Value of Dobutamine Technetium-99m-Sestamibi SPECT and Echocardiography in the Detection of Coronary Artery Disease Compared with Coronary Angiography

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The value of dobutamine echocardiography and ^{99m}Tc-sestamibi SPECT imaging was evaluated as a noninvasive diagnostic method for assessing coronary artery disease (CAD). Twenty-seven patients who underwent coronary angiography were submitted to two separate injections of ^{99m}Tc-sestamibi, one under control conditions and the other after reaching a peak dobutamine infusion rate. Simultaneous ECG and echocardiographic monitoring was also performed during stepwise dobutamine infusion. Whereas the overall sensitivity and specificity of dobutamine sestamibi SPECT imaging were 94% and 88%, these values for dobutamine ECG and echocardiography were 61%, 55% and 84%, 88%, respectively. When dobutamine echocardiography and ^{99m}Tc-sestamibi SPECT imaging were evaluated together, the diagnostic accuracy reaches almost 100%. Dobutamine echocardiography is of value in determining ischemic threshold earlier than clinical symptoms and allows simultaneous evaluation of ventricular performance and contractile function associated with perfusion abnormalities on ^{99m}Tc-sestamibi SPECT imaging. Our experience shows that ^{99m}Tc-sestamibi SPECT imaging, when combined with dobutamine echocardiography, is a safe, practical, well tolerated method with high diagnostic accuracy for the evaluation of CAD.

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Stress testing is widely used in the diagnostic and functional evaluation of patients with suspected coronary artery disease (CAD). Dynamic exercise is the most commonly used stress in ambulatory patients. However, many patients with chest pain cannot exercise adequately because of poor motivation, peripheral vascular disease, musculoskeletal or neurological disorders. In such conditions, an alternative stress would be useful to evaluate coronary reserve.

Dipyridamole-thallium scintigraphy is a useful alternative to dynamic exercise (*1,2*). Dipyridamole induces coronary vasodilatation by blocking cellular adenosine uptake, which leads to a subsequent increase in both myocardial and arterial wall adenosine concentration. Direct intravenous administration of adenosine has also been used in combination with ^{201}Tl scintigraphy (*3*). These techniques are useful for detecting CAD but do not offer the option of detecting an ischemic threshold with which to assess coronary reserve. Moreover, these agents are contraindicated in patients with severe congestive heart failure, baseline hypotension, asthma or severe chronic obstructive pulmonary disease. These limitations have prompted the use of pharmacological stimulation by sympathomimetic agents to induce myocardial ischemia. Dobutamine is a potent stimulator of beta-1, beta-2 and alpha-1 adrenoreceptors with more inotropic than chronotropic activity (*4,5*) and produces hemodynamic changes that mimic those produced by physical exercise.

In this study, we evaluated the diagnostic value of simultaneously applied ^{99m}Tc-methoxyisobutyl isonitrile (sestamibi) for myocardial perfusion and two-dimensional echocardiography for regional wall motion at the same dobutamine dose in the detection of CAD.

MATERIALS AND METHODS

Patient Population

The study group consisted of 27 patients who had anginal chest pain history without ECG evidence of myocardial infarction. There were 23 men and 4 women aged between 30 to 66 yr (mean: 47.2 ± 8 yr).

Coronary Angiography

All patients underwent selective coronary angiography for suspected CAD. Selective coronary angiography in multiple projections was performed by the Judkin's technique within 20 days of dobutamine two-dimensional echocardiography and ^{99m}Tc-sestamibi SPECT imaging with no clinical change in the patient's status between studies. Significant CAD was defined as more than 50% narrowing in one or more major coronary vessels.

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Dobutamine Infusion Protocol

Beta blockers and long-acting nitrates were discontinued 48 hr and 6 hr, respectively, prior to testing. Dobutamine was administered intravenously by an infusion pump at increasing doses of 5–30 μg/kg·min at 5-min intervals. ECG monitoring was continued throughout the infusion. Blood pressure, heart rate and 12-lead ECG were recorded every 5 min. Criteria for the termination of dobutamine infusion were: (1) angina, (2) significant arrhythmia, (3) severe hypertension (systolic blood pressure ≥200 mmHg or diastolic blood pressure ≥110 mmHg), (4) decrease in the systolic blood pressure (20 mmHg or more), (5) heart rate of more than 70% of the target heart rate, (6) maximal dobutamine infusion dose (30 μg/kg·min), (7) new wall motion abnormality (WMA) on two-dimensional echocardiography and (8) ST-segment depression more than 4 mm on ECG.

ECGs obtained during dobutamine infusion were graded as normal, ischemic or nondiagnostic. An ischemic response was defined as development of >1 mm of horizontal or downsloping ST-segment depression 0.08 sec after J-point in a lead with a normal baseline ST segment. The ECGs were interpreted as nondiagnostic if the ST depression has developed in a lead with baseline ST-segment abnormality.

Two-Dimensional Echocardiography

This was first performed under basal conditions before dobutamine infusion using all classic views (parasternal long-axis and short-axis, apical four-chamber and two-chamber) (*6*). Complete recordings were again obtained at each dose of dobutamine until the maximal tolerated dose and 5 min after the end of infusion. All studies were recorded on a video cassette recorder for later analysis.

Analysis of Dobutamine Echocardiograms

All echocardiograms were interpreted independently by three experienced observers unaware of the patients' clinical and angiographic data. Ventricular segmentation was used according to anatomic landmarks (*7*). The site of coronary artery stenosis was predicted according to a previously described technique (*8*). The anteroseptal and anterior segments were considered specific for the left anterior descending artery (LAD), the basal anterolateral segment for the left circumflex (LCx) and the right ventricular free wall for the right coronary artery (RCA).

Segmental wall motion was graded on a four-point scale (0 = normal; 1 = hypokinesia; 2 = akinesia and 3 = dyskinesia).

An abnormal or positive dobutamine echocardiogram was defined as one showing the development of a new WMA not present at baseline. More specifically, for those studies without WMA at rest, any new dobutamine-induced WMA was considered positive. For those studies with baseline WMA, a positive study consisted of one showing either a higher grade WMA in the baseline abnormal segment (i.e., from hypokinetic to akinetic) or any new WMA in a different segment.

Technetium-99m-Sestamibi SPECT Imaging

At the highest infusion rate, 740 MBq ^{99m}Tc-sestamibi was injected intravenously. One hour after the injection, tomographic imaging was performed. Rest images were taken after 24 hr with a second dose (740 MBq) of ^{99m}Tc-MIBI. Tomographic images were obtained with a circular field of view rotating gamma camera (GE 400 AC/T) equipped with a high-resolution, parallel-hole collimator centered on the 140-keV photopeak with a 20% window. Sixty-four views were collected by using a 64 × 64 acquisition matrix for 30 sec each over 180°, starting from 45° right anterior oblique (RAO) to 45° left posterior oblique (LPO) projections. A series of transaxial slices were reconstructed from the raw scintigraphic data with a backprojection technique using a Ramp-Hanning filter. No attenuation correction was used. One-pixel thick oblique tomograms parallel to the long- and short-axes of the left ventricle were reconstructed from the transverse slices.

Analysis of Dobutamine ^{99m}Tc-Sestamibi SPECT Images

All scintigrams were reviewed independently by two experienced observers without knowledge of the patients' clinical and angiographic data.

A semiquantitative segmental visual analysis technique with a five-point scoring system, developed previously by Cedars Sinai group for ^{201}Tl SPECT interpretation was used (*9*) (Fig. 1).

The perfusion defects on ^{99m}Tc-sestamibi images were assigned to a vascular distribution according to previously described individual coronary artery territories for ^{201}Tl imaging (*9–11*) (Fig. 1). The anterior wall and upper septum were assumed to represent the distribution of the LAD; the posterolateral wall, the LCx distribution; and the inferior wall, the distribution of the posterior descending coronary artery which is usually supplied by the RCA. An apical abnormality alone was interpreted as indicating CAD but was not considered specific for involvement of any single vessel.

RESULTS

There were no complications during dobutamine infusion. No significant arrhythmia was observed during the test. Isolated ventricular premature contractions were observed but did not require the interruption of dobutamine infusion or use of an anti-arrhythmic drug. Reasons for dobutamine infusion termination are listed in Table 1 and the hemodynamic responses to dobutamine infusion are listed in Table 2. Heart rate, systolic blood pressure and double product (heart rate × systolic blood pressure) increased significantly ($p < 0.01$), during dobutamine infusion.

All patients' angiographic, electrocardiographic, echocardiographic and scintigraphic data are summarized in Table 3. Significant CAD was present in 18 of 27 patients.

Nine patients had one-vessel, six patients had two-vessel and three patients had three-vessel CAD. Normal or noncritical CAD was detected in nine patients.

During dobutamine infusion, the sensitivity and specificity of ST-segment depression were 61% (11/18) and 55% (5/9), respectively (Tables 4 and 5).

In 15 of 18 patients with CAD, the wall motion score index was higher at peak dobutamine infusion than during the baseline test, indicating increased WMA. The overall sensitivity and specificity of dobutamine stress echocardiography for CAD were 83% (15/18) and 88% (8/9) (Table 4). In 19 patients without rest WMA, the sensitivity and specificity of new WMA for CAD was 70% (7/10) and 88% (8/9). In eight patients with rest WMAs, three had three-vessel CAD, three had two-vessel CAD and two had one-vessel CAD. Additional dobutamine-induced WMAs were present in all of these patients (Table 3).

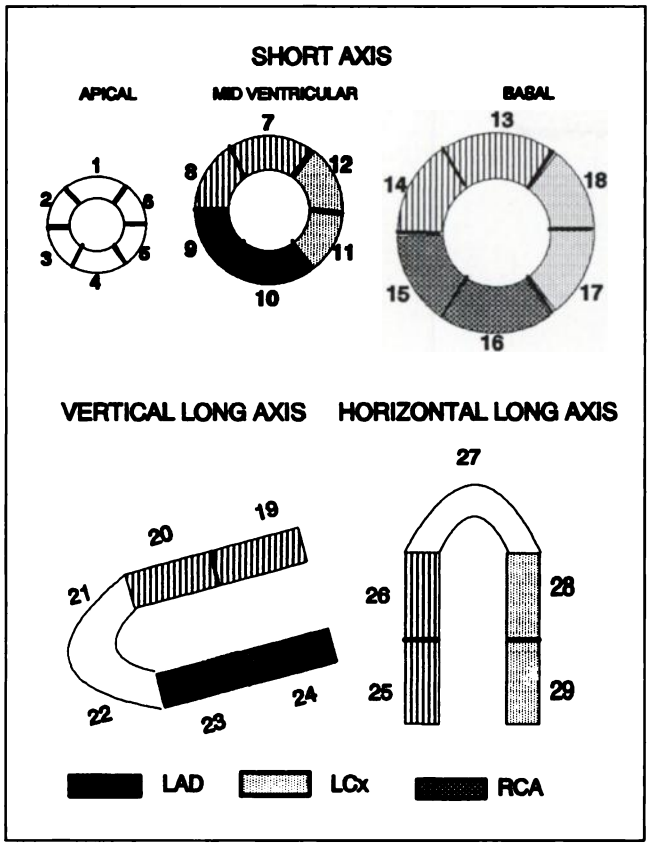

FIGURE 1. Schematic presentation of three short-axis and vertical and horizontal long-axis slices displaying myocardial segments and the distributions of the three major coronary arteries. Short-axis: (1, 7, 13) anterior, (2, 8, 14) anteroseptal, (3, 9, 15) inferoseptal, (4, 10, 16) inferior, (5, 11, 17) inferolateral, (6, 12, 18) high lateral. Vertical long-axis: (19) anterobasal, (20) anterior, (21) anteroapical, (22) inferoapical, (23) inferior, (24) inferobasal. Horizontal long-axis: (25) proksimal septal (26) distal septal, (27) apical, (28) distal lateral, (29) proksimal lateral. LAD = left anterior descending artery; LCx = left circumflex, RCA = right coronary artery.

Seventeen of the 18 CAD patients developed reversible ^{99m}Tc-MIBI perfusion defects, resulting in a sensitivity of 94% (Table 4). One patient with normal coronary arteries had a reversible MIBI defect, resulting in a specificity of 88%.

The location of stress-induced ^{99m}Tc-MIBI perfusion defects correlated well with the distribution of angiographically diseased vessels in 17 of 18 patients (94%).

TABLE 1
Reasons for Dobutamine Infusion Termination

Reason	No. of patients
Angina	2
New wall motion abnormality	14
Heart rate response (70% of maximal heart rate achieved)	1
Maximal dose (30 μg/kg·min)	8
Ischemic ECG changes	2

TABLE 2
Hemodynamic Responses to Dobutamine Infusion

	Rest	Maximum dose
Heart rate (bpm)	77.4 ± 14.3	111 ± 24.6*
Systolic blood pressure (mmHg)	135.0 ± 17.8	148 ± 29.5*
Diastolic blood pressure (mmHg)	88.6 ± 21.7	74.6 ± 14.0
Double product	10.449 ± 3.556	15.540 ± 4.226*

*$p < 0.01$.

Figure 2 shows a dobutamine-induced severe reversible defect in the LCx coronary artery territory. A severe reduction of ^{99m}Tc-sestamibi uptake at stress and minimal activity reduction at rest was observed in the posterolateral wall in short- and horizontal long-axes tomograms. The posterolateral abnormality is not visualized on the vertical long-axis tomograms since this region is not seen in this view.

DISCUSSION

Our results indicate that dobutamine infusion at increasing doses up to 30 μg/kg·min is a feasible and well tolerated stress test in the detection of CAD. This technique allows detection of CAD with high sensitivity and specificity.

In patients without WMA at baseline studies, the sensitivity and specificity of two-dimensional echocardiography was less (70% and 88%, respectively) than those in patients with resting WMA. Two of these three patients had mild stenosis and one had a distal coronary lesion with well preserved myocardial function. This finding suggests that distal lesions and mild stenosis may not affect functional reserve.

The single false-negative dobutamine ^{99m}Tc-sestamibi SPECT test occurred in a patient with 60% distal LAD stenosis. This finding was attributed to the well developed collateral circulation.

A false-positive scintigraphic result was observed in a patient with multi-segmental, noncritical stenoses with wall irregularities in the RCA. Although the inferior left ventricular wall is a difficult area to interpret with SPECT imaging and gives rise to false-positive results, the reversibility of the defect in this patient was clearly seen and significant ST depression was developed during the dobutamine stress test. These findings raise the question of disparity between the angiographic and physiologic severity of coronary disease as also reported by White et al. (*12*).

Mason et al. performed thallium scintigraphy during dobutamine infusion to overcome the problems of early redistribution of thallium and inadequate exercise (*13*). They found a similar sensitivity and specificity (94% and 87%, respectively). Since ^{99m}Tc-sestamibi does not have significant redistribution, there is no need to continue dobutamine infusion during imaging. Instead, two-dimensional echocardiography can be performed during dobutamine

TABLE 3
Clinical, Angiographic, Echocardiographic and Scintigraphic Data

Patient no.	Coronary artery stenosis			Dob. stress test			Dob. echocardiogram		Sestamibi SPECT	
	LAD	LCx	RCA	Angina	ECG	Dose	Rest	Extension with Dob	Stress	Rest
1	100	0	0	+	+	15	AS(2)	AS(3)	AS(3),Ap(4)	AS(2),Ap(4)
2	0	0	0		+	25	0	0	0	0
3	100	90	60		+	25	AS(1),PL(1)	AS(3),PL(1)	AS(3),I(2)	AS(3)
4	60	0	80		+	20	PL(2),Ap(1)	AS(3)	AS(2),IL(2)	0
5	90	0	100		+	25	0	AS(1),Ap(1)	AS(2),Ap(2),I(2)	Ap(2)
6	90	0	80	+	0	30	AS(1),Ap(1)	Ap(3)	AS(3),Ap(3),IS(2)	AS(1),Ap(2)
7	0	0	0		0	30	0	0	0	0
8	0	95	0		0	30	0	PL(1)	IL(3)	0
9	0	0	80		0	30	0	PS(1)	I(2)	0
10	0	80	0		0	30	0	PL(1),A(1)	AS(2),IL(2)	0
11	85	80	85	+	+	20	AL(1)	AS(1),I(2)	A(3),I(2)	0
12	0	0	0		+	30	0	I(1)	0	0
13	0	0	0		+	30	0	0	0	0
14	70	60	0		0	30	0	Ap(3)	AS(2),IL(2)	0
15	0	0	0		0	30	0	0	0	0
16	0	0	0		+	30	0	0	0	0
17	60	0	0		+	30	0	Ap(1)	0	0
18	0	0	0		0	30	0	0	0	0
19	80	0	0		0	30	0	0	A(3)	0
20	75	0	60		0	30	PL(1)	AS(1)	AS(2),I(1)	0
21	85	0	0		+	20	0	Ap(1)	AL(3)	0
22	0	0	40		0	30	0	0	I(2)	0
23	0	0	0		0	30	0	0	0	0
24	90	80	70		+	20	Ap(1)	AS(2)	AS(3),I(2)	AS(2)
25	75	0	60		+	25	0	0	AL(2),I(2)	0
26	60	0	0		+	30	0	0	A(2)	0
27	0	0	95		+	15	PL(1),I(1)	PL(3),I(3)	I(2),IL(2)	0

Dob. = dobutamine; A = anterior; AS = anteroseptal; IS = inferoseptal; I = inferior; IL = inferolateral; HL = high lateral; Ap = apical; PL = posterolateral; PS = posteroseptal.
Segmental WMA grading: 0 = normal; 1 = hypokinesia; 2 = akinesia; 3 = dyskinesia.
Perfusion defect scoring: 0 = normal; 1 = mild; 2 = moderate; 3 = severe reduction; 4 = abscence of sestamibi uptake.

infusion to evaluate wall motion at the same time. Dobutamine stress echocardiography has shown promise as a clinically useful technique in several studies (*14–16*). Marwick et al. (*17*) compared the accuracy of dobutamine stress echocardiography in the diagnosis of ischemia with that of ^{99m}Tc-sestamibi using the same stress in the same patient group and reported that dobutamine echocardiography and ^{99m}Tc-sestamibi SPECT have similar accuracy in the diagnosis of ischemia and better correlation with each other than with angiographic indices of CAD severity. Speady et al. (*18*), Warner et al. (*19*) and Mahmarian et al. (*20*) also have reported that dobutamine stress thallium is a sensitive method for the detection and localization of CAD.

TABLE 4
Comparative Sensitivity, Specificity, Predictive Value and Accuracy of Dobutamine Stress Echocardiography, Electrocardiography and ^{99m}Tc-MIBI SPECT

	Sensitivity	Specificity	Predictive value	Accuracy
Dobutamine ECG	61%	55%	91%	59%
Dobutamine echocardiogram	83%	88%	93%	85%
MIBI SPECT	94%	88%	94%	92%

Flow reduction through a diseased coronary artery may become significant and lead to ischemia under various conditions of stress. Stimuli belong to two main categories, those that produce coronary vasodilation mediated through an increase in heart work (muscular exercise or dobutamine administration) and those capable of producing primary vasodilation independent of heart work (e.g., dipyridamole and adenosine). In the normal heart, an increase in myocardial oxygen demand as reflected in the double product (heart rate × systolic blood pressure) is accompanied by a parallel increase in flow so that a linear relationship exists between these two variables and a constant supply demand ratio is maintained for the entire range of heart work. In case of reduced flow reserve in one region of the heart due to coronary stenosis, an increase in myocardial oxygen demand is not accompanied by an increase in flow.

Beta adrenergic inotropic agents such as dobutamine increase coronary flow dramatically (*21*) and may increase resistance to flow through a stenotic coronary artery (*22*).

TABLE 5
Comparative Sensitivities of Dobutamine ECG, Two-Dimensional Echocardiography and MIBI Imaging for One-Vessel, Two-Vessel and Three-Vessel CAD

Significant CAD	ECG		Two-dimensional echocardiography		^{99m}Tc-MIBI	
(>%50 narrowing)	(+)	%	(+)	%	(+)	%
One-vessel disease	5/9	55	7/9	77	8/9	88
Two-vessel disease	3/6	50	5/6	83	6/6	100
Three-vessel disease	3/3	100	3/3	100	3/3	100
Overall	11/18	61	15/18	83	17/18	94

In large doses, dobutamine can increase heart rate, double product and myocardial oxygen demand and induce ischemia (*23*). The induced coronary hyperemia which occurs during dobutamine infusion is a result of increased myocardial oxygen demand. Meyer et al. have shown that the increase in coronary flow is heterogenous in patients with significant CAD (*24*). Dobutamine-induced ischemia leads to deterioration of perfusion and contractile function in the ischemic zone (*25*). Our hemodynamic data confirm that dobutamine-induced myocardial ischemia is primarily related to an increase in myocardial oxygen consumption.

Although pharmacological stress has the limitation of not being a functional and physiological test, dobutamine infusion, contrary to dipyridamole, mimics physiological exercise to a degree by increasing myocardial oxygen demand. Dipyridamole infusion produces a difference in perfusion between the areas, with normal and limited coronary reserve, without causing ischemia due to an insufficient increase in oxygen demand. On the other hand, dobutamine infusion allows for an estimate of the severity of stenosis by means of the double product at the onset of ischemia. Dipyridamole prevents the use of a similar approach because of the uncoupling of flow and double product. Theoretically, the administration of vasodilators such as dipyridamole and adenosine should produce greater dishomogeneity of coronary flow when compared with the exercise and dobutamine stress tests. Although these agents directly increase coronary flow, increased myocardial tracer uptake during high coronary flow states is not linearly related to flow for ^{201}Tl and ^{99m}Tc-sestamibi (*26*). At hyperemic flows above 2 to 2.5 times the baseline flow, the uptake of these tracers is less than absolute flow because of lower myocardial tracer extraction at high flow velocities.

The following properties of dobutamine make it an ideal pharmacologic stress agent:

1. It can be administered easily and safely.
2. The onset and cessation of action is rapid (average plasma active half-life of 120 sec) (*27*).
3. A controlled and predictable hemodynamic response can be obtained even in high doses, and dobutamine has been shown to be relatively resistant to inducing arrhythmias (*28*).
4. It is not influenced by patient motivation or ability to exercise.
5. The graded stress of dobutamine provides physiologic data not available with other agents such as dipyridamole.

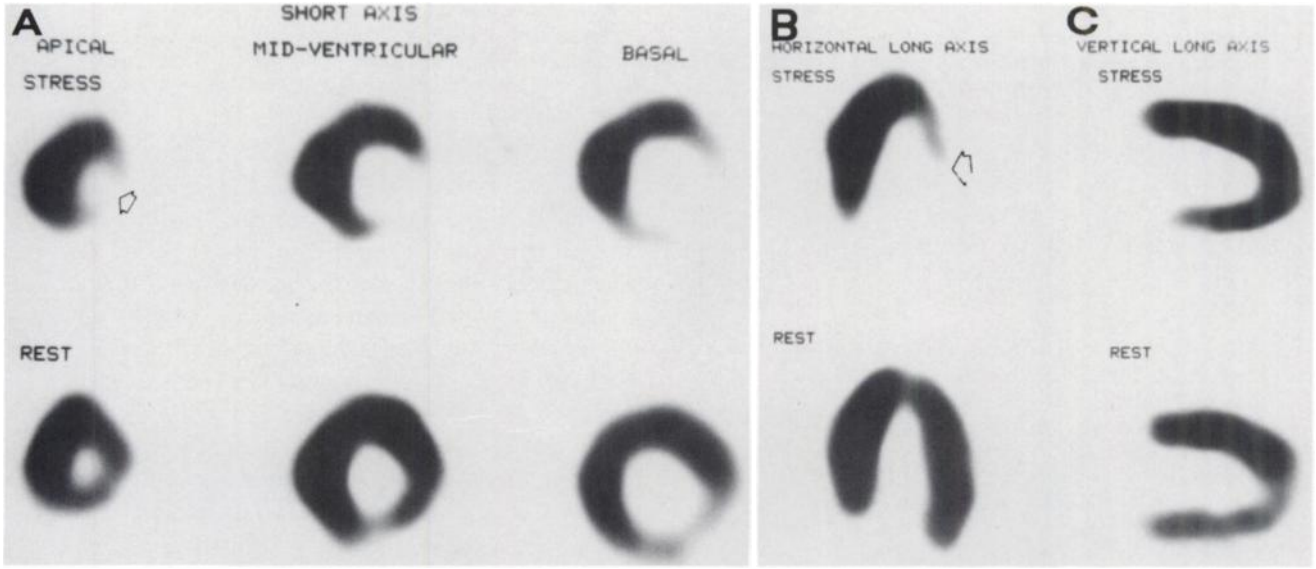

FIGURE 2. Dobutamine stress and rest ^{99m}Tc-sestamibi images in short-axis (A), horizontal long-axis (B) and vertical long-axis (C) images demonstrate an extensive reversible defect throughout the posterolateral wall of the left ventricle which corresponds to angiographically documented LCx coronary artery stenosis.

Although dobutamine ^{99m}Tc-sestamibi SPECT imaging by itself is a valuable diagnostic tool in the detection of CAD, simultaneously applied two-dimensional echocardiography is of great help in determining early ischemic changes, thereby increasing the safety of the test. It also provides additional information about ventricular function and regional wall motion in comparison with regions of corresponding perfusion defects detected on ^{99m}Tc-sestamibi SPECT imaging.

We conclude that dobutamine ^{99m}Tc-sestamibi SPECT imaging, when combined with echocardiography, offers a safe, readily available and highly sensitive and specific screening test for detecting CAD.

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