Additive Value of Low-Dose Dobutamine to Technetium-99m Sestamibi-Gated Single-Photon Emission Computed Tomography for Prediction of Wall Motion Improvement in Patients Undergoing Coronary Artery Bypass Graft

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Summary

Background: The two most useful methods for myocardial viability assessment are perfusion imaging and dobutamine echocardiography.

Hypothesis: The present study investigated the additive value of a new method, dobutamine technetium 99m (^{99m}Tc)-sestamibi-gated single-photon emission computed tomography (SPECT), which combines these two modalities, to the prediction of wall motion improvement after revascularization.

Methods: Fifty-five consecutive patients with ischemic cardiomyopathy, who were referred for viability evaluation, underwent resting and dobutamine (dose, 5–10 µg/kg/min) gated SPECT with ^{99m}Tc-sestamibi. Of these patients, 36 underwent coronary artery bypass graft (CABG) within 1 month of the study and 32 had repeat resting gated SPECT within 1 year. Global and regional wall motion, wall thickness, and perfusion were simultaneously analyzed at rest and after dobutamine using the 20-segment model; the sestamibi uptake and wall motion response to dobutamine of each segment were rated quantitatively. Based on these findings, the segments were categorized as normal, viable, or nonviable. The predictive values for wall motion improvement were assessed by perfusion, using cutoffs of 50 and 60% of sestamibi uptake, and

thereafter by the addition of dobutamine response in the segments that were rated nonviable.

Results: Of the 1,080 myocardial segments studied, 906 (84%) had abnormal wall motion and were analyzed for viability. Concordance between perfusion and wall motion response to dobutamine was 60% with the 50% cutoff of sestamibi uptake, and increased to 65% with the 60% sestamibi cutoff ($p < 0.04$). The respective predictive values of wall motion improvement using the 50 and 60% cutoff points were as follows: sensitivity 93 and 70%, respectively, ($p < 0.01$); specificity 59 and 86% ($p < 0.001$), respectively; accuracy 77% for both. The addition of the wall motion response to dobutamine to the assessment of the nonviable segments by perfusion (60% cutoff) increased the sensitivity from 70 to 85% ($p = 0.001$) and the negative predictive value from 70 to 81% ($p = 0.009$); the positive predictive value remained high (86 vs. 82%). No additive value of wall motion response to dobutamine was demonstrated for nonviable segments by perfusion with a 50% cutoff.

Conclusion: Dobutamine sestamibi-gated SPECT is a feasible method for the analysis of myocardial perfusion, function, and contractile reserve of individual myocardial segments in patients with ischemic cardiomyopathy. Viability assessment based on a threshold of 60% uptake of sestamibi, with the addition of the wall motion response to dobutamine in the nonviable segments, seems to yield better predictive values for wall motion improvement after CABG.

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Introduction

In patients with severe ischemic cardiomyopathy, assessment of the amount of viable myocardium is crucial to therapeutic decision making.^{1–3} A pooled analysis of 37 studies by Bax *et al.*⁴ showed that perfusion imaging (by thallium and sestamibi), ¹⁸F-fluorodeoxyglucose (¹⁸FDG) metabolic imaging

with positron emission tomography (PET), and dobutamine echocardiography are useful techniques for assessing myocardial viability, with a high sensitivity in predicting wall motion improvement, in patients after revascularization.^{4–13} However, the specificity of the perfusion agents, especially thallium, is low. The use of technetium-99m (^{99m}Tc)-labeled sestamibi, which has been found to have a metabolic impact on myocardial uptake,^{14,15} is somewhat controversial.^{16–24} Several studies have reported that the use of sestamibi leads to an underestimation of the extent of wall motion improvement after revascularization when compared with both thallium²⁴ and FDG.²³ By contrast, according to others, sestamibi injection under nitrate administration improves viability assessment; this is also true for low-dose dobutamine.^{25–28}

Iskandrian and Azio²⁶ described a novel approach consisting of dual isotope and gated single-photon emission computed tomography (SPECT) combined with low- and high-dose dobutamine, which more properly defines the dysfunctional myocardium. However, the predictive value of low-dose dobutamine-gated SPECT after revascularization has not been fully investigated.

The aims of the present study were as follows: (1) to investigate the feasibility and safety of ^{99m}Tc-sestamibi-gated SPECT at rest and during low-dose dobutamine infusion in patients with ischemic cardiomyopathy; (2) to study the correlation between sestamibi uptake at different cutoff thresholds and contractile reserve in each myocardial segment; and (3) to evaluate the predictive values of sestamibi uptake at 50 and 60% thresholds in the assessment of regional and global ventricular improvement after coronary artery bypass graft (CABG) and with the addition of the wall motion response to dobutamine.

Methods

Study Population

The study population consisted of 55 consecutive patients (52 men, 3 women, mean age 63 ± 9 years) with ischemic cardiomyopathy and left ventricular ejection fraction (LVEF) of ≤ 40% at rest, who were referred for viability assessment. All patients had had a previous myocardial infarction and had undergone coronary catheterization demonstrating significant triple coronary artery disease (≥ 70% narrowing). The mean New York Heart Association (NYHA) functional score of the group was 2.2 ± 1.5. Mean anginal score according to the Canadian Cardiovascular Society Classification (CCSC) was 1.6 ± 2. Patients with significant valvular disease, recent myocardial infarction, intractable heart failure, serious arrhythmia, or chronic atrial fibrillation were excluded. The patients continued their regular medication, including angiotensin-converting enzyme inhibitors, nitrates, diuretics, digoxin, calcium-channel blockers, and beta-blocker agents.

Of the 55 patients, 36 underwent CABG within 1 month of viability assessment. Three of these died during follow-up and one had recurring angina. The remaining 32 patients were re-

assessed within 1 year after CABG. Referral for CABG was based on clinical, angiographic, and scintigraphic or echocardiographic viability assessment.

Gated SPECT Protocol

All patients underwent the same imaging protocol. Technetium-99m-labeled sestamibi, 30 mCi (1110 MBq), was injected intravenously and flushed with 10 cc of saline solution. Resting imaging was started 1 h after injection. Gated SPECT acquisition was performed with an SP4-HR gamma camera (Elsint, Haifa, Israel) with high-resolution collimator, using the step-and-shoot method: 30 projections, 20 s per projection, 8 frames per R-R cycle, 180° (45° right anterior oblique and left posterior oblique). Total acquisition time was 12.5 min. Thereafter, dobutamine was infused, starting with a dose of 5 µg/kg/min for 5 min and then increasing to 10 µg/kg/min. Heart rate and blood pressure measurements and electrocardiogram (ECG) tracings were made under basal conditions and repeated during each dose of dobutamine infusion. After a 2 min infusion of the higher dose, a second gated SPECT acquisition was performed with the patient still in supine position, using the same protocol as at rest.

Repeated resting gated SPECT was performed within 1 year of CABG with the same gamma camera, acquisition, and processing protocols.

The raw data were reconstructed with the use of a Butterworth filter, with a 0.55 cutoff and an order of 2.5. The slices in the short axis were divided into thirds—distal, middle, and basal—and each slice was further divided into six segments: anterior, anterolateral, inferolateral, inferior, inferoseptal, and anteroapical. The apex zone was divided into two segments, anteroapical and inferoapical, selected from the long axis. Therefore, a total of 20 segments per patient was studied.

Regional ^{99m}Tc-sestamibi activity was analyzed quantitatively by a circumferential profile method, similar to that described by Liu *et al.*²⁹ The perfusion of each segment was scored according to the average ^{99m}Tc-sestamibi uptake on a scale of 0 to 3, as follows: 0 = normal perfusion (> 80% uptake); 1 = mild defect (80 to 65% uptake); 2 = moderate defect (65 to 50% uptake); 3 = severe defect (< 50% uptake). The viable and nonviable segments were also distinguished according to two cutoff points of uptake: 50 and 60%.

Wall motion of each of the 20 segments was scored visually on a corresponding 4-point scale: 0 = normal wall motion and thickening, 1–2 = mild/moderate hypokinesis and reduced wall thickening, 3 = akinesis or dyskinesis. Only segments with both abnormal wall motion and thickening were analyzed for viability: those with improvement (elevation in score of at least 1) or worsening (reduction in score of at least 1) in response to dobutamine were considered viable; those that did not respond to dobutamine were considered nonviable. In segments with very low uptake of sestamibi, visualization of wall motion was allowed after enhancement of counts in the gated images. In a few segments with a discordance between wall motion and thickening, viability was defined as a change in both wall motion and thickening. Left ventricular ejection

fraction (LVEF) and end-systolic and end-diastolic volumes were calculated at rest and during dobutamine infusion by the method described by Germano *et al.*³⁰

These results were compared with regional wall motion and thickening (elevation in score of at least 1) and global LV function after CABG. Perfusion and wall motion assessments were done by two independent nuclear cardiologists. Disagreement was found in 6% of segments and was resolved by consensus.

The predictive values of wall motion improvement after CABG were assessed separately by perfusion at 50 and 60% sestamibi uptake and by wall motion response to dobutamine. They were then reassessed by the addition of the wall motion response to low-dose dobutamine. Each segment that was considered nonviable by the sestamibi cutoff points of 50 and 60% but responded to dobutamine was regarded positive for prediction of wall motion improvement.

Statistical Analysis

Results are given as means $\pm$ standard deviations. To compare mean continuous parameters between groups, Student's *t*-test was performed. Pearson correlation coefficient (*r*) and the significance for it (*p*) were calculated between variables. Probability values ≤ 0.05 were considered statistically significant. Sensitivity, specificity, and positive and negative predictive values were calculated. To analyze statistically significant relationships in the distribution of categorical variables, the chi-square test was performed.

Results

All patients tolerated the dobutamine infusion well. Premature ventricular beats were observed in 11 patients (20%). In only five patients did the dobutamine dose need to be reduced from 10 to 5 $\mu\text{g/kg/min}$.

Mean heart rate, blood pressure, LVEF, and end-systolic and end-diastolic LV volumes at rest and at the end of dobutamine infusion are shown in Table I. A significant increase in heart rate was noted with dobutamine (81 ± 15 vs. 97 ± 19 beats/min, $p < 0.001$), but the systolic and diastolic blood

pressures did not change. Mean initial LVEF was low ($26 \pm 8\%$) and did not increase significantly with dobutamine ($28 \pm 10\%$). End-systolic and end-diastolic volumes decreased with dobutamine, but not to a significant degree ($p = 0.3$). One patient with insufficient gating results was excluded from further evaluation.

Correlation between Sestamibi Uptake and Contractile Reserves

In all, 1,080 segments were evaluated. Of these, 174 (16%) demonstrated normal wall motion and thickening; the remaining 906 segments (84%) had abnormal wall motion and were analyzed for viability. Concordance of the viable and nonviable grouping of the 906 segments by wall motion response to dobutamine and sestamibi uptake, using a cutoff point of 50%, demonstrated agreement in 343 (60%) segments ($p < 0.001$). With the use of a perfusion cutoff point of 60%, agreement was noted in 591 segments (65%) ($p < 0.001$, Fig. 1). Of the 906 segments, 573 (63%) were considered viable by perfusion with a 50% cutoff, compared with only 322 segments (36%) by response to dobutamine ($p < 0.001$). However, with a 60% cutoff, only 376 segments (41%) were considered viable, a figure closer to that obtained by dobutamine response ($p = 0.03$).

The relationship between sestamibi uptake and wall motion response to dobutamine is demonstrated in Figure 2. The following numbers of segments responded to dobutamine: of 263 segments with an uptake of over 80%, 134 (51%); of 104 segments with an uptake of 80–65%, 53 (51%); of 206 segments with an uptake of 65–50%, 79 (38%); and of 333 segments with an uptake $< 50\%$, 56 (17%), ($p < 0.001$).

Results of Wall Motion Improvement after Coronary Artery Bypass Graft

Of the 36 patients who underwent CABG, 3 died during follow-up: 2 had intractable heart failure with $\text{EF} < 20\%$ that did not improve after CABG, and the third patient had sudden cardiac death; 32 who were stable and had no angina or car-

TABLE I Findings for heart rate, blood pressure, and left ventricular parameters at rest and with dobutamine ($n = 54$)

	Rest	Dobutamine	p Value
Heart rate (beats/min)	81 ± 15	97 ± 19	0.001
Systolic blood pressure (mmHg)	131 ± 24	132 ± 24	NS
Diastolic blood pressure (mmHg)	79 ± 12	77 ± 18	NS
LVEF (%)	26 ± 8	28 ± 10	NS
EDV (ml)	205 ± 82	187 ± 81	NS
ESV (ml)	156 ± 76	142 ± 77	NS

Abbreviations: LVEF = left ventricular ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, NS = not significant.

		Perfusion cutoff point = 50%		Perfusion cutoff point = 60%	
		Viable	Nonviable	Viable	Nonviable
Wall motion response to dobutamine	Viable	266	56	187	135
	Non-viable	307	277	180	404

No. of segments: 906

(A) Agreement = 60% $p < 0.001$ (B) Agreement = 65% $p < 0.001$

FIG. 1 Concordance between sestamibi uptake and wall motion response to dobutamine segments with respect to findings: Viable or nonviable segments using a cutoff point of 50% (A) and 60% (B).

FIG. 2 Graph showing the relationship between sestamibi uptake (%) and wall motion response to dobutamine. ■ = Dobutamine response, □ = sestamibi uptake.

diac symptoms were reassessed for perfusion and wall motion. Of the 640 segments, 192 septal segments were excluded because of wall motion abnormalities associated with CABG, which are irrelevant to viability. Another five segments were excluded because the findings were inconclusive. Of the 443 analyzable segments, 310 had a wall motion abnormality prior to CABG, and these were assessed for viability by sestamibi uptake and by wall motion and thickening response to dobutamine.

The respective predictive values of sestamibi uptake using 50 and 60% thresholds for wall motion improvement after CABG were as follows: sensitivity 93 and 70% ($p < 0.007$); specificity 59 and 86% ($p < 0.001$), respectively; accuracy 77% for both. Positive predictive values were 73 and 86% ($p = 0.04$), and negative predictive values were 87 and 70%, respectively ($p < 0.02$).

When wall motion response to dobutamine was added to the assessment of segments considered nonviable by perfusion, we considered a positive or negative response to dobutamine as a true positive for the prediction of wall motion. Of the 310 segments, 74 (24%) showed improvement in wall motion and 41 (13%) showed worsening of wall motion, indicating stress-induced ischemia, and were considered viable. In the segments graded nonviable by sestamibi, using a 50% threshold of sestamibi uptake, the addition of wall motion response to dobutamine did not increase the number of true-positive segments, and there were no significant changes in the

predictive values (Table II). However, when a 60% threshold of sestamibi was used with the addition of wall motion response to dobutamine, the sensitivity increased from 70 to 85% ($p = 0.001$), and the negative predictive value increased from 70 to 81% ($p = 0.009$). The positive predictive value remained high (86 vs. 82%, $p = \text{NS}$) (Table II). It is of note that the 172 of the 310 segments (55%) were regarded as nonviable with a cutoff of 60%.

Prediction of Global Function Improvement

A linear correlation was found between the number of segments that responded to dobutamine prior to CABG and improved global function after CABG ($r = 0.76$, $p < 0.0001$). The assessment of LVEF by gated SPECT prior to and during dobutamine infusion showed that an increment of at least 5% in LVEF was predictive of LVEF improvement after CABG. Only 12 patients (37%) demonstrated significant increase of LVEF after CABG (Fig. 3). The negative and positive predictive values of dobutamine-gated SPECT for global function improvement after CABG were both 75%. We found that a wall motion response to dobutamine in a mean of 8 ± 2 (of 20) segments or more indicated improvement in global LV function.

Discussion

Relationship between Sestamibi Uptake and Inotropic Response

The present study showed a moderate concordance in terms of segment viability and nonviability between wall motion response to dobutamine and sestamibi uptake by individual myocardial segments. The concordance improved from 60 to 65% ($p = 0.004$) when the cutoff point of sestamibi uptake, used to distinguish the viable and nonviable segments, was raised from 50 to 60%.

There are several studies comparing myocardial perfusion by thallium or sestamibi scintigraphy with contractile reserve by dobutamine echocardiography for viability assessment, and most have considerably discordant findings.³¹⁻³⁸ However, like Panza *et al.*³¹ and others,³⁶ the present study dem-

TABLE II Comparison of predictive values of sestamibi uptake of 50 and 60%, and with addition of dobutamine response

	50% Threshold		60% Threshold	
	Sestamibi uptake	Sestamibi and dobutamine response	Sestamibi uptake	Sestamibi and dobutamine response
Sensitivity (%)	158/170 (93)	164/170 (96)	119/170 (70) ^a	144/170 (85) ^a
Specificity (%)	82/140 (59)	81/140 (58)	121/140 (86)	109/140 (78)
Accuracy (%)	240/310 (77)	245/310 (79)	240/310 (77)	253/310 (82)
Positive predictive value (%)	158/216 (73)	164/223 (74)	119/138 (86)	144/175 (82)
Negative predictive value (%)	82/94 (87)	81/87 (93)	212/172 (70) ^b	109/135 (81) ^b

^a $p = 0.001$.

^b $p = 0.009$.

FIG. 3 Graph showing the relationship between left ventricular ejection fraction (LVEF) before and after coronary artery bypass graft (CABG).

onstrated a relationship between the magnitude (thallium) or percentage (sestamibi) of perfusion uptake and the proportion of myocardial segments with wall motion response to dobutamine. Earlier researchers have already shown that the amount of viability depends on the degree of fibrosis.³⁹ Baumgartner *et al.*³⁹ suggested that contractile reserve, as evidenced by a positive dobutamine response, requires at least 50% of viable myocytes in a given segment, whereas scintigraphic methods identify also segments with less viable myocytes. This may explain the relatively low rate of contractile reserve in viable segments by perfusion.

Predictive Values of Gated SPECT with Different Sestamibi Cutoff Points

The optimal sestamibi activity for predicting reversible regional dysfunction has been investigated in earlier studies.¹⁶⁻²³ Some showed that the use of a 51% sestamibi threshold, as accepted, with thallium 201 underestimates the extent of viable myocardium.^{23, 24} By contrast, Udelson *et al.*²² reported that after rest injection, quantified sestamibi activity paralleled thallium redistribution activity. According to these authors, the prediction of wall motion improvement was similar after revascularization of the two agents if a cutoff of 60% of the peak activity of both sestamibi and thallium was used. These results support our study in which comparison of the predictive values of sestamibi with cutoff points of 50 and 60% for wall motion improvement after CABG showed that the overall accuracy was the same, but the positive predictive value of the 60% cutoff was significantly higher; however, its negative predictive value was lower than the sestamibi cutoff value of 50%.

Additive Effect of Dobutamine

The recent approach to the assessment of contractile reserve using low-dose dobutamine combined with perfusion^{26, 27} seems to improve the predictive values of dobutamine-gated SPECT after revascularization. Leoncini *et al.*²⁸ showed that dobutamine-gated SPECT enhances the reliability of nitrate-enhanced sestamibi SPECT when it is used to predict revers-

ible dysfunction in hypokinetic segments, but perfusion quantitation remains superior in akinetic segments.

In the present study, we employed another approach to assess viability, namely, quantitative sestamibi uptake as a basis with the addition of contractile reserve evaluation in segments with lower uptake of sestamibi. Our results showed that in the evaluation in segments with sestamibi uptake of < 50%, there was no enhancement of the predictive value of sestamibi for wall motion improvement after CABG. However, adding the response of dobutamine assessment in segments with 60% uptake and lower yielded a significant increase in sensitivity (from 70 to 85%).

It seems that the best prediction of wall motion improvement is supplied by sestamibi, using a cutoff point of 60% combined with a positive finding for the presence of contractile reserve in segments with perfusion below this point. The positive and negative predictive values were 82 and 81%, respectively.

Prediction of Improvement in Left Ventricular Ejection Fraction

Gated SPECT, because of its ability to calculate LVEF prior to and during dobutamine infusion, has been found to be quite accurate in the prediction of global functional improvement after CABG both by our group, using multigated radionuclide ventriculography with dobutamine,¹² and others.³⁻⁹

Limitations of the Study

Data acquisition during dobutamine was performed with one dose of 10 µg/kg/min. It was impossible to increase the dobutamine dose gradually on-line for wall motion assessment with each dose, as for echocardiography. Furthermore, a 12.5 min infusion with the dose of dobutamine used here, instead of gradually increasing the dose, may lead to an underestimation of contractile reserve in some segments on the one hand, or cause a worsening in wall motion (13% of 310 segments) in cases of severe blood flow reduction on the other. Use of a dual-head camera to shorten the acquisition time may improve the results. Furthermore, the lack of stress perfusion data is a major limitation. The assessment of wall motion in segments with severely reduced uptake, although enhanced, may be somewhat inaccurate. Our method provides no data on the completeness of revascularization or the status of the grafts at follow-up. As such, sensitivity and specificity do not reflect how well the patients do clinically, which is far more important than nominal and often meaningless changes in wall motion.

Conclusions

Dobutamine gated SPECT seems to be an effective technique for the assessment of perfusion and wall motion in patients with ischemic cardiomyopathy. This technique has several advantages: it assesses perfusion and function of the same segments by one acquisition, and it enables a quantitative correlation between perfusion and wall motion in indi-

vidual segments, as well as the assessment of contractile reserve by inotropic provocation. The additive effect of dobutamine in segments considered nonviable by perfusion heightens the predictive accuracy of wall motion improvement after CABG. Dobutamine plus sestamibi uptake seems to be better than uptake alone for viability assessment.

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