DIPYRIDAMOLE THALLIUM-201 MYOCARDIAL PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IN CORONARY ARTERY DISEASE

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ABSTRACT

We performed dipyridamole Tl-201 myocardial perfusion tomographic studies imaging in 38 patients with suspected or known coronary artery disease to determine the sensitivity, specificity , and accuracy of the procedure in the detection of coronary artery disease and in localization of individual stenosed vessel. The overall sensitivity, specificity , accuracy, positive predictive value, and negative predictive value of the test were 96.8% , 42.9% , 86.8%, 88.2%, and 75.0 %, respectively. And those for the detection of stenosed vessels were 75.8%, 46.4%, 66.7%, 75.8%, and 43.3%, respectively. The sensitivity in the detection of individual stenosed vessel was significantly higher in vessels with severe than with moderate stenosis (54.5% vs. 87.5%). Fixed defects usually indicate very severe and complete occlusion of coronary arteries. Reversible defects generally indicate significant but nonocclusive coronary artery stenosis. We conclude that dipyridamole thallium-201 myocardial perfusion tomography is a useful noninvasive test for coronary artery disease.

INTRODUCTION

Exercise thallium-201 myocardial perfusion tomographic study has been widely used in the detection of coronary artery disease, assessment of myocardial viability , and evaluation of prognosis.[1-6] However, there are many patients who cannot exercise adequately for the test due to noncardiac causes. The pharmacologic stress test has been introduced as an alternative to exercise stress test.[7] Many investigators had reported very good results with dipyridamole Tl-201 myocardial perfusion tomographic study.[8-12] Pharmacologic stressors are useful for patients who cannot exercise for various reasons including physical limitations, peripheral vascular disease, limi-ting orthopedic disorders and aortic aneu-rysm.The purpose of administration of dipyri-damole is to create a disparity in coronary blood flow bet-ween normal and stenosed arteries by vaso-dilatory effects of dipyri-damole.

This study was performed to evaluate the sensitivity , specificity, accuracy, positive predictive value , and negative predictive value for the detection of coronary artery disease and for the localization of individual abnormal vessel. The ability of the test to evaluate severity of coronary artery disease was also examined.

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MATERIALS AND METHODS

Patient population. The study group consisted with 38 patients suspected of coronary artery disease referred to our department for dipyridamole Tl-201 myocardial perfusion tomographic study. The clinical data and the hemodynamic parameters of the patient population are cited in Table 1. Thirteen patients had previous myocardial infarction diagnosed by electrocardiography (ECG) and clinical history. In all patients beta-blockers and anti-anginal medications (long acting nitrates and calcium antagonists) were discontinued at least 48 hours before radionuclide studies.

Study protocol. The patients were asked to fast overnight and remain fast until the redistribution images were finished. Dipyridamole was administered in an intravenous infusion with a total dose of 0.56 mg/kg over a period of 4 minutes. Two minutes after the infusion was completed, thallium-201 was injected rapidly via the infusion line. Imaging was begun at 10 minutes after thallium-201 injection. Two sets of tomographic images were acquired after single injection. The stress images taken within 10 minutes after the thallium-201 injection and the redistribution images were obtained 3 hours later .

Coronary angiography . Coronary angiography was performed by Sheldinger technique. Angiographic results were reported in consensus by two experienced observers. Angiographic demon-stration of 50% or more narrowing of anyone of the epicardial coronary arteries was considered abnormal. A luminal stenosis of 50 to 75% was considered moderate, while a luminal stenosis more than 75% was considered severe.

Thallium-201 imaging. SPECT imaging was performed using a large field of view gamma camera (Toshiba ,GCA 901A) equipped with a low-energy , high resolution , parallel hole collimator and connected with a dedicated computer system (TOSBAC GHS 901a). Thirty-six projections (35 second/projection) were obtained over a semicircular 180 degrees arch which extended from the 45 degrees right anterior oblique to the 45 degrees left posterior oblique position .Two 20% symme-trical window centered on the 69-80 keV. and 135 keV. peaks were used. The projection images were stored in 64x64 matrix. Filtered backprojection was performed with a Butter-worth filter with a cut-off frequency of 0.15 cycle/pixel, order 5 , to reconstruct transverse axial tomograms Sagittal and oblique tomograms parallel to the long axis and short axis of the left ventricle were then extracted from the filtered transaxial tomograms by performing co-ordinate transformation with the appropriate interpolation. No attenuation or scatter correction was applied.

Data analysis. In each patient, corresponding dipyridamole and redistribution tomographic images were evaluated for direct comparison. For each study, tomograms were divided into 29 myocardial segments, as shown in Figure 1. Each segment was assigned to one of the major vascular territories. The anterior descending artery (LAD) territory included the anterior wall (segments 1,7,13,-19,20), septum (segments 2,3,8,9,14,15,-25,26), and apical wall (segments 21,22,27). The lateral wall (segments 5,6,11,12,17,-18,28,29,) was assigned to the left circumflex artery (LCX). The inferior wall (segments 4,10,16,23,24) was assigned to the right coro-nary artery (RCA) if coronary angiography showed right dominant circulation, and was assigned to the LCX if coronary angiography revealed left dominant circulation.

Regional thallium-201 activity was visually analyzed on the three short- axis (one apical, one mid-ventricular and one basal) tomograms and on one horizontal and one vertical long-axis tomograms. The Tl-201 myocardial perfusion stress and rest images were reviewed and marked, *'N'* for normal thallium-201 uptake , *'R'* for reversible thallium-201 defects and *' F '* for fixed or irreversible thallium-201 defects,

independently by two experienced observers, the studies with discordant readings were reviewed by the third observer and agreement of two out of three observers was considered .

Statistical analysis. Data are expressed as mean $\pm$ 1 SD Differences of the mean value were assessed by Student's *t* test for paired or unpaired data, as appropriate. Chi square analysis was used to assess differences between proportions. A probability (*P*) value < 0.05 was considered statistically significant. Sensitivity was defined as the number of true-positives devided by the sum of true-positives and false-negatives x 100. Specificity was defined as the number of true-negatives devided by the sum of true-negatives and false-negatives x 100. Diagnostic accuracy was defined as the sum of true-positives and true-negatives devided by the total. Positive predictive value (PPV) was defined as true-positives devided by the sum of true- and false-positives. Negative predictive value (NPV) was defined as true-negatives devided by the sum of true- and false-negatives.

RESULTS

Coronary angiography

The results of coronary angiography are summarized in Table 2. Of the 38 patients ,31(81.6%) had at lease one major coronary artery stenosis of 50% or more of luminal diameter. There were 10 patients with single-vessel disease, 10 with double-vessel disease and 11 with triple-vessel disease. Six patients had normal coronary arteries and one had angiographically insignificant stenosis (40,40,45% stenosis of LAD, RCA and LCX, respectively), thus, constituted seven patients with negative angiographic findings. Individual vessel analysis showed 22 coronary arteries with moderate (50 % to 75%) luminal stenosis and 40 coronary arteries with severe (more than 75%) luminal stenosis.

Dipyridamole test results

Hemodynamic parameters recorded at rest and at peak exercise and dipyridamole-induced ECG changes are presented in Table 1.

Tl-201 myocardial perfusion imaging

At visual analysis, 30 of 31 patients with significant stenosis of at least one coronary artery showed abnormal Tl-201 myocardial perfusion images (sensitivity 96.8%) (Table 3). On the otherhand, 3 of 7 patients without significant coronary narrowing showed normal findings (specificity 42.9%) Fig. 2 and 3 show two representative examples of dipyridamole stress / redistribution Tl-201 myocardial perfusion images in a patient with normal study and a patient with coronary artery disease documented at angiography.

The overall sensitivity , specificity and diagnostic accuracy of dipyridamole Tl-201 myocardial perfusion tomography in the detection of individual stenosed vessels were 75.8%, 46.4%, and 66.7% ,respectively (Table 4). Sensitivity , specificity, and diagnostic accuracy in each of the individual vascular territories were not significantly different. The overall sensitivity, specificity and diagnostic accuracy in the identification of individual stenosed coronary artery in patients with single-vessel disease were 66.7%, 38.9%, and 48.1% respectively (Table 5). In multivessel disease the overall sensitivity, specificity, and accuracy were 77.4% , 60.0%, and 74.6% respectively. Sensitivity of dipyridamole Tl-201 myocardal perfusion tomography in the detection of LAD and accuracy of LAD and LCX were significantly ($P<0.05$)higher in patients with multivessel disease than with single-vessel disease . There was otherwise no significant difference of sensitivity, specificity, and accuracy in the detection of other individual stenosed vessels between the two groups ($P > 0.05$) .

Comparison between patients with and without previous myocardial infarction. There were 13 patients (41.9% of CAD patients) with history and ECG diagnosis of previous myocardial infarction (Table 6). Overall sensitivity in the detection of coronary artery disease was not different between the patients with and without prior myocardial infarction.

Effects of the severity of coronary artery stenosis on diagnostic accuracy. Individual vessel analysis showed 22 coronary arteries (35.5%) with moderate (50-75%) luminal stenosis and 40 coronary arteries (64.5%) with severe (>75%) luminal stenosis . The effect of stenosis severity on detection of lesions is shown in Table 7. The overall sensitivity in the identification of individual diseased vessels with severe luminal stenosis (87.5%) was significantly ($P < 0.05$) higher compared to those with moderate luminal stenosis (54.5 %).

The distribution of 'fixed' and 'reversible' perfusion defects The distribution of 'fixed' and 'reversible' perfusion defects in relation to severity of coronary artery stenosis was shown in Table 8. Of 84 abnormal segments, 43 were 'fixed' and 41 were 'reversible'. Fifteen (34.9%) of fixed and 3 (7.3%) of reversible defects were in the territories of vessels with 100% luminal stenosis. The remaining 28 (65.1%) fixed and 38 (92.7%) reversible defects were in the territories of nonocclusive vessels.

DISCUSSION

The principle of vasodilator stress myocardial perfusion imaging was first introduced by Strauss and Pitt[7] who showed that dimethyladenosine increased coronary blood flow and Tl-201 uptake to normal area of myocardium, while regions of myocardium perfused by coronary artery with a haemodynamically significant coronary stenosis had reduced flow reserve and ,thus less thallium-201 uptake. Dipyridamole is a complex pyrimidine derivatives with a molecular weight of 504. It is lipophilic and is metabolized by hepatic biotransformation with subsequent biliary and fecal excretion.[13] In human , intravenous dipyridamole infusion results in a mild decreased in blood pressure , a slight reflex increase in heart rate, a slight increase in cardiac output but no change in myocardial oxygen demand. Coronary vascular resistance significantly decreases and coronary sinus flow increases, with a small increase in pulmonary artery pressure.[14,15] The vasodilator effect of dipyridamole is up to 20 to 40 minutes.[16] The initial myocardial distribution of intravenously administration of Tl-201 is proportional to blood flow when the tracer is administered following dipyridamole infusion. Under condition of myocardial ischemia, dipy-ridamole-induced vasodilatation results in diminished Tl-201 myocardial uptake and delayed redistribution similar to that observed with exercise scintigraphy.[17,18,19] Redistribution perfusion defects are seen with comparable frequency on serial myocardial scintigrams acquired with vasodilators stress or exercise stress in patients with CAD who underwent both tests at different time.

We studied the clinical utility of dipyridamole Tl-201 myocardial perfusion tomographic images in patients with known or suspected coronary artery disease who underwent coronary arteriography. Very good overall sensitivity, accuracy , positive predictive value, and negative predictive value in the detection of coronary artery disease was observed. The specificity was rather low, probably due to referral bias . The results in this study is corresponded to the results reported by other investigators.[8-12] The sensitivity in the identification of coronary artery disease in patients with and without previous myocardial infarction was not different (Table 3).

The overall sensitivity, specificity, accuracy, and NPV in the identification of individual stenosed vessels were moderate (Table4). Only the sensitivity in the detection of LAD was high. The

low accuracy could be due to many factors, for example, false positive due to technical factors and soft tissue attenuation, the assignment of myocardial regions to the coronary arteries, the degree of coronary stenosis, the effects of collateral circulations, and also the possibility of coronary spasm. Similar results were reported by many investigators.[8-12]

We found that the overall diagnostic accuracy in the detection of individual stenosis vessels were significantly higher ($P<0.05$) in patients with multivessel disease than those with single-vessel disease (Table 5). There were low specificity of LAD in both groups and LCX in the single-vessel disease patients.

We analyzed the effects of severity of coronary artery stenosis (Table7) and observed that the overall sensitivity in the detection of individual diseased vessel was significantly ($P<0.05$) higher in coronary arteries with severe luminal stenosis (87.5%) than those with moderate luminal stenosis (53.6 %). This could be due to the fact that coronary blood flow is significantly decreased in more severe coronary artery stenosis and thallium-201 uptake, over a wide range of physiologic blood flow , is proportional to coronary blood flow.[20-22] The more severe luminal stenosis the more severe diminished coronary blood flow and thallium-201 uptake. So the severely ischemic lesions appears more prominent than areas with less ischemia.

By visual analysis of the Tl-201 myocardal perfusion images, there were 84 abnormal segments of which 43 were fixed perfusion defects and 41 were reversible perfusion defects. Of 18 segments of perfusion defects in the areas profused by vessels with total occlusion (100%stenosis) , 15 segments (83.3%) were fixed and 3 segments (16.7%) were reversible defects.The reason why not all of the areas profused by totally occluded vessels were infarcted may be the collateral circulations.[23] On the other hand , of 43 fixed defects, only 15 segments (34.9%) were in the territories of coronary arteries with 100% luminal stenosis and 28 fixed defects (65.1%) were in the territories of nonocclusive coronary arteries. Cuocolo et al[24] reported that with thallium-201 'reinjection' 47% of 122 myocardial regions with irreversible defects on standard stress-redistribution thallium-201 imaging demon-strated enhance uptake of thallium-201. Contrariwise, there is growing consensus that about 90% of transmural acute myocardial infarctions are caused by an occlusive intracoronary thrombus overlying an ulcerated or fissured stenotic atheroma.[25] Platelet aggregation and activation and vasospasm may contribute to the development of myocardial infarction even in the absence fixed critical stenoses.[26] Although not all of the fixed defects were in the areas supplied by complete stenosis, ' fixed defects' still denoted very severe coronary artery stenosis. However, in this study, about two third (61.0%) of reversible defects were in the areas perfused by coronary arteries with severe but incomplete occlusion (76-99% luminal stenosis). This is suggestive that reversible defects represents areas of high-risk of cardiac events and indicate catheterization and revascularization. Brown et al[27] showed that the number of Tl-201 redistribution defects was the best predictor of future cardiac events as determined by logistic regression analysis in CAD patients without prior myocardial infarction.

Study limitations There were some limitations to the study that should be considered . The first limitation might be the lack of computer quantitation of coronary angiography and SPECT quantitation was not applied. The second was the assignment of myocardial segments which might not really confined to the assigned coronary artery. There was variation in size of the myocardial wall in diseased heart as seen in thallium-201 images. The soft tissue attenuation of anterior wall by breast tissue and the inferior wall by the diaphragm. Referral bias was another factor. Because at present, Tl-201 myocardial perfusion study is generally accepted as a clinical tool in the diagnosis of coronary artery, patients with normal thallium-201 studies were usually not

referred to coronary angiography but patients with abnormal thallium-201 studies were more likely to proceed to the procedure . So the number of patients with normal angiogram was disproportionately low .

CONCLUSIONS

Dipyridamole Tl-201 myocardial perfusion single photon emission computed tomography is a useful noninvasive means to evaluate patients suspected of coronary artery disease . It provides very good sensitivity, accuracy , PPV, and NPV in the detection of coronary artery disease. Although specificity is low, probably due to referral bias and technical factors. The accuracy of detection of individual coronary artery stenosis is higher in patients with multivessel than in patients with single-vessel disease. The sensitivity of detection of individual coronary artery stenosis is better in severe (>75%) stenosis than in moderate (50-75%) stenosis. The fixed defects usually indicate very severe , critical and often complete occlusion of coronary arteries. The reversible defects, on the other hand, generally indicate significant but nonocclusive coronary artery stenosis. We conclude that dipyridamole thallium-201 myocardial perfusion study is safe and useful for the evaluation of coronary artery disease .

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Table 1 Clinical data and haemodynamic parameters recorded at rest and at dipyridamole stress test in the patient population (n = 38 cases)

Clinical data and haemodynamic parameters	
age (years)	59 ± 9 (range40-77 years)
Sex (men/women)	21/17 age 58 ± 8 / 60 ± 8
History of myocardial infarction	13 cases
Dipyradamole dose	44.0 ± 13.5 mg.
Rest	
Heart rate (bpm)	71.0 ± 14.2
Systolic blood pressure (mmHg)	139.2 ± 23.2
Diastolic blood pressure (mmHg)	85.3 ± 13.8
Dipyridamole test	
Heart rate (bpm)	91.0 ± 13.0
Systolic blood pressure (mmHg)	130.7 ± 24.2
Diastolic blood pressure (mmHg)	78.3 ± 13.2
% of maximal predicted heart rate	56.5 ± 8
Dipyridamole stress ECG	
Positive	15 cases
Negative	23 cases

Table 2 Coronary arteriographic results in 31 patients

coronary artery disease	cases	LAD	LCX	RCA	Lt.mian
Single-vessel	10	6	2	1	1
Double-vessel	10	8	5	7	0
Tripple-vessel	11	11	11	11	0
Total	31	25	18	19	0
Severity of stenosis vessels (n)					
Moderate stenosis	22	6	10	6	1
Severe stenosis	40	19	8	13	-

Table 3 Sensitivity , specificity , accuracy , positive predictive value (PPV) , negative predictive value (NPV). in the detection of coronary artery disease in 38 patients.

	no. of patients	%	patients with previous MI	No previous MI
Sensitivity	30/31	96.8	100%(13/13)	94.4% (17/18)
Specificity	3/7	42.9	—	42.9% (3/7)
Accuracy	33/38	86.8	—	80.0% (20/25)
PPV	30/34	88.2	—	80.9% (17/21)
NPV	3/4	75.0	—	75.0% (3/4)

Table 4 Sensitivity , specificity , diagnostic accuracy, and predictive values in the detection of individual stenosed vessels in 31 patients with coronary artery disease

	LAD	LCX	RCA	Overall
Sensitivity	92.0% (23/25)	66.7% (12/18)	63.2% (12/19)	75.8% (47/62)
Specificity	20.0% (1/5)	50.0% (6/12)	54.5% (6/1)	46.4% (13/28)
Accuracy	80.0% (24/30)	60.0% (18/30)	60.0% (18/30)	66.7% (60/90)
PPV	85.2% (23/27)	66.7% (12/18)	70.6% (12/17)	75.8% (47/62)
NPV	33.3% (1/3)	50.0% (6/12)	50.0% (6/12)	43.3% (13/30)
		$P > 0.05$		

LAD = left anterior descending artery, LCX = left circumflex artery,
RCA = right coronary artery
PPV = positive predictive value, NPV = negative predictive value

Table 5 Sensitivity , specificity, and accuracy in the detection of stenosed vessels in patients with single-vessel and multivessel disease

	Single-vessel disease			Multivessel disease		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
LAD	66.7%	33.3%	55.6%	100.0%	0.0%	90.5%
LCX	50.0%	28.6%	33.3%	68.8%	80.0%	71.4%
RCA	100.0%	50.0%	55.6%	61.1%	66.7%	61.9%
All vessels	66.7%	38.9%	48.1%	77.4%	60.0%	74.6%

Table 6 Sensitivity of dipyridamoleTl-201 myocardial perfusion SPECT in the detection of CAD in patients with and without previous myocardial infarction

Coronary artery disease	Previous MI	Sensitivity (%)	No previous MI	Sensitivity(%)
Single-vessel	3	100.0%	7	85.7%
Double-vessel	5	100.0%	5	100.0%
Tripple-vessel	5	100.0%	6	100.0%
Total	13	100.0%	18	94.4%

Table 7 Sensitivity in the detection of stenosed vessels in territories supplied by arteries with moderate (50- 75%) and severe (76-100 %) stenosis in 31 patients

	no. stenosed vessels	Moderate stenosis (50 - 75 %)	Severe stenosis (76-100 %)
LAD	25	83.3% (5/6)	94.7% (18/19)
LCX	18	60.0% (6/10)	75.0% (6/8)
RCA	19	16.7% (1/6)	84.6% (11/13)
All vessels	63	54.5% (12/22)	87.5% (35/40)

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

Table 8 Number of fixed and reversible perfusion defects in the areas supplied by coronary arteries with varying degree of luminal stenosis

Perfusion defects (n=112)	% of luminal stenosis			
	100%	90-99%	76-89%	50-75%
Fixed (43segments)	15 (34.9%)	17 (39.5%)	5 (11.6%)	6 (14.0%)
Reversible(41segments)	3 (7.3%)	17 (41.5%)	8 (19.5%)	13 (31.7%)

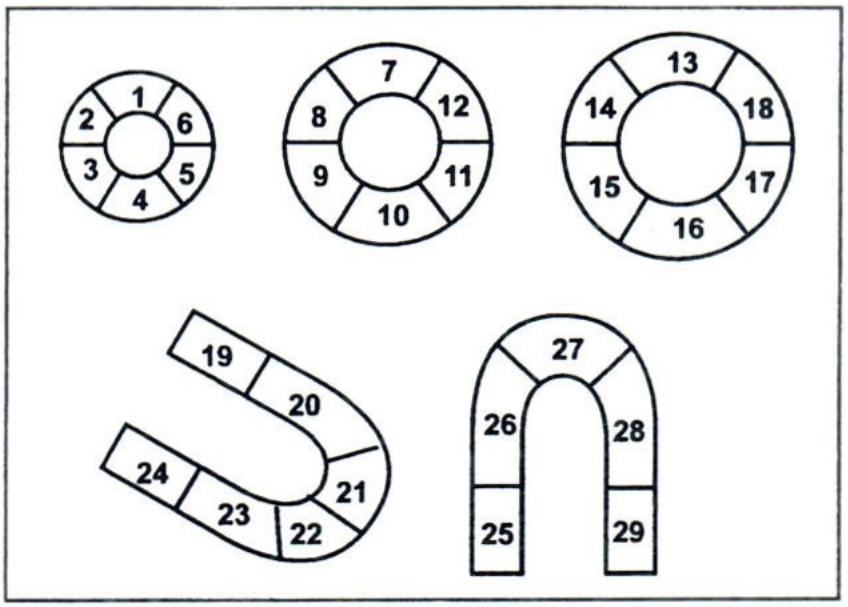

Fig.1 The perfusion images were divided into 29 segments as illustrated, represen the anterior wall (segments 1, 7, 13, 19, 20), the anteroseptal wall (segments 2, 8, 14), the inferoseptal wall (segments 3, 9, 15), the septum (segments 25, 26), the anterolateral wall (segments 6, 12, 18), the inferolateral wall (segments 5, 11, 17), the lateral wall (segments 28, 29), the inferior wall (segments 4, 10, 16, 23, 24), and the apical wall (segments 21, 22, 27).

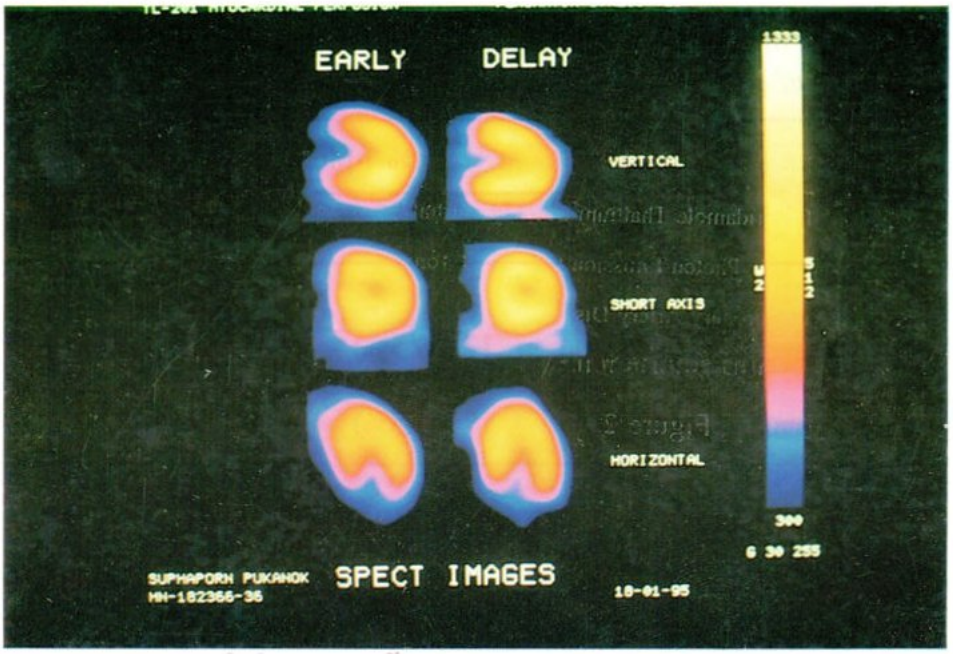

Fig.2 Dipyridamole stress and redistribution images of thallium-201 myocardial perfusion SPECT study in a patient with normal coronary arteriogram. There is homogeneouus distribution of radioactivity in allof the myocardial walls.

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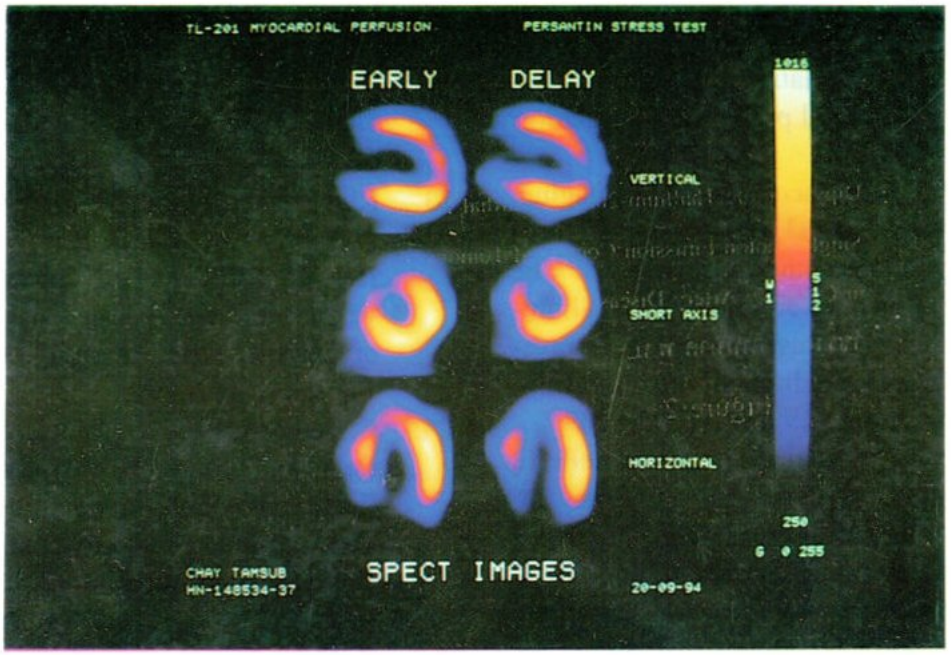

Fig.3 Dipyridamole stress and redistribuution images of thalliuum-201myocardial perfusion SPECT study in a patient with coronary artery disease. Coronary arteriography showed 80% stenosis of the left main coronary artery, 70% stenosis of LAD, 65% stenosis of RCA and normal LCX. TI-201 myocardial perfusion images show fixed defects of apex, anterior wall and septum. The inferior and lateral walls look normal.

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

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