0.44	0.8
WMSI at peak stress	2.96 ± 0.45	2.89 ± 0.43	0.6
Nr of dyssynergic segments	3.4 ± 2.4	3.1 ± 2.2	0.9
Prevalence of viability	14 (37%)	7 (39%)	0.9
Number of viable segments	0.73 ± 1.19	0.87 ± 1.42	0.8
Viability index	0.26 ± 0.39	0.24 ± 0.30	0.8
Prevalence of ischemia	17 (45%)	10 (56%)	0.5
Functional recovery	16 (42%)	9 (50%)	0.6
Number of recovered segments	0.71 ± 1	0.78 ± 0.9	0.8
Recovery index	0.24 ± 0.35	0.28 ± 0.37	0.9

WMSI = wall motion score index.

The effect of coronary artery patency on myocardial viability and functional outcome.

There was no significant difference (Table 2) between myocardial regions subtended by occluded and those with stenotic but patent coronary arteries with regard to resting, low-dose and peak wall motions score indexes, prevalence of ischemia, myocardial viability and functional recovery, number of viable and recovered segments and indexes of viability and functional

recovery (figure 2) . No significant correlation was found between percentage diameter stenosis and viability index (r= - 0.12) or recovery index (r = - 0.18).

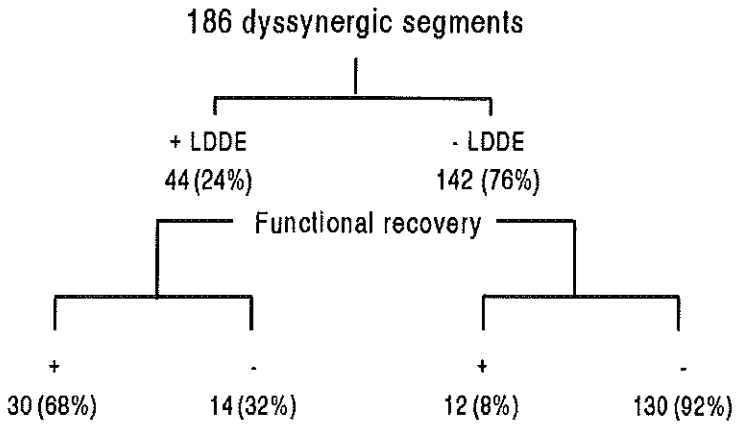

Figure 1. Flow-chart with the results of low-dose dobutamine echocardiography (LDDE) for the detection of viability and the prediction of functional recovery after revascularization.

The effect of the grade of coronary collateral circulation in occluded arteries.

In myocardial regions subtended by occluded coronary arteries, there was no significant difference in the previously mentioned parameters between regions with different grades of collaterals (table 3).

DISCUSSION

There is a growing evidence that patients with chronic left ventricular dysfunction late after acute myocardial infarction may have a variable amount of viable myocardium in the infarct region which is amenable to improvement after revascularization (3-6). Despite the evidence of favourable effect of infarct-related artery patency and collateral circulation on the functional outcome of the infarct region in recent myocardial infarction (12-17), it is not known if such favourable effects of these angiographic findings exist in patients with chronic left ventricular dysfunction late after myocardial infarction.

The present study

This is the first study which evaluates the influence of patency of coronary arteries and the grade of collateral circulation on the functional outcome of dyssynergic segments after myocardial revascularization in patients with chronic left ventricular dysfunction. Our results show that in patients with left ventricular dysfunction late after acute myocardial infarction and significant stenosis of coronary arteries subtending severely dyssynergic myocardium, the prevalence and extent of both myocardial viability assessed by low dose dobutamine and functional recovery after surgical revascularization are not related to the severity of coronary stenosis in the related arteries. Similarly in dyssynergic regions subtended by occluded coronary arteries, the prevalence and extent of both myocardial viability and functional recovery were not related to the grade of collateral circulation. These angiographic findings could not identify myocardial segments with a higher probability of functional recovery following revascularization. In contrast, low-dose dobutamine echocardiography could predict improvement of severely dyssynergic segments after revascularization with a moderate sensitivity and a high specificity.

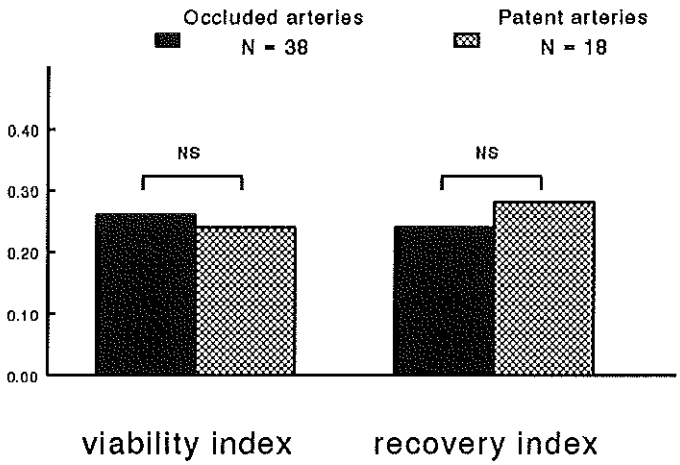

Figure 2. Viability and recovery indexes in myocardial regions with severe dyssynergy in presence of occlusion or patency of the related coronary artery.

Comparison with previous studies

Patency of the infarct-related artery and the presence of high grade collateral circulation distal to an occluded coronary artery have been associated with more favourable changes of left ventricular function and geometry after acute myocardial infarction (12-17). It has been shown that in patients with recent anterior myocardial infarction, the severity of the baseline residual stenosis of the infarct related artery is an important predictor of change in left

ventricular volumes in the first year after infarction. Total occlusion of the infarct-related artery was associated with greater left ventricular dilatation and functional impairment (15,16). Meijer et al. (17) reported that in patients with anterior myocardial infarction studied 3 months after acute anterior myocardial infarction, ejection fraction improved in patients with patency of the infarct-related artery but not in patients with reocclusion. They concluded that after successful thrombolysis of acute myocardial infarction, reocclusion without reinfarction withholds salvaged myocardium from regaining contractility with deleterious consequences for regional and global left ventricular function and for remodelling. Similarly, the presence of high grade collateral circulation was associated with a significant reduction of infarct size and better segmental and global left ventricular function (10,12,14). The lack of favourable effect of coronary artery patency on the presence and extent of myocardial viability and the functional outcome of dyssynergic segments after revascularization in our study can be explained by the chronic nature of left ventricular dysfunction and coronary angiographic findings in our patients studied at a mean of 4 $\pm$ 5.3 years after infarction as opposed to patients with recent myocardial infarction. In patients with recent infarction acute coronary occlusion results in left ventricular dysfunction and evolutional changes of left ventricular function which are dependent on myocardial flow after recanalisation by thrombolysis or through collaterals to occluded arteries. Consequently, the amount of necrotic and viable myocardium will vary according to the amount of myocardial flow after the initial coronary occlusion (10,12,14). However, in patients with chronic left ventricular dysfunction as in our study, the anatomic status of the infarct related artery may not be representative of the status in the vulnerable early phase of myocardial infarction. Coronary artery occlusion may have developed gradually allowing for the development of adequate collateral channels which may be visualised or not with routine angiography (18,19). This gradual process of occlusion and collateralization may help to maintain adequate blood flow to severely dyssynergic but viable myocardium which is capable of functional recovery after complete revascularization. On the other hand, the presence of a patent artery supplying a dyssynergic area in patients with chronic left ventricular dysfunction does not mean necessarily that the artery was patent in the early period following the infarction. Late recanalization of occluded arteries may have occurred after the development of substantial myocardial necrosis. Marzullo et al. (6) showed that in patients with regional left ventricular dysfunction studied 19 $\pm$ 34 months after myocardial infarction, resting coronary flow is equally reduced in viable compared to non viable segments identified at positron emission tomography. However, coronary flow reserve after dipyridamole adminstration was higher in viable segments and was comparable to coronary flow reserve in segments with mild reduction of resting perfusion. These data show that in patients with chronic left ventricular dysfunction, the vasodilator reserve constitutes an important factor in

maintaining myocardial viability rather than resting flow which is already reduced in both viable and non viable dyssynergic regions. Finally, the selection of patients with severe regional dyssynergy in our study would result in exclusion of patients in whom the less severe residual coronary artery stenosis resulted in considerable myocardial salvage and consequently they had normal or mildly impaired regional left ventricular function.

Table 3. Regional echocardiographic data in myocardial areas with severe dyssynergy subtended by occluded coronary arteries in presence of different grades of angiographically visualised collateral circulation.

	Grade 1 (N = 7)	Grade 2 (N = 10)	Grade 3 (N = 21)
WMSI at rest	2.76 ± 0.40	2.82 ± 0.31	2.66 ± 0.42
WMSI at LDD	2.57 ± 0.46	2.60 ± 0.50	2.34 ± 0.52
WMSI at peak stress	3.01 ± 47	3.07 ± 0.49	2.85 ± 0.41
Prevalence of viability	2 (29%)	4 (50%)	8 (38%)
Nr of viable segments	0.65 ± 1.12	0.73 ± 1.40	0.75 ± 1.61
Viability index	0.23 ± 0.39	0.26 ± 0.37	0.30 ± 0.43
Prevalence of ischemia	3 (43%)	5 (50%)	9 (43%)
Functional recovery	2 (29%)	4 (50%)	10 (48%)
Nr of recovered segments	0.61 ± 1	0.80 ± 0.93	0.71 ± 1.15
Recovery index	0.20 ± 0.35	0.29 ± 0.42	0.23 ± 0.39

WMSI = wall motion score index.

The influence of collateral circulation to occluded arteries

We found that in patients with chronic left ventricular dysfunction and occluded coronary arteries subtending regions with severe dyssynergy, the grade of collaterals visualized by angiography was not related to the prevalence or extent of myocardial viability assessed by low dose dobutamine echocardiography. Di Carli et al. (5) reported similar findings in 42 patients with chronic left ventricular dysfunction in myocardial regions subtended by occluded coronary arteries undergoing positron emission tomographic imaging for the assessment of myocardial viability. Sambuceti et al. (18) reported that in 19 patients with angina and isolated occlusion of the left anterior descending or left circumflex coronary artery who had no previous myocardial infarction,

the angiographic score of collateral circulation was not associated with differences in myocardial function or perfusion at baseline or during pacing. However, a trend to a higher maximal blood flow after dipyridamole adminstration and a higher coronary reserve was found in patients with than without high grade collaterals. Our study is the first to demonstrate that the prevalence and extent of post revascularization regional improvement of dyssynergic segments subtended by occluded coronary arteries are not related to the grade of the collateral circulation identified by routine angiography. This may be explained by the fact that angiography can detect epicardial collateral channels with a luminal diameter >100 μm, while most of the subendocardial and intramural channels may be as small as 20 μm (19). Sabia et al. (20) reported that in 33 patients with recent myocardial infarction and occluded infarct-related artery, there was no significant correlation between angiographic collateral garde and myocardial perfusion assessed by myocardial contrast echocardiography, inferring the importance of small collateral circuits that can not be visualized at angiography in maintaining myocardial perfusion in myocardial regions with occluded coronary arteries.
These non visualized channels may keep adequate myocardial flow to prevent permanent damage of the hibernating dyssynergic segments which might improve after restoration of normal coronary flow with revascularization as demonstrated in our study. In contrast to our findings and those reported by Di Carli et al.(5), Marzullo et al. (6) found that non viable segments were more likely to be perfused by an occluded vessel and less collateralized than viable segments. However, the number of coronary arteries analyzed in that study was small comprising 14 arteries of which 6 were patent.

Limitations of the study: Most of the analyzed myocardial regions were subtended by occluded coronary arteries (68%). However, we did not select patients on basis of the severity of coronary stenosis. This high prevalence of occluded coronary arteries represents the severity of coronary artery disease in a population selected for coronary artery bypass grafting. Among occluded coronary segments, only few segments showed absent collaterals. This may be explained by chronic ischemia in this symptomatic population allowing for the development of high grade collaterlas in most of the occluded arteries. In the study of Di Carli et al. (5), only 18% of occluded arteries subtending severely dyssynergic regions had absent collateral circulation, which is similar to our findings. Follow-up coronary angiography after coronary artery bypass grafting was performed only in 33% of patients. However, adequacy of revascularization of the analyzed segments is demonstrated by the abolition of ischemia and angina during dobutamine stress echocardiography and symptomatic improvement following coronary artery bypass grafting. Furthermore, the parameters of myocardial viability at low-dose dobutamine were comparable in regions with or without occluded coronary arteries.

Conclusion

In patients with chronic left ventricular dysfunction following myocardial infarction, the presence of total occlusion of coronary arteries supplying severely dyssynergic regions does not imply a lower prevalence or extent of myocardial viability or functional recovery following revascularization even in absence of high grade collaterals visualized at angiography. The potential benefit of revascularization of these segments is equivalent to that of segments with patent coronary arteries. Independent on the severity of coronary stenosis in these patients, noninvasive evaluation of myocardial viability using techniques like low-dose dobutamine echocardiography is still required to identify myocardial regions with high probability of functional recovery following revascularization.

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SUMMARY AND CONCLUSIONS

Dobutamine stress testing is a safe, feasible and accurate method for the diagnosis and functional assessment of coronary artery disease especially in patients with limited exercise capacity (1-12). In patients with left ventricular dysfunction, low-dose dobutamine echocardiography is a useful method for the assessment of myocardial viability and the prediction of functional improvement spontaneously (13,14) or after revascularization (15). In this work, the value of various electrocardiographic, echocardiographic and scintigraphic markers of myocardial ischemia and viability was evaluated. Furthermore, we demonstrated the value of dobutamine stress testing in particular clinical indications that have not been previously assessed including symptomatic patients with previous myocardial infarction and patients after coronary artery bypass surgery.

Dobutamine electrocardiography

Despite that a recent study disregarded the value of electrocardiographic recordings during dobutamine stress testing and recommended to save the cost of recording (16), our study underscores the value of electrocardiographic observation during dobutamine stress testing for the detection of myocardial viability and ischemia. The occurrence of ST-segment elevation during dobutamine stress testing after a recent Q- wave myocardial infarction was associated with a higher prevalence and extent of late functional improvement of both regional and global left ventricular function compared to patients without ST-segment elevation (17). The accuracy of ST-segment elevation for the prediction of late functional improvement was comparable to that of low-dose dobutamine echocardiography in patients with anterior myocardial infarction and in those who underwent myocardial revascularization. Similarly, in patients with recent Q wave myocardial infarction, T-wave normalization at low-dose dobutamine was associated with echocardiographic markers of myocardial viability and improved the accuracy of low-dose dobutamine echocardiography for the prediction of spontaneous improvement of regional left ventricular function (18).

The value of some electrocardiographic changes induced by dobutamine in the diagnosis and assessment of the severity of myocardial ischemia has been investigated. The significance of exercise-induced T-wave normalization is controversial (19,20). Most of the previous studies were performed in a heterogenous population. Our study indicates that in patients with non Q-wave myocardial infarction and negative T-waves undergoing dobutamine stress testing for evaluation of myocardial ischemia, the prevalence of ischemia assessed by myocardial perfusion scintigraphy and echocardiography was significantly higher in patients with than without T-wave normalization. This unique electrocardiographic finding has a moderate accuracy for the diagnosis of ischemia in this selected patient population (21).

In patients without previous myocardial infarction, dobutamine-induced ST-segment elevation was a specific marker of ischemia on echocardiography and myocardial perfusion scintigraphy. Although this finding was uncommon in patients without previous myocardial infarction, it was associated with more severe ischemia in this small group of patients compared to patients who had ischemia without ST-segment elevation (22).

Similarly, we have demonstrated that in patients with coronary artery disease and transient wall motion abnormalities during dobutamine stress echocardiography, the occurrence of ST-segment depression is associated with more severe ischemia in myocardial segment with normal baseline contraction (23).

While these electrocardiographic findings do not always provide additional data to those obtained by simultaneous imaging techniques, they may be of greater interest in presence of equivocal changes or subopitmal imaging quality.

Particular aspects in the detection of myocardial ischemia in patients with myocardial infarction

The detection of significant coronary stenosis of the infarct related artery on basis of inducible ischemia is important to clarify the relationship between the patient' symptoms and myocardial ischemia and to predict improvement of symptoms after revascularization. Unfortunately the echocardiographic detection of additional wall motion abnormalities may be limited by the pre-existence of resting wall motion abnormalities. It has been suggested that myocardial perfusion scintigraphy should be preferred to echocardiography in patients with previous myocardial infarction (2). Our study shows that while the sensitivity of echocardiography is lower in regions with severe compared to mild and moderate wall motion abnormalities, the sensitivity was similar in normal myocardial regions compared to those with severe wall motion abnormalities. The presence of regional wall motion abnormalities was not particularly related to a false negative study. Additionally, the sensitivity of dobutamine stress echocardiography for detecting remote and infarct-related coronary artery stenosis was similar. Thus, we demonstrated a good overall accuracy of dobutamine stress echocardiography in patients after myocardial infarction with similar regional accuracy in infarct and remote segments.

Similarly, dobutamine thallium scintigraphy had a good accuracy for detecting coronary artery disease on basis of reversible hypoperfusion in this population. The severity of fixed perfusion abnormalities was a limiting factor for detecting infarct-related artery stenosis only in the left circumflex and right coronary artery territories, probably due to a larger myocardial mass in the left anterior descending coronary artery territories which tend to maintain an adequate normal myocardial mass functioning as a substrate for ischemia.

An interesting finding of our study in patients with previous myocardial infarction undergoing dobutamine stress testing is that left ventricular function at rest is a powerful predictor of systolic blood pressure response to high-dose dobutamine as opposed to the findings of previous studies in a heterogenous population which failed to detect a difference in functional abnormalities with or without dobutamine-induced hypotension (24,25). This may be explained by the low likelihood of developing cavitary obstruction in patients with left ventricular dysfunction in contrast to patients with normal left ventricle who may develop hypotension due to marked increase of contractility and cavity obliteration during dobutamine infusion.

Additional values of sequential changes of contractility from low to high dose dobutamine

The classic timing of echocardiographic assessment of myocardial viability and ischemia is at low and high dose dobutamine echocardiography respectively. In this study we have demonstrated that observation of contractile response of akinetic segments at both low and high dose dobutamine may provide additional data regarding myocardial ischemia and viability that cannot be obtained by one stage assessment. Akinetic segments exhibiting a biphasic response, defined as improvement at low-dose, followed by worsening at high dose dobutamine demonstrated the highest prevalence of ischemia assessed by simultaneous thallium SPECT imaging (26). This observation may help to improve the sensitivity of dobutamine stress echocardiography for the detection of functionally significant coronary artery disease in patients with myocardial infarction.

The phenomenon of akinesis becoming dyskinesis at high dose dobutamine stress echocardiography has been disregarded as a marker of myocardial ischemia in absence of improvement of thickening at low-dose dobutamine (27). In this work we demonstrated that this pattern is constantly associated with absence of echocardiographic signs of viability at low dose dobutamine as well as absence of functional improvement after surgical revascularization (28). The negative predictive value of low-dose dobutamine echocardiography for post-operative functional improvement was significantly higher in akinetic segments with than without dyskinesis at peak stress. Thus, 2 stages assessment of viability in this setting provided additional data to those obtained only at low-dose stage.

Combination of ischemic markers as a predictor of more severe ischemia

In patients with coronary artery disease and inducible ischemia during dobutamine stress echocardiography or myocardial perfusion scintigraphy, the absence of angina pectoris during the test may be interpreted as an indictor of less severe functional abnormalities. In our study we demonstrated that in patients with anatomically and functionally significant coronary artery disease,

the extent and severity of myocardial ischemia are not different with or without angina during dobutamine stress test (23,29). Consequently, in patients with a positive echocardiographic or scintigraphic test for ischemia, it would be inappropriate to underestimate the severity of myocardial ischemia in absence of inducible angina.

The significance of a negative dobutamine stress echocardiographic study for ischemia in patients with coronary artery disease and reversible perfusion defects on simultaneous myocardial perfusion scintigraphy has not been investigated. Theoretically this may imply that ischemia was not of enough severity to provoke left ventricular dysfunction. Our study shows that in patients with coronary artery disease and reversible perfusion defects on dobutamine MIBI SPECT, the extent and severity of reversible hypoperfusion and presumably myocardial ischemia are not different with or without transient wall motion abnormalities (30). A negative echocardiographic study in this population was more common in females and was associated with a lower peak rate pressure product. This confirms the lower sensitivity of echocardiography compared to myocardial perfusion scintigraphy in submaximal stress tests and can be explained by the late occurrence of mechanical dysfunction following impairment of perfusion in the ischemic cascade (31). The clinical implication of this study is that MIBI imaging may be required in patients undergoing dobutamine stress echocardiography in whom the test ends at submaximal level without evidence of myocardial ischemia.

CONCLUSIONS

1) Dobutamine stress echocardiography is an accurate, safe and relatively cheap method for the diagnosis of significant coronary artery disease and the assessment of myocardial viability in patients with left ventricular dysfunction.

2) Dobutamine perfusion scintigraphy may be recommended in conjunction with negative submaximal dobutamine echocardiographic studies.

3) The absence of symptoms during a positive dobutamine echocardiographic or scintigraphic study in patients with coronary artery disease should be disregarded as a marker of less severe ischemia.

4) Observation of contractile response of akinetic segments at both low and high dose dobutamine echocardiography provides additional data regarding myocardial ischemia and viability that cannot be obtained by evaluation of only one stage.

5) Dobutamine stress echocardiography is an accurate method for the diagnosis of coronary artery disease in symptomatic patients after myocardial infarction,

with comparable sensitivity for the detection of remote and infarct-related artery stenosis.

6) Left ventricular function after myocardial infarction is a powerful predictor of systolic blood pressure response to high dose dobutamine stress test.

7) Electrocardiographic changes during dobutamine stress test can provide important clues regarding the presence and extent of both myocardial ischemia and viability in patients with coronary artery disease.

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SAMENVATTING EN CONCLUSIES

De dobutamine stress test is een veilige en geschikte methode voor de diagnose en funktionele inschatting van coronairlijden, in het bijzonder bij patiënten met een onvoldoende inspanningstolerantie. Ook bij patiënten met een doorgemaakt hartinfarct heeft de test waarde voor het inschatten van de uitgebreidheid van het coronairlijden. Bij patiënten met een gestoorde hartspier functie in rust, is lage dosis dobutamine echocardiografie een nuttige methode voor de bepaling van hartspier vitaliteit en de voorspelling van herstel van funktie. Bij hartspierdelen die stilstaan (akinetisch) is zowel stress met lage als hoge dosis dobutamine essentieel voor de diagnostiek van ischemie en vitaliteit. Indien de dobutamine echocardiografische studie normaal is, maar de stress submaximaal, wordt perfusie scintigrafie aanbevolen.

De afwezigheid van typische druk op de borst tijdens een positieve dobutamine test is niet gerelateerd aan minder zuurstoftekort van het hart. Electrocardiografische veranderingen tijdens de dobutamine test kunnen belangrijke aanwijzingen geven betreffende de aanwezigheid en uitgebreidheid van zuurstoftekort en vitaliteit van de hartspier.

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ABSTRACTS

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