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The Effect of Time Interval Between $^{99m}T_c$-sestamibi Injection and Image Acquisition on Quantitative Data of Gated SPECT Myocardial Perfusion Imaging at Stress and Rest Phases

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Abstract: According to several recent studies in favor of delayed ^{99m}Tc methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) redistribution, the aim of this study was to find whether different time intervals between ^{99m}Tc-MIBI injection and image acquisition could affect quantitative data of gated SPECT Myocardial Perfusion Imaging (MPI). Eighty five patients with moderate pretest probability of coronary artery disease according to "Framingham Risk Score" enrolled in the study. Myocardial perfusion imaging with SPECT was performed on the basis of two-day protocol with stress-phase images obtained at 15/180 and rest-phase images obtained at 60/120 minutes after injection of 666-814 MBq 99mTc-MIBI. Then quantitative data of MPI were obtained and compared at mentioned time intervals. The changes of five parameters including Summed Stress Score (SSS), Summed Motion Score (SMS), Summed Thickening Score (STS), Stroke Volume (SV) and Ejection Fraction (EF) were not significant however; the End Systole Volume (ESV) and End Diastolic Volume (EDV) changes were significant. Also SSS has not significant changes. The results of this study imply that the time interval between the injection and acquisition may affect the detection of endocardial and epicardial surfaces in 99mTc-MIBI myocardial perfusion scanning which afford significant changes in EDV and ESV. While these changes are in a same direction and correlated so, the functional parameters as EF, SV, SMS and STS do not change significantly.

Key words: SPECT, myocardial perfusion, scintigraphy, ^{99m}Tc-MIBI, quantitative myocardial analysis

INTRODUCTION

^{201}Thallium is a beneficial radiotracer for myocardial perfusion scintigraphy for the evaluation of patients with Coronary Artery Disease (CAD) (Pohost *et al*., 1977; Okada *et al*., 1980; Haghighatafshar and Farhoudi, 2016). However, ^{201}Tl presents some disadvantages and a major limitation of ^{201}Tl is its lower energy is not required for myocardial scintigraphy because of attenuation and scattering from overlying tissues. ^{99m}Tc-sestamibi has a higher photon energy that is required for gamma camera imaging with considerable less attenuation. Labeling myocardial perfusion agent with ^{99m}Tc-MIBI is attractive due to physical advantages of ^{99m}Tc-sestamibi over ^{201}Tl and more eligible biological characteristics, consist of rapid lung and liver clearance and slow myocardial washout (Brown *et al*., 1983; Gibson *et al*., 1983; Ghaedian *et al*., 2015). Experimental studies have shown a high relevance between the myocardial distribution of blood flow and $^{1.03}$ ^{99m}Tc-MIBI in animals with coronary artery stenosis (Li *et al*., 1988; Heo *et al*., 1988; Glover and Okada 1990; Leppo and Meerdink, 1989; Meerdink and Leppo, 1990 Mousa *et al*., 1990; Okada *et al*., 1988). Because of proper correlation of ^{99m}Tc-MIBI with perfusion has been called a "chemical microsphere" (Li *et al*., 1990).

A time interval of 30 min to 6 h is reported between ^{99m}Tc-MIBI injection and myocardial imaging in previous studies (Santoro *et al*., 1990). Theoretically in the attendance of ^{99m}Tc-MIBI myocardial redistribution, so delay may cause an underestimation of the myocardium at risk (initial defect) (Gibbons *et al*., 1989; Frans *et al*., 1989). Some recent evidence suggests difference between early and delay ^{99m}Tc-MIBI imaging for finding of ischemic coronary artery disease (Franceschi *et al*., 1990; Fallahi *et al*., 2014). According to recent studies in favor of delayed ^{99m}Tc-MIBI Redistribution (1995), the aim of

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this study was to find whether different time intervals between ^{99m}Tc-MIBI injection and image acquisition could affect quantitative data of gated SPECT Myocardial Perfusion Imaging (MPI).

MATERIALS AND METHODS

Study population: In an outpatient setting, 85 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 asthma, obstructive pulmonary disease, myocardial infarction, evidence of high degree atrio-ventricular blocks, left bundle branch block, cardiomyopathy and valvular heart disease.

Patient preparation: Patients fasted for at least 4 h before the pharmacological stress. Consumption of nitrates, caffeine containing foods or drugs and long acting aminophylline were holded from 24 h befor
e 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 the injection of 666-814 MBq 99mTc-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^{-1} dipyridamole over a 4 min period. Myocardial perfusion imaging with Single Photon Emission Computed Tomography (SPECT) were performed at 15 min and 3 h after injection of 666-814MBq of 99mTc-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.

Image analysis: 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 AND DISCUSSION

Eighty five patients were studied. The mean age of the patients was 56.23±9.25 year. Overall 32 (37.6%) were male while 53 (62.4%) were female (All subjects were white Caucasians). In the studied population, 24 (28.2%) of the patients had diabetes mellitus. The method of stress protocol was dipyridamole infusion in 58 cases (68%) and treadmill exercise test in 27 patients (32%).

Quantitative data of MPI with SPECT were evaluated at 15/180 and 60/120 min after injection of ^{99m}Tc-MIBI at stress and rest phase, respectively. In our previous study (Fallahi *et al*., 2014) we demonstrated that with early imaging at stress phase sensitivity and normalcy rate of MPI was increased and the best relationship between scintigraphic score of ischemia and angiographic score of coronary artery disease (as a gold standard test) was achieved. Therefore in this study we considered quantitative data of the 15min as gold standard. In comparison of quantitative data of the 60, 120 and 180 min with quantitative data of the 15 min, the following results were achieved.

Mean SSS, SMS, STS, SV and EF of the 15 min and 180 min at stress phase and 60 and 120 min at rest phase were calculated. In comparing the data obtained, correlation and p-value are shown in Table 1 and 2 as seen none of these changes did not significant however; the EDV and ESV changes were significant.

Myocardial Perfusion Imaging (MPI) is considered as one of the most accurate diagnostic procedure to assess the coronary artery diseases (Fallahi *et al*., 2014). In majority of ^{99m}Tc-MIBI studies, 1-3 hr time interval between injection and imaging is declared but an interval up to 6 hr could be seen in the rest (Frans *et al*., 1989; Franceschi *et al*., 1990). In contrast to the prior concept of non-redistributed ^{99m}Tc-MIBI, some studies have demonstrated redistribution of ^{99m}Tc-MIBI in early or late phases (Fallahi *et al*., 2014). There was no significant statistical difference in the diagnostic accuracy between 1 and 3 h post-stress scintigraphy in Taillefer *et al*. (1991) study but surprisingly the ischemic/normal wall ratios were statistically higher at 3 h (0.84) than at 1 h (0.73). They declared that the sensitivity of coronary artery disease detection in mild ischemic defects might be affected with this event.

Taillefer *et al*. (1991) indicated 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, eventuates to this partial correction of the ischemic/ normal wall ratio over time.

Table 1:Mean of quantitative data of gated SPECT MPI at stress phase based on the imaging time

Variables	Mean stress 15 min	Mean stress 180 min	Correlation	p-values
SSS	252 (5.410)	2.43(6.322)	0.708	0839
STS	1.80 (5.558)	1.92(5.468)	0.873	0.503
SMS	4056 (8.889)	4.88(8.005)	0805	0450
SV	3.9.16 (10.359)	39.47(11.087)	0.704	0.774
EF	68.59 (11.831)	67.44(11.724)	0.813	0.79
EDV	59.02 (23.76)	61.87(27.08)	0.94	0.004
ESV	19.69 (17.97)	22.01(18.41)	0.96	0<0.001

Table 2: Mean of quantitative data of gated SPECT MPI at rest phase based on the imaging time

Variables	Mean rest 60 min	Mean rest 120 min	Correlation	p-values
SSS	0.97 (3.551)	0.77 (3.760)	0.964	0.053
STS	2.21 (5.974)	2.26 (5.797)	885	0.294
SMS	5.27 (10.340)	4.33 (8.202)	0.809	0.274
SV	39.51 (9.259)	39.41 (9.222)	0.812	0.515
EF	68.59 (13.215)	67.41 (11.794)	0.859	0.187
EDV	62.06 (25.56)	60.74 (23.92)	0.86	0.36
P- Value	21.85 (19.08)	21.85 (18.14)	0.92	1.00

Li *et al.* (1990) demonstrated that close to ^{201}Tl scintigraphy the severity of primary ischemia is underestimated due to redistribution of ^{99m}Tc-MIBI in dogs with transient myocardial ischemia although the extension of ^{201}Tl redistribution was much higher than the ^{99m}Tc-MIBI.

Similar results were declared in Franceschi *et al.* (1990) study in nine patients who underwent SPECT myocardial imaging at 20 min, 1, 2, 4 and 6 hr post injection of 25-30mCi of ^{99m}Tc-MIBI at stress. They 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 in both mild and severe defects: 0.70 at 20 min, 0.80 at 4 h and 0.84 at 6 hr. Reperfusion was more significant at 4-6 h. But, they had no comment on the influence of late imaging on sensitivity of CAD detection.

In order to prevent the influence of myocardial redistribution on diagnosis of CAD Taillefer *et al.* (1991) recommended that ^{99m}Tc-MIBI imaging should be done utmost 1-1.5 h following the post stress injection. They trusted that this restriction could not interfere significantly in interpretation of stress myocardial perfusion scintigraphy but they recommended the assessment of^{99m}Tc-MIBI myocardial redistribution when the risk assessment and effect of thrombolytic therapy in patients with acute MI is considered.

Maurea demonstrated that redistribution of ^{99m}Tc-MIBI is frequent in patients with chronic CAD. In consequence they proposed a delayed resting ^{99m}Tc-MIBI scintigraphy for assessing myocardial viability in patients with chronic CAD.

Our previous study (Fallahi *et al.*, 2014) demonstrated that after injection of ^{99m}Tc-MIBI, it redistributed so early will increase sensitivity and normalcy rate Imaging in stress phase and delayed imaging in rest phase.

This study investigated the change of quantitative MPI parameters at the stress phase between 15-180 min and at the rest phase between 60-120 min post injection. Results imply that, SSS, SMS, STS, SV and EF do not change significantly while EDV and ESV show significant changes. As the change in SSS is not significant, we can conclude that the perfusion parameters which show the extent of hypoperfusion ischemic area do not change significantly between 15-180 min interval at the stress phases. Most of the functional parameters did not change significantly, however the EDV and ESV changes were significant. To find the cause of these circumstances, generation of these features is explained briefly as follows.

In order to calculate the Sum Stress Score (SSS), first the polar map of myocardium should normalize to its maximum pixel. This means that, the final value of each pixel is a relative value and trivial change in SSS parameter shows that all of the segments redistribute in a same manner and their ratio do not change meaningly.

To calculate the functional parameters, first the maximal count of Mid-Myocardial Surface (MMS) should be determined ("Automatic Quantification of Ejection Fraction from Gated Myocardial Perfusion SPECT", Guido Germano-"Automatic Quantitation of Regional Myocardial Wall Motion and Thickening From Gated Technetium-99m Sestamibi Myocardial Perfusion Single-Photon Emission Computed Tomography", Guido Germano). Then for each count profile, an asymmetric Gaussian is fitted. The endocardial and pericardial limits are determined with a specific fractional of Standard Deviation (SD) far from the MMS. In this manner the endocardial surface and epicardial surface are generated and then the functional parameters calculated as below:

End systole Volume (EDV): The volume within endocardial surface at end systole phase.

End diastole volume (ESV): The volume within endocardial surface at end diastolic phase.

Stroke Volume (SV): SV=EDV-ESV
Ejection Fraction (EF): EF= (EDV-ESV)/EDV ×100

Regional Wall Motion (WM): The distance between a given point of the endocardial surface at end-diastole and end-systole. The distance measures perpendicularly to the average MMS between the end-diastole and end-systole.

Regional Wall Thickening (WT): The variation in thickness between the end-diastole and end-systole and is expressed as the percent increases from diastolic thickness.

As the calculated EDV and ESV changed significantly over time we can conclude that the estimated endocardial and epicardial surfaces will change based on the post-injection time interval. It might be happened because of decreasing in SD value according to redistribution of radiopharmaceutical from myocardial tissues.

Non significant change of WM claims that while the estimated position of endocardial differs by redistribution, the distance between end-diastole and end-systole does not change obviously at a given point on epicardial surface. The same conclusion can be reached for WT. Although, the estimated position of endocardial and epicardial differ s over time but the ratio of variation of their distance to end-diastole thickness does not change significantly. According to correlated ascending variation in EDV and ESV, SV and EF which depends on difference of EDV with ESV (EDV-ESV) does not change significantly.

These theories claim that redistribution may affect the detection of epicardial and endocardial surfaces but as the variation of detected epicardial and endocardial surfaces are linearly correlated in a same direction, the relative parameters (SSS, EF, SV, SMS and STS) do not change significantly in time interval between the injection and acquisition. Our results might be affected by the normal MPI of the majority of patients therefore excess researches are recommended.

CONCLUSION

The results of this study imply that the time interval between the injection and acquisition may affect the detection of endocardial and epicardial surfaces in ^{99m}Tc-MIBI myocardial perfusion imaging which affords significant changes in EDV and ESV. As these changes are in a same direction and correlated, the functional parameters as EF, SV, SMS and STS do not change significantly. On the other hand, the results imply that the SSS does not change based on time interval and the redistribution may affect normal and ischemic areas in a same manner, however further investigations on effect of time interval on clinical interpretation and decision seems necessary.

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