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Original Article

Comparative evaluation of the diagnostic accuracy of ^{99m}Tc-sestamibi gated SPECT using five different sets of image acquisitions at stress and rest phases for the diagnosis of coronary artery disease

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Abstract: On the basis of some new evidences in favor of delayed ^{99m}Tc methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) redistribution, doubts about the appropriate time of acquisition following radiotracer injection may be raised. The goal of this study was to find the best acquisition time at stress and rest phases to achieve the highest sensitivity and normalcy rate for ^{99m}Tc-MIBI SPECT. Ninety four patients with moderate pretest probability of coronary artery disease (CAD) according to "Framingham Risk Score" enrolled in the study. Myocardial perfusion imaging (MPI) with SPECT was performed on the basis of two-day protocol with stress- and rest-phase images obtained at 15, 60, 120 and 180 minutes after injection of 666-814 MBq ^{99m}Tc-MIBI. According to the time of image acquisition at stress/rest phases, five protocols were defined: A, 15/180 min, B, 15/15 min, C, 180/180 min, D, 180/15 min and E, 120/120 min for stress and rest images, respectively. The sensitivity of MPI for the diagnosis of angiographically proven CAD were 77.3%, 50%, 63.6%, 45.5%, 68.2% and normalcy rate were 72.1%, 72.1%, 75.5%, 70.6%, 92.6% in protocol A, B, C, D and E, respectively. A significant association between SSS and Gensini score was detected only with protocol A (p=0.038). The most sensitive and specific two-day protocols for MPI with ^{99m}Tc-MIBI were protocol A and E, respectively. In addition, the best relationship between scintigraphic score of ischemia and angiographic score of CAD was achieved using protocol A (i.e. early acquisition at stress phase and late acquisition at rest phase).

Keywords: SPECT myocardial perfusion scintigraphy, ^{99m}Tc-MIBI, redistribution

Introduction

^{201}Thallium is recognized as a useful tracer for myocardial perfusion scintigraphy for the evaluation of patients with coronary artery disease (CAD) [1, 2]. However, ^{201}Tl chloride presents some disadvantages and is not ideal for imaging purposes because of its physical and biologic characteristics [3]. A major limitation of ^{201}Tl is its lower photon energy, is not optimal for myocardial imaging because of attenuation and scattering from overlying tissues. ^{99m}Tc-sestamibi has a higher energy that is optimal for gamma camera scintigraphy with substantially less attenuation. The development of a myocardial perfusion agent labeled with ^{99m}Tc-MIBI is attractive due to the ^{99m}Tc-MIBI is the most interesting as myocardial perfusion agent, because of physical advantages of ^{99m}Tc-sestamibi over ^{201}Tl and more favorable biological characteristics, including rapid lung and liver clearance and slow myocardial washout [3, 4]. ^{99m}Tc-MIBI has been proved to provide high quality images of the myocardium in animal models [5] and patients [6]. *Experimental studies have shown an excellent* correlation between the myocardial distribution of blood flow and ^{99m}Tc-MIBI in animals with coronary artery stenoses [5-11]. Because of its good correlation with perfusion ^{99m}Tc-MIBI has been termed a "chemical microsphere" [12].

The concept is that there is no significant myocardial redistribution after ^{99m}Tc-MIBI administration so this property makes it useful in evaluating acute conditions such as thrombolysis for

acute myocardial infarction [13] or unstable angina [14]. Patients can be stabilized before diagnostic imaging. The reported time interval between ^{99m}Tc-MIBI injection and myocardial imaging in previous studies was in range of 30 min to 6 hr [15]. Some studies have reported a time interval of up to 6 hr in acute condition, mainly for medical (patient's stabilization) and practical (injection performed during the night) considerations. Theoretically, in the presence of ^{99m}Tc-MIBI myocardial redistribution, such delay may cause an underestimation of the myocardium at risk (initial defect) [16, 17]. There are also few data available on the difference between early and late ^{99m}Tc-MIBI imaging for detection of ischemic coronary artery disease [18]. The aim of this study was to find the best time intervals between injection of ^{99m}Tc-MIBI and imaging at stress and rest phases.

Materials and methods

Study population

In an outpatient setting, 94 patients who were referred to our nuclear medicine department for myocardial perfusion imaging were prospectively studied. All patients had pretest intermediate probability of CAD according to Framingham Risk Score, who had no history of active severe obstructive pulmonary disease, asthma, myocardial infarction, clinical or electrocardiographic evidence of high degree atrioventricular blocks, left bundle branch block, echocardiographic evidence of cardiomyopathy, valvular heart disease.

Patient preparation

Patients fasted for at least 4 hr before the pharmacological stress. Consumption of nitrates, caffeine containing foods or drugs and long acting aminophylline were holded from 24 hr before the dipyridamole stress test.

Image acquisition sequence

A commercial sestamibi kit (AEOI, Tehran, Iran) was used and the labeling and quality control procedures were performed according to the manufacturer's instructions. The gated SPECT was performed after the injection of 666-814 MBq ^{99m}Tc-MIBI at peak treadmill exercise or following dipyridamole infusion. For treadmill exercise, the Bruce protocol was used and continued for a minimum of 60-90 s after radiotracer injection. The standard pharmacological stress was done with intravenous injection of 0.56 mg/kg dipyridamole over a 4 min period. Myocardial perfusion imaging with single photon emission computed tomography (SPECT) were performed at 15 minutes, 1 hr, 2 hr and 3 hr after injection of 666-814 MBq of ^{99m}Tc-MIBI at stress using a rotating, dual head gamma camera (ADAC, Solus, Milpitas, CA) equipped with a low energy high resolution parallel hole collimator. We used a 15% window around the 140 kev photo peak. Patients were positioned supine. Thirty two projections at 30 sec were obtained over a 180 degree left posterior oblique on a 64*64*16 matrix and 38.5 cm detector mask. The rest studies were performed with a similar imaging protocol in the same time intervals on the following day.

Image analysis

Five protocols were defined as; protocol A: stress 15 min and rest 3 hr, protocol B: stress 15 min and rest 15 min, protocol C: stress 3 hr and rest 3 hr, protocol D: stress 3 hr and rest 15 min and protocol E: stress 2 hr and rest 2 hr. Two blinded expert nuclear physicians visually reviewed the images based on the standard 20-segment model.

Coronary angiography

Coronary angiography was performed for 40 patients (42.6%) within this period and the findings were reported by consensus of two expert cardiologists who were blinded to the results of MPI. Significant CAD was definded as at least 50% stenosis in one or more main coronary arteries or their major branches.

Gensini score

The extent and severity of CAD was evaluated by "Gensini Score" [19] and "Coronary Artery Score". Gensini score shows the extent and severity of CAD incorporating the location and degree of intra luminal stenosis. In this scoring system, the degree of stenosis in the coronary arteries are 0 for no stenosis, 1 for 1%-25% stenosis, 2 for 26%-50% stenosis, 16 for 91%-99% stenosis and 32 for 100% stenosis. This score was then multiplied by a factor that copes with importance of location of the lesion in the coronary arteries. In this scoring system 5 is

Table 1. Sensitivity, normalcy rate and accuracy of defined protocols

Protocol	Sensitivity	Normalcy rate	Area under ROC (Accuracy)	Significance
A	77.3%	72.1%	.753 (75.3%)	P<0.0001*
B	50%	72.1%	.648 (64.8%)	P=.037*
C	63.6%	75%	.706 (70.6%)	P=.004*
D	45.5%	70.6%	.611 (61.1%)	P=.118
E	68.2%	92.6%	.883 (88.3%)	P<0.0001*

*Significant *P* Value.

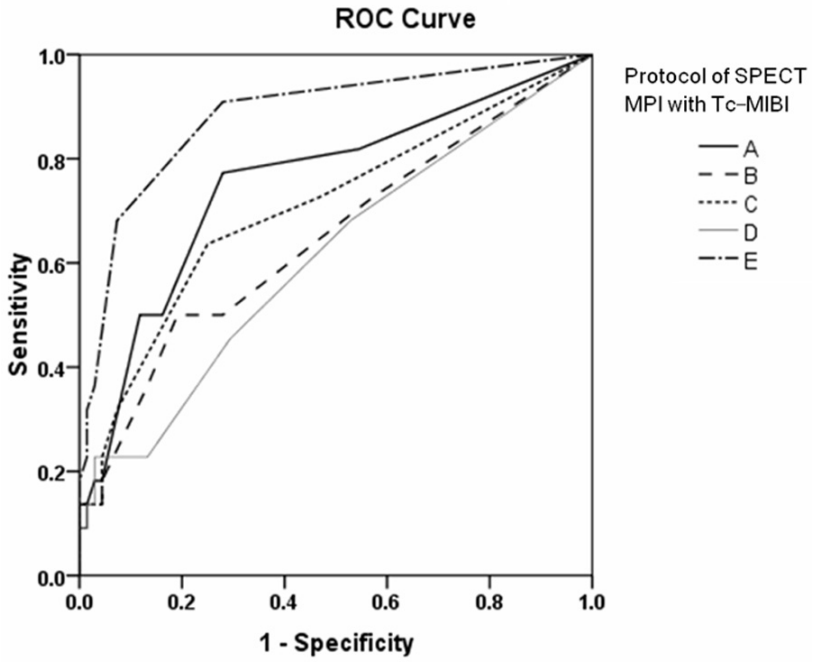

Figure 1. Receiver operating characteristic curve for five different procedures of myocardial perfusion scan with ^{99m}Tc-MIBI.

used for the left main coronary, 2.5 for the proximal left anterior descending (LAD) and proximal left circumflex (LCx), 1.5 for the mid region of the LAD, 1 for the distal LAD, the first diagonal, the proximal, mid and distal region of the right coronary artery, the postero descending, the mid and distal region of the LCx (2 for both of them if LCx is dominant) and 0.5 for the second diagonal and the posterolateral branch. The "Gensini Score" was expressed as the sum of the scores for all coronary arteries. Coronary artery index was the number of vessels with significant stenosis [19].

Statistical analysis

Receiver operating characteristic (ROC) curve analysis was used for comparing five defined protocols. The area under the curve represents the accuracy of each five defined protocols. All statistical analysis was performed using SPSS version 16 for Windows (SPSS Inc., Chicago, Illinois). A *P*-value of <0.05 was considered to indicate a statistically significant difference for all compared variables.

Results

Ninety four patients were studied and were followed for total of 24 months. No case was dropped out during the course of study. The mean age of the patients was 56.22 ± 9.26 years. Overall 36 (38.3%) were male while 58 (61.7%) were female (All subjects were white Caucasians). In the studied population, 26 (27.7%) of the patients had diabetes mellitus. The method of stress protocol was dipyridamole infusion in 63 cases (67%) and treadmill exercise test in 31 patients (335). Forty patients (42.6%) had angiographic evaluation in this period (as a gold standard test). Among this subgroup of patients 17 cases (18.1%) had normal angiography, while 23 patients (24.5%) had significant (≥50%) stenosis in one or more coronary artery. During 2 years follow up 54 cases (57.45) didn't have any cardiovascular events and were considered as low likelihood for CAD (instead of gold standard angiography). In comparison between different scintigraphic protocols sensitivity and normalcy rate of each protocol are shown in **Table 1**.

In **Figure 1**, receiver operating characteristic curve (ROC) for five different procedures of myocardial perfusion scan with ^{99m}Tc-MIBI is shown. As seen protocol E (stress 120 min and rest 120 min) and protocol A (stress 15 min and rest 180 min) respectively have the highest accuracy between different scintigraphic proto-

Table 2. Categorization of stenosis and extension of coronary stenosis on the basis of Gensini score quartile

Severity and extension of stenosis	Gensini Category (Quartile)	Percentile	Gensini score
No significant stenosis	1	<25	0≤Score<3
Mild	2	25-49	3≤Score<6
Moderate	3	50-74	6≤Score<36
Severe	4	≥75	Score≥36

cols and the accuracy of protocol D is the lowest.

The patients were divided to four categories on the basis of severity and extension of coronary stenosis by Gensini score quartile (**Table 2**). Comparison between extension of ischemia in scintigraphy (SSS) and severity and extension of stenosis on the basis of Gensini score is shown in **Table 3**. As seen the relationship between angiography and scintigraphy in detecting of severity and extension of coronary stenosis is significant only in protocol A. Between 16.1%-24.1% of patients who had low extension of perfusion defect (SSS≤3), showed severe coronary artery stenosis (gensini≥3) in angiography.

Discussion

For about 2 decades, the relatively rapid myocardial redistribution of ^{201}Tl has been considered to be an advantage since difference between ischemia and scar may be achieved with a single injection of the radiotracer. However, recent studies have shown that the detecting viable myocardium in irreversible thallium defects can be enhanced by the reinjection of ^{201}Tl at rest or 24 hr delayed imaging [20]. Although myocardial distribution of ^{201}Tl and ^{99m}Tc-MIBI is proportional to coronary blood flow, but other biologic and physical characteristics are different. Lack of rapid myocardial redistribution of ^{99m}Tc-MIBI following its intravenous injection at stress is one of the most important differences in the pharmacokinetics of the two radiopharmaceuticals. This characteristic indicates that timing of imaging after the injection at stress is not as critical as with ^{201}Tl.

This property is important particularly in the evaluation of acute conditions such as unstable angina or thrombolysis for acute myocardial infarction. Following ^{99m}Tc-MIBI administration and medical therapy, imaging is performed after stabilization of the patient's condition. Furthermore, it is preferable for optimal SPECT imaging not to have significant changes in the myocardial activity during acquisition. The best compromise between a high myocardial count rate and low background activity (decreased lung and liver uptake) is achieved between 1 and 2 hr following the injection of ^{99m}Tc-MIBI at stress [21].

Most of the clinical studies which used ^{99m}Tc-MIBI have reported a time interval with a range of 1 to 3 hr between injection and scintigraphy, although some others have used an interval up to 6 hr [17, 18]. This has been particularly reported in the evaluation of unstable angina or thrombolysis where stabilization of the patient's condition is critical [21].

It was believed that ^{99m}Tc-MIBI had no redistribution in comparison with Thallium, but some researches have shown early or delayed ^{99m}Tc-MIBI redistribution. Taillefer et al. [21] couldn't show any remarkable statistical difference in the diagnostic accuracy between 1-hr and 3-hr post-stress imaging but they showed that the ischemic/normal wall ratios were statistically higher at 3 hr (0.84) than at 1 hr (0.73). They expressed that this might affect the diagnostic certainty and possibly the sensitivity of coronary artery disease detection in mild ischemic defects. Our results indicated that image earlier after ^{99m}Tc-MIBI injection at stress improved detection of coronary artery disease.

Taillefer et al. [21] showed that differential myocardial net clearance; the normally perfused walls showing a significantly faster clearance (26%) than the ischemic myocardial walls (15%) at 3 hr post injection at stress, leads to this partial correction of the ischemic/normal wall ratio over time. Li et al. [12] showed redistribution of ^{99m}Tc-MIBI in dogs with transient myocardial ischemia which leads to underestimation of the severity of primary ischemia. This finding was similar to ^{201}Tl imaging but the extention of ^{99m}Tc-MIBI redistribution was much less than the ^{201}Tl.

Franceschi et al. [18], reported similar findings in nine patients studied with SPECT myocardial

Table 3. Comparison between different scintigraphic protocols of myocardial perfusion SPECT concerning severity and extension of coronary stenosis

Risk stratification by MPS	Protocol	Extension and severity of coronary stenosis (Gensini Category)				
		No significant stenosis	Mild stenosis	Moderate stenosis	Severe stenosis	Total
NI/Near-NI (SSS≤3)	A	10 (34.5%)	8 (27.6%)	4 (13.8%)	7 (24.1%)	29
	B	10 (34.5%)	8 (27.6%)	5 (17.2%)	6 (20.7%)	29
	C	12 (37.5%)	7 (21.9%)	7 (21.9%)	6 (18.8%)	32
	D	11 (35.5%)	7 (22.6%)	8 (25.8%)	5 (16.1%)	31
	E	12 (37.5)	7 (21.9%)	7 (21.9%)	6 (18.8%)	32
Low risk (3<SSS≤8)	A	2 (28.6%)	1 (14.3%)	4 (57.1%)	0 (0%)	7
	B	1 (20.0%)	1 (20.0%)	2 (40.0%)	1 (20.0%)	5
	C	0 (0%)	2 (50.0%)	1 (25.0%)	1 (25.0%)	4
	D	1 (20.0%)	2 (40.0%)	0(0%)	2 (40.0%)	5
	E	0 (0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	3
Intermediate Risk (8<SSS≤13)	A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
	B	1 (50.0%)	0 (0%)	1 (50.0%)	0 (0%)	2
	C	0 (0%)	0 (0%)	1 (100.0%)	0 (0%)	1
	D	0 (0%)	0 (0%)	1 (100.0%)	0 (0%)	1
	E	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	1
High Risk SSS>13	A	0 (0%)	0 (0%)	1 (25.0%)	3 (75.0%)	4
	B	0 (0%)	0 (0%)	1 (25.0%)	3 (75.0%)	4
	C	0 (0%)	0 (0%)	0 (0%)	3 (100.0%)	3
	D	0 (0%)	0 (0%)	0 (0%)	3 (100.0%)	3
	E	0 (0%)	0 (0%)	0 (0%)	3 (100.0%)	3
Significance	A			0.038		
	B			0.350		
	C			0.065		
	D			0.061		
	E			0.103		

imaging at 20 min, 1, 2, 4 and 6 hr post injection of 25-30 mCi of ^{99m}Tc-MIBI at stress. They have found significant differences between the clearance rates of ischemic and normal myocardium. The ^{99m}Tc-MIBI washout from ischemic myocardial defects was 16% at 6 hr post injection and 27% ± 8% for normal myocardium. The ischemic/normal wall ratio increased with time for both mild and severe defects: 0.70 at 20 min, 0.80 at 4 hr and 0.84 at 6 hr. Reperfusion was more significant at 4-6 hr. But their data did not indicate whether the sensitivity of CAD detection was decreased by late imaging.

Taillefer et al. [21] suggested that ^{99m}Tc-MIBI imaging should not be performed later than 1-1.5 hr following the post stress injection in order to avoid the effect of myocardial redistribution on the diagnosis of CAD. They believed that this limitation does not represent a significant drawback in clinical practice for stress myocardial perfusion imaging but the impact of ^{99m}Tc-MIBI myocardial redistribution should be evaluated when the risk assessment and effect of thrombolytic therapy in patients with acute MI is considered.

Maurea et al. [22] reported that resting ^{99m}Tc-MIBI redistribution frequently occurs in patients with chronic CAD. Therefore they suggested that resting ^{99m}Tc-MIBI imaging should be delayed when assessing myocardial viability in patients with chronic CAD.

Our study demonstrated that after injection of ^{99m}Tc-MIBI, it redistributed so early imaging in stress phase and delayed imaging in rest phase will increase sensitivity and normalcy rate. Some studies have reported a time interval of up to 6 hr between ^{99m}Tc-MIBI injection and

imaging in acute condition, mainly for practical and medical concerns mentioned above. In the presence of myocardial redistribution, delayed imaging may cause an underestimation of the myocardium at risk.

Based on our study, protocol A (stress 15 min and rest 180 min) was the most sensitive ($P<0.0001$) in comparison with five defined protocols. Our study with higher study population had similar findings to previous researches and corroborated them. Based on this study the highest normalcy rate (92.6%) was related to protocol E (stress 120 min and rest 120 min), ($P<0.0001$). This study showed that the relationship between angiography and scintigraphy in detecting severity and extension of coronary stenosis was significant only in protocol A ($P<0.038$). In some cases it seems that balance ischemia is the reason of low extension of perfusion defect ($SSS\leq3$) despite severe coronary artery stenosis ($gensini\geq3$) in angiographic findings.

Conclusion

The most sensitive and specific two-day protocols for MPI with ^{99m}Tc-MIBI were protocol A and E, respectively. In addition, the best relationship between scintigraphic score of ischemia and angiographic score of CAD was achieved using protocol A (i.e. early acquisition at stress phase and late acquisition at rest phase).

Disclosure of conflict of interest

None.

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