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Simultaneous Dobutamine Stress Echocardiography and Technetium-99m Isonitrile Single-Photon Emission Computed Tomography in Patients With Suspected Coronary Artery Disease

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Objectives. **The purpose of this study was to determine the relative value of dobutamine stress echocardiography and technetium-99m isonitrile single-photon emission computed tomography (mibi SPECT) in the detection of myocardial ischemia.**

Background. **Stress-induced new wall motion abnormalities and transient perfusion defects are both used for the diagnosis of myocardial ischemia.**

Methods. **One hundred five consecutive patients with either proved or suspected coronary artery disease, who were referred for perfusion scintigraphy, were studied by a combination of the two techniques. Both echocardiographic and mibi SPECT images were visually analyzed. Three patients were excluded from the final analysis because of unsatisfactory examinations: two with noninterpretable stress echocardiograms and one with noninterpretable mibi SPECT images. The response to stress was concordantly classified by both techniques in 68% of patients (kappa = 0.51).**

Results. **Dobutamine stress echocardiography revealed the presence of ischemia in 38 and mibi SPECT in 45 patients (overall agreement = 74%, kappa = 0.46). The agreement was higher in patients without previous myocardial infarction (84%, kappa = 0.62). When regional analysis was performed, concordance of stress echocardiography and mibi SPECT occurred in 84% of the 306 regions (kappa = 0.45). Regional agreement was also slightly higher in patients without previous infarction (88%, kappa = 0.50). In 21 patients without previous myocardial infarction who underwent coronary angiography, the overall sensitivity of dobutamine stress echocardiography and mibi SPECT for the diagnosis of coronary artery disease (diameter stenosis >50%) was 75% and 83%, respectively, with a specificity of 89% (eight of nine patients) for both tests.**

Conclusions. **Dobutamine stress echocardiography represents a reasonable alternative to dobutamine mibi SPECT for the functional assessment of patients with suspected myocardial ischemia and without previous myocardial infarction.**

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The noninvasive detection of myocardial ischemia remains an important clinical problem. Numerous methods have been introduced to induce ischemia, such as exercise testing (1–3), pharmacologic stress using dipyridamole, dobutamine (4–6) or atrial pacing (7). Ischemia may be detected using the electrocardiogram (ECG), perfusion scans (8,9) or echocardiography (10–12). The diagnostic accuracy of the stress ECG alone is limited. Nuclear perfusion studies give accurate results but are expensive. By comparison, stress echocardiography is a widely available, a relatively cheap method for detecting myocardial ischemia, and it has been the subject of increasing interest and use in different clinical settings, such as detection of coronary artery disease (5,13), assessing the results of interventions (14) or predicting perioperative cardiac risk (15–17). Dobutamine is a beta-adrenergic agonist with positive inotropic and chronotropic effects. These properties make it suitable for inducing myocardial oxygen demand and provoking myocardial ischemia in cases of coronary stenosis. Pharmacologic stress imaging with dobutamine has recently been used in conjunction with both thallium scintigraphy and echocardiography (8). With both, dobutamine provided good diagnostic accuracy for the presence of coronary artery disease. However, no study has been performed for comparing the diagnostic merit of the two methods. In addition, no comparative study has been carried out with technetium-99m isonitrile (mibi). In particular, recent reports have demonstrated that dobutamine stress echocardiography has a good diagnostic accuracy for the diagnosis of coronary artery disease, which is similar to

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that obtained with dobutamine thallium scintigraphy (5,8). However, the recent introduction of single-photon emission computed tomography (SPECT) has improved the diagnostic accuracy of scintigraphic technique for the detection of myocardial ischemia and mibi has contributed to improve the image quality of tomographic studies (9,15,18). So far, the agreement between dobutamine-induced wall-motion abnormalities (detected by echocardiography) and transient perfusion defects (detected by mibi SPECT) for the diagnosis and localization of myocardial ischemia has not been explored.

Accordingly, the aim of this study was to establish the correlation between the two tests in a consecutive group of patients with chest pain and proved or suspected coronary artery disease who underwent simultaneously performed dobutamine stress echocardiography and mibi SPECT.

Methods

Study patients. The study group consisted of 105 consecutive patients referred to the nuclear cardiology laboratory at the Thoraxcenter for the evaluation of suspected myocardial ischemia. Their ages ranged from 24 to 81 years (mean ± SD 62 ± 12); 58 were men and 47 women. Fifty-nine patients had a previous myocardial infarction. At the time of the study, 55 patients were receiving beta-adrenergic blocking agents administered either alone or in combination with nitrates or calcium channel blocking agents, or both.

Dobutamine stress echocardiography. After the patients gave written informed consent, two-dimensional precordial echocardiography was performed. Standard parasternal and apical views were recorded on videotape. Dobutamine stress echocardiography was performed according to a previously described protocol (11). Dobutamine was infused through an antecubital cannula starting at a dose of 10 μg/kg per min, increasing by 10 μg/kg every 3 min to a maximum of 40 μg/kg per min, which was continued for 6 min. In patients not achieving 85% of age-predicted maximal exercise heart rate, atropine (up to 1 mg) was given intravenously if necessary with the continuation of dobutamine.

The ECG was continuously monitored throughout dobutamine infusion, 12-lead ECG recorded each minute and cuff blood pressure taken every 3 min. Two-dimensional echocardiogram was continuously monitored and was recorded on videotape for the last minute of each stress stage and continuously after atropine administration. The infusion was stopped if the patient developed an obvious new wall motion abnormality, ST segment depression >2 mm 80 ms after the J point, ST segment elevation, ventricular tachycardia or any complication considered to be due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine or atropine if these did not revert spontaneously and quickly.

The assessment of echocardiographic images was performed by two experienced investigators after acquisition without knowledge of the patients' clinical data or coronary anatomy but with knowledge of the doses of dobutamine and atropine used. When there was disagreement between the two off-line assessors, a third investigator viewed the images without knowledge of the previous assessments and a majority decision was achieved. For this semiquantitative assessment, the left ventricular wall was divided into 14 segments, as described by Edwards et al. (19) and scored using a 4 point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic and 4 = dyskinetic. To analyze wall motion, images recorded on videotape were subsequently reviewed at various playback speeds. Both systolic wall thickening and inward wall motion were visually evaluated. An increase in score between rest and stress in one or more segments, that is, a new or worsened wall motion abnormality, constituted a positive test. In our laboratory both inter- and intraobserver agreement for stress echocardiographic assessment are 91% (20); recent data indicate that assessment of 100 stress echocardiograms is adequate training for diagnostic accuracy in this technique (21), and all investigators in our center have such experience. We did not use a continuous loop format for assessment of pharmacologic stress echocardiography in all patients because we have previously tested whether cine loop analysis of dobutamine echocardiography had advantages over analysis of images from video tape and found the same results by the two techniques (10).

Mibi SPECT imaging at rest and at peak stress. Approximately 60 s before termination of the stress test, an injection of 370 MBq of ^{99m}Tc mibi was administered. The stress mibi SPECT images were acquired, on average, 1 hour after dobutamine ended. Thirty-two projections (180° scanning) were obtained with an acquisition time of 45 s/projection. For each patient, six oblique (short-axis) slices were defined from the apex to the base and three sagittal slices from the septum to the lateral wall. For rest studies, patients were injected with 370 MBq of ^{99m}Tc mibi at least 24 h after the first study using the same protocol. One experienced observer visually assessed the uptake of radiotracer in studies both at rest and during exercise, giving a semiquantitative score based on a scale of 4 grading (1 = normal, 2 = decreased uptake, 3 = severely decreased uptake, 4 = absence of uptake). A persistent perfusion defect was defined when a score ≥2 in one or more segments was present both during exercise and at rest. Moreover, it was decided in advance to consider a nonreversible defect of the septal segments in the two basal short-axis slices as normal (four segments). A perfusion defect was considered reversible when the score at rest improved by at least one grade with respect to the exercise scan in two or more contiguous segments. A significant but incomplete improvement of perfusion from the exercise to the rest scan (persistence of at least one segment with a score ≥2 in the scan at rest) was regarded as an ischemic response and, for the purpose of data analysis, was classified as a reversible defect.

For each technique, three different responses to stress were defined: normal (absence of rest and stress abnormalities), ischemic (reversible scintigraphic perfusion defects

and transient wall motion abnormalities during stress echocardiography) and fixed abnormalities—infarction (fixed scintigraphic perfusion defects, echocardiographic wall motion abnormalities at rest without worsening at peak stress). When both reversible and fixed defects were present, the response was classified as ischemic. To allow a valid comparison of each technique in localizing ischemia, the 47 segments of the left ventricle on SPECT and the 14 echocardiographic segments were grouped into the following six major regions: anterior, posterior, lateral, interventricular septum (subdivided in anterior and posterior septum) and apex. Furthermore, for analysis of regional agreement the six major regions were further grouped into three myocardial areas: 1) anterior and septal, 2) posterior and lateral, and 3) apical. For analyzing reasons for discrepancies, the original six-region model was used to detect adjacent abnormalities. The results obtained by the two methods were then compared.

Coronary angiography. Coronary angiograms using the Judkins technique were performed within 3 months in 71 patients. Significant coronary artery disease was defined as a diameter stenosis >50%.

Statistical analysis. All continuous variables are expressed as mean value ± SD. The agreement between mibi SPECT and stress echocardiography was defined as the percent of concordant diagnoses and was also assessed by calculating the kappa value; kappa values between 0.75 and 1 were considered indicative of good agreement, those between 0.40 and 0.75 indicative of moderate agreement and those between 0 and 0.40 indicative of poor agreement. McNemar's test was used to compare the percent of concordant diagnoses between paired data (22). A p value < 0.05 was considered significant.

Results

Feasibility of dobutamine stress test. The dobutamine stress test was completed without serious complications in all patients. The clinical variables of patients are shown in Table 1. In the study group, 66 patients reached 85% of the age-predicted maximal exercise heart rate. On average, the heart rate achieved was 88% compared with the theoretic maximal exercise heart rate of these 66 patients; 28 patients required atropine to reach the target heart rate. Three patients were excluded from final analysis: two because of technically inadequate echocardiograms at peak stress and one patient because of poor quality mibi SPECT images (liver uptake interfered with myocardial uptake). Thus, 102 of 105 patients had analyzable data with both tests and were included in the study. The overall success rate of the study was 98%; no patient was excluded from analysis on the basis of poor image quality on the rest echocardiogram. In 13 patients, because parasternal views were inadequate, only the apical views were analyzed; however, all segments were visualized in at least one view.

Table 1. Results of Dobutamine Stress Test

Rest heart rate (beats/min)	70 ± 13
Peak heart rate (beats/min)	131 ± 16
Rest systolic blood pressure (mm Hg)	138 ± 22
Rest diastolic blood pressure (mm Hg)	81 ± 18
Peak systolic blood pressure (mm Hg)	151 ± 26
Peak diastolic blood pressure (mm Hg)	78 ± 10
Rate-pressure product (rest)	9,725 ± 2,500
Rate-pressure product (peak)	19,798 ± 4,311
Peak theoretical maximal exercise heart rate (%)	88 ± 13
Chest pain (no.)	35
ST segment depression (no.)	21
ST segment elevation (no.)	7
Atropine used (no.)	44

Data are expressed as mean value ± SD or number of patients.

Relations between wall motion and myocardial perfusion. The results of dobutamine echocardiography and dobutamine mibi SPECT in the 102 patients are presented in Figure 1. Echocardiography revealed new wall motion abnormalities in 38 patients and wall motion abnormalities at rest without further worsening at peak stress in 31 patients; test results were negative in 33 patients. On mibi SPECT, reversible perfusion defects were detected in 45 patients, and fixed perfusion defects alone in 28; the test results were negative in 29 patients. The two methods concordantly classified 69 patients (68%, kappa = 0.51). The majority of discrepancies were due mainly to pattern discordance in which both tests showed an abnormal pattern but the type of abnormality was different, that is, rest wall motion abnormality versus reversible perfusion defect (11 patients) or new wall abnormality versus fixed perfusion defect (8 patients). In these 19 patients, both tests were definitely abnormal but, by definition, the results were discordant.

For detection of presence or absence of myocardial

Figure 1. Results of simultaneous dobutamine echocardiography (ECHO) and ^{99m}Tc-technetium isonitrile single-photon emission computed tomography (SPECT). Squares marked 24, 28 and 17 display number of patients concordantly classified by both methods. "Infarction" = a rest wall motion abnormality without further worsening during stress on echocardiography and a fixed perfusion defect on SPECT; "Ischemia" = a new wall motion abnormality on echocardiography and a reversible perfusion defect on SPECT.

		ECHO		
		Normal	"Ischemia"	"Infarction"
SPECT	Normal	24	2	3
	"Ischemia"	6	28	11
	"Infarction"	3	8	17

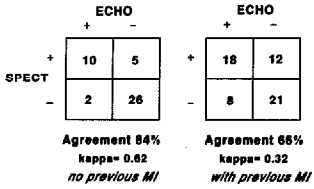

Figure 2. Agreement for ischemia between dobutamine echocardiography (ECHO) and ^{99m}technetium isonitrile single-photon emission computed tomography. The agreement is higher in patients without previous myocardial infarction (MI) (left panel).

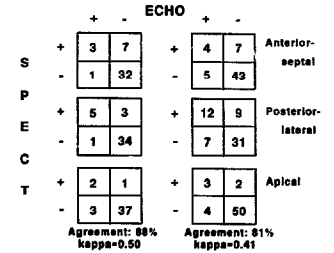

Figure 3. Regional agreement for ischemia between dobutamine echocardiography (ECHO) and ^{99m}technetium isonitrile single-photon emission computed tomography (SPECT) in 306 regions. The set of 2 × 2 tables at left represents data of patients without previous myocardial infarction, and the row at right represents data of those without previous myocardial infarction. The agreement was slightly higher in patients without infarction.

ischemia (that is, new wall motion abnormalities and reversible perfusion defects), the overall agreement between the two methods was 74% (75 of 102 patients, kappa = 0.46). The agreement increased when we separately analyzed data of patients without previous myocardial infarction (84%, kappa = 0.62, Fig. 2). The specific reasons for discrepancies in patients with normal wall motion at rest are reported in Table 2. Of seven patients, three had a different but abnormal pattern (ischemia versus infarction), whereas four patients with an ischemic response on one test were classified as normal on the other test.

The overall regional agreement was 84% (kappa = 0.45). Slightly better agreement was found if we again separated the group without previous infarction from that with previous infarction (88%, kappa = 0.50; 81%, kappa = 0.41, respectively, Fig. 3). Altogether, 50 areas were found with diverging results, 16 areas in 43 patients without previous myocardial infarction and 34 areas in 59 patients with previous infarction. In 19 areas the two methods showed a discordant pattern (new wall motion abnormalities vs. fixed perfusion defects or wall motion abnormalities at rest vs. reversible perfusion defects) in the same area. In 20 areas the two methods showed abnormalities in one of the adjacent segments. Two patients had single, distal and moderate stenoses on the left anterior descending artery (which is a usual cause for a negative stress test result) and results of dobutamine stress echocardiography were negative in those cases. There were only nine areas where we could not explain the discordant results of the two methods and coronary angiography had not been performed to validate the result of one of the methods.

Table 2. Disagreement Between Myocardial Ischemia in Patients With No History of Myocardial Infarction

Pt No.	mibi SPECT	Echo	Coronary Angiography
42	Ischemia	Negative	Not done
59	Ischemia	Negative	LAD stenosis
69	Ischemia	Infarction	LAD distal stenosis
76	Ischemia	Infarction	3VD
102	Ischemia	Negative	LAD distal stenosis
12	Negative	Ischemia	Open stent RCA (false positive?)
57	Infarction	Ischemia	Not done

Echo = dobutamine echocardiography; LAD = left anterior descending coronary artery; mibi SPECT = ^{99m}technetium single-photon emission computed tomography; RCA = right coronary artery; 3VD = multiple-vessel disease.

Relation of dobutamine stress test to coronary angiographic findings. Of 105 consecutive patients, 21 met the criteria of no previous myocardial infarction, normal wall motion at rest and a recent coronary angiogram (<3 months). Twelve of these 21 patients had significant coronary artery stenosis (>50% diameter stenosis). Four of these 12 patients had single-vessel disease; in all 4, the stenoses were located on the left anterior descending artery and in 2 they were on the distal portion of this artery. Another three patients had two-vessel disease—two patients with stenoses on the right coronary and left anterior descending artery branches and one patient with left circumflex and left diagonal branch stenoses—and five patients had triple-vessel disease. In the other nine patients, no significant coronary stenosis was detected; four of the nine had a normal coronary angiogram and five had recent balloon angioplasty or atherectomy with no significant coronary abnormality at the time of the catheterization and the dobutamine stress test. The mean age and hemodynamic data of this subgroup were comparable with those of the whole group.

Echocardiography detected 9 and mibi SPECT detected 10 of the 12 patients with significant coronary abnormalities. Both tests had one false positive result (Table 3). Combining the results of echocardiography and mibi SPECT the sensitivity increased (11 of 12), whereas specificity decreased slightly (2 of 9 false positive). Poor agreement was found between ST segment changes during stress testing and the coronary angiographic findings (42%, kappa = 0.077); this

Table 3. Comparison of Dobutamine Echocardiography and mibi SPECT in Patients With Coronary Angiography and Normal Wall Motion at Rest

	CAD + (sensitivity)	CAD − (specificity)
Echo+	9/12 (75%)	1/9 (89%)
SPECT+	10/12 (83%)	1/9 (89%)
Echo+ or SPECT+	11/12 (92%)	2/9 (78%)

CAD+ = patients with angiographically proved coronary artery disease; CAD− = no significant coronary stenosis at the time of cardiac catheterization. Echo+ = new wall motion abnormality during dobutamine stress test; SPECT+ = reversible perfusion defect on ^{99m}-technetium isonitrile (mibi) single-photon emission computed tomography during stress test.

result can be explained in part by the displacement of ECG leads during dobutamine echocardiography. The agreement between the presence of chest pain and angiographic findings was acceptable (71%, kappa = 0.43). The results of echocardiography and mibi SPECT were in agreement in 15 of 21 cases (71%, kappa = 0.43). Three patients with single-vessel disease (all with distal lesions and moderate stenoses) had negative findings on stress echocardiography whereas SPECT did not detect one case of single-vessel disease and one of double-vessel disease.

Discussion

Dobutamine stress testing is increasingly used to elicit myocardial ischemia and detect significant coronary artery disease, mostly in conjunction with echocardiography (5,11). Recently dobutamine stress echocardiography and 201-thallium scintigraphy have been used in different clinical settings, such as the diagnosis of coronary disease, the assessment of the results of coronary angioplasty or risk stratification before vascular surgery (8,14,15). However, it is unclear to what extent the two tests provide concordant information; for obvious financial considerations, stress echocardiography should be favored if it gives the same information as perfusion scintigraphy. The widespread use of perfusion scintigraphy is limited by the high cost of the procedure and the exposure of the patients to radiation. Our primary goal was to establish the potential role of dobutamine stress echocardiography as an alternative to perfusion scintigraphy. To our knowledge, this is the first large scale study in which dobutamine stress echocardiography and perfusion scintigraphy were performed simultaneously. In addition, this is the first study in which 99m-technetium isonitrile (mibi) has been used in conjunction with SPECT imaging during dobutamine stress testing. Our patient group was primarily referred for pharmacologic perfusion scintigraphy to investigate chest pain. Dobutamine (with the addition of atropine, when necessary) induced new or worsened wall motion abnormalities in 38 (37%) of 102 patients, whereas transient perfusion defects were detected in 45 (44%). Chest pain occurred in 35 patients and pathologic ST segment deviation in 28 (ST depression in 21 and ST elevation in 7). The overall agreement between the two methods for the detection of presence or absence of myocardial ischemia was 74%. When the results of both tests were positive, the agreement for the localization of transient defects was good. The concordance was similar to that found by others (17) as well as by our group (1,23) in a comparison of exercise perfusion imaging with immediate postexercise echocardiography. The agreement between echocardiography and SPECT for detection of ischemia was better in patients with normal (84%) than in those with abnormal wall motion at rest. However, in both patient groups, the incidence of a positive SPECT finding was greater than that of a positive echocardiographic finding. This trend was more evident in the group with abnormal wall motion at rest, in which a transient perfusion defect more frequently occurred in the infarcted area without a deterioration of wall motion or wall thickening in the same area. These results are similar to those found in correlative echocardiographic and scintigraphic studies during physical exercise (1,17).

Several mechanisms can be advocated to explain these discrepancies. 1) It is well known that perfusion scintigraphy can detect myocardial malperfusion in addition to true myocardial ischemia leading to a greater number of positive scintigraphic than echocardiographic results. This outcome is consistent with our recent observation that positive results are more frequently found with exercise perfusion scintigraphy, than with exercise echocardiography in patients with moderate coronary stenoses. In contrast, the rate of positivity with both techniques was similar in patients with severe stenoses. In the present study, because patients were primarily referred for scintigraphic study rather than coronary angiography, we did not use coronary angiography as a standard. Instead, we compared the functional consequences of myocardial ischemia detected by the two noninvasive methods. Therefore, the hypothesis of the influence of the severity of coronary artery stenoses on the different tests could not be verified.

2) The higher incidence of a positive SPECT result in the infarcted area, and especially in akinetic areas, requires another explanation. Quinones et al. (17) clearly delineated the possible explanations of this discrepancy when 201-thallium was used as a radiotracer. In our study, we used mibi instead of thallium, because we assumed that it was more suitable for SPECT imaging as a result of its high energy (18) and lack of significant redistribution. The latter property of the radiotracer could overcome the problem of differential regional washout rate, which could be the cause for reversible perfusion defects not directly related to malperfusion or ischemia.

3) Another explanation for the higher incidence of transient perfusion defect in akinetic areas at rest is hibernating myocardium and also the tethering effect of the infarcted area on the noninfarcted myocardium (17). However, the clinical and prognostic significance of areas with fixed echocardiographic defects showing partial redistribution on perfusion scintigraphy is uncertain and deserves further

investigation. In particular, studies have to address the impact of coronary revascularization in these areas.

Study limitations. Some limitations to the present study should be acknowledged. 1) Both regional wall motion and myocardial perfusion were assessed visually. Although we have found a small intra- and interobserver variability in the interpretation of SPECT images, the lack of quantitative analysis could affect the results (25). Quantitative analysis of exercise wall motion assessed by echocardiography has been attempted in normal persons (26). However, a semiquantitative reading of perfusion scintigraphy and echocardiography is the routinely applied method in most clinical laboratories (2–4).

2) Coronary angiography was not used as the reference standard in all patients. However, we do not consider this a major limitation because our goal was to compare the value of two different tests to assess the functional significance of coronary disease. Furthermore, it would not be correct to assess the diagnostic value of the tests in patients in whom the application of coronary angiography was strongly dependant on the test results.

Conclusions. Our study indicates good agreement between echocardiography and mibi SPECT with respects to the response to dobutamine in patients with normal wall motion at rest for the detection myocardial ischemia. More studies are warranted in patients with previous myocardial infarction in whom the concordance was less satisfactory.

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