Original article, Cardiology

The Value of Tc-99m MIBI Washout Rate in Detection of Ischemia compared with standard Myocardial Perfusion Imaging

Moustafa, H. Abu-Gabel, M. Omar, M and Elmaghrapy, Sh.

Oncology and Nuclear Medicine Department, Kasr Al-Aini Hospital[,] Cairo University, Egypt.

Objective: we aimed to estimate the rate of MIBI washout of myocardium in patients with clinical ischemia as compared to the degree of reversibility between stress and rest studies. **Patients and methods**: this prospective study included 50 patients [34 males (60%) & 16 females (40 %)] with mean age 55.3 \pm 10.1 years. All patients underwent ECG-gated SPECT Tc-99m MIBI myocardial perfusion imaging. Two days protocol (rest/stress) was used, the rest study was performed at 90 min and delayed images at 4 hours post-injection. While in stress phase images were performed after 30 min. The polar map of perfusion images acquired at stress and rest images at 90 min to detect reversibility. Also, polar map of 90 min was compared with delayed perfusion images at 4 h to calculate washout rate.

Key words: Tc-99m MIBI, CAD

Corresponding Author: Moustafa, H.

Results: there was higher WR in the ischemic myocardial region of LAD (21.18 ± 7.2) compared to the normal one (9.96 ± 2.49), (p < 0.001). Also, in the region of RCA WR was 19.17±3.86 in ischemic wall versus 9.59 ± 1.69 in normal walls (p<0.02) and (LCX) WR was 17.02 ± 2.6 in ischemic wall versus 9.63 ± 1.76 in normal walls (p<0.04). Additionally, the linear correlation of regional WR of each vascular territory was compared with the corresponding degree of reversibility with statistically significant for LAD (0.77), LCx (0.86) and RCA (0.64).

Conclusion: There is higher WR of MIBI in ischemic walls in all vascular territories with significant correlation with its degree of reversibility that may potentiate the results of stress study.

Email: drhosna1947@gmail.com.

INTRODUCTION:

Coronary artery disease (CAD) is the leading cause of death in adults in the USA; accounting for approximately a third of all deaths in subjects over the age of 35 years ⁴. Over the past 20 years, the mortality rate owing to CAD has decreased. This is related to better detection of patients with known or suspected CAD and treatment². Myocardial better subsequent perfusion imaging is а well-established noninvasive technique that provides incremental value over clinical risk factors for the detection of CAD. It is a highly validated technique, widely available, with a clear role in the assessment of patients with CAD as stated by internationally published guidelines.^{3 4} The instrumentation, radiopharmaceuticals, and methodology used for myocardial perfusion scintigraphy have evolved over the years including single-photon emission tomography (SPECT), gated SPECT, SPECT/CT, and PET/CT. However. the underlying physiological principles that make myocardial perfusion imaging an important diagnostic tool remain unchanged.Washout rate of 99mTc-MIBI was suggested as diagnostic tool that helps in detection of CAD⁵. It has been reported that delayed images within few hours can uncover enhanced washout rate (WR) in impaired myocardium⁶⁷, it has also been studied that delayed MIBI scan with higher image contrast between normal and ischemic regions due to enhanced MIBI WR in

ischemic regions may be more sensitive to detect the severity of myocardial ischemia than the early scan⁸. Such rapid WR was observed in ischemic myocardium deducing that the ability of myocyte to retain the tracer was impaired⁹.

Aim of the work: Estimation the washout rate of MIBI for normal and ischemic myocardium and comparing the washout rate for ischemic myocardium by the degree of reversibility of stress induced perfusion defect.

MATERIALS AND METHODS:

This prospective control study was performed in Nuclear Medicine Unit, Cairo University during the period from September 2014 till February 2015. It included **50** patients [34 males & 16 females] with mean age 55.3 ± 10.1 years. All the patients underwent ECG-gated single-photon emission computed tomography *(SPECT)* technetium-99m MIBI myocardial perfusion imaging.

Inclusion criteria: All patients with high risk criteria referred for myocardial perfusion scan of different age and sex including patients referred after therapeutic revascularization (coronary artery bypass graft or angioplasty) for evaluation. Preoperative cardiac evaluation in patients with chronic coronary artery disease. Also, Patients with history of previous myocardial ischemia or ICU admission.

Exclusion Criteria: No normal volunteers were included in this study. Patients who underwent pharmacological stress studyor patients with

unstable angina or ischemic cardiomyopathy who were unable to do sufficient exercise for stress test were excluded from the study.

Myocardial perfusion scan (MPS): All patients underwent the two days protocol (rest & exercise stress) of myocardial perfusion SPECT, with extra delayed imaging in the rest study.

Stress protocol: Graded treadmill exercise was performed according to a modified Bruce protocol (Table 4). The radiopharmaceutical was injected when the patient had achieved maximal exercise or peak patient tolerance, and the exercise study was continued for further one minute to reach maximum tracer extraction. A dose of 15 to 25 mCi (555 to 925 MBq) of ^{99m}TcMIBI was injected intravenously according to body weight for each study.

Imaging protocol: For the rest study, each patient was imaged twice; early imaging at 90 minutes post injection and late washout imaging at 4 hours after the same injection. Stress imaging was done at 30 minutes post injection. Dual-head gamma camera with the detectors at 90 degrees, equipped with Lowenergy high-resolution collimator was used. Photon peak =140 kev with energy window of \pm 20 %. Zoom factor of 1.3, matrix: (64x64), Patient: supine with raised left arm for; 180 degree from right anterior oblique 45° to left posterior oblique position 135°. The projection data from the ECG-gated SPECT scan were summed and perfusion images were

reconstructed with 3D ordered subsets expectation maximization (OSEM) algorithm and built-in processing that preserved the linearity between photon counts in projection data and pixel values in reconstructed images. Cardiac SPECT software reconstructed crosssectional cardiac images along the short and long axes of the heart to form: transaxial (short axis), coronal (horizontal long axis) and sagittal (vertical long axis) using Butter worth filter.

Quantitative evaluations: 3D sampling of the entire myocardial region was used to convert perfusion images into 2D polar map or bull'seye display generated with circumferential slice count profiles obtained from the short-axis SPECT slices, with the apex at the center of the display and the base of the ventricle at the periphery. The whole LV myocardium is divided into 17 segments and each group of represent the coronary segments artery supplying blood to that region and permit visual estimation of the degree and extent of the perfusion abnormality for each vascular territory ¹⁰. **Calculation of perfusion** defect: Each segment was scored visually based on the tracer uptake as: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, absent tracer uptake in rest and stress images. A summed rest score (SRS) and summed stress score (SSS) were obtained by adding the scores of the 17 segments of the rest and stress images, respectively. The summed difference score (SDS) was determined by subtracting the SRS from the SSS and then patients were classified according to their results into: Normal group (SSS <4) and Abnormal group (SSS \geq 4), abnormal studies. Tomographic images were used for quantitative estimation of functional parameters such as myocardial motion, end systolic volume and end diastolic volume, with subsequent estimation of ejection fraction of left ventricle ¹¹.

Calculation of reversibility percentage¹²**:** Calculation of reversibility percentage of stress induced perfusion defect was done using quantification methods applied on hypoperfused segments in relation to each vascular territory the polar maps of stress and rest study by the following formula:¹³

> % Revsibility of certain segments = <u>uptake in rest study - uptake in stress study</u> <u>Its uptake in rest study</u> × 100%

Calculation of washout rate¹⁴ : Calculation of regional washout rate (RWR) was done by using the polar map of perfusion images acquired at initial 90 min as the baseline of MIBI uptake and then the polar map of delayed perfusion images at 4 hrs was compared with the baseline uptake to calculate WR for each pixel in the 2D polar map using the formula: ¹⁵

% Washout Rate of certain segmentste

 $\frac{\text{Ce} - (\text{Cd} \times \text{decay factor})}{\text{Ce}} \ge 100\%$

Ce: segmental counts in early imaging Cd: segmental counts in delayed imaging

=

Decay factor: = $1/(1/2)^{x}$, x = (time difference)/6. Regional washout rate was then

estimated based on LAD, RCA and LCX vascular territories, and compared to the reversibility percentage of stress induced perfusion deficit in the segments representing the corresponding vascular territory, assuming that washout rate of normal myocardium is < 12%¹⁴ .*Statistical methods*: All statistical analyses were performed using computer software SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows [2007]. Continuous values of RWR of the three vascular territories in both normal and abnormal stress study were expressed as mean \pm standard deviation. Differences of numerical variables between these two groups were analyzed by independent-samples t test. A (p < 0.05) was considered statistically significant. The relationships between the degree of reversibility and rate of RWR were analyzed with Pearson linear correlation. The significant washout rate cut off values and their sensitivity and specificity was calculated using receiver operating curve (ROC).

RESULTS:

The study included 50 patients, [34 males (70%) & 16 females (40 %)] with mean age 55.3 ± 10.1 years. Regarding the prevalence of risk factors; hypertension, diabetes and

smoking were recorded within the study group by 46 %, 30 % and 22 % respectively.

1. **Perfusion analysis:** Out of the 50 patients undergoing cardiac exercise stress testing with subsequent SPECT imaging; 22 patients [44%] had normal perfusion (SSS <4) and 28 patients [56%] had abnormal perfusion (SSS \geq 4). The latter were further classified into *Subgroup A*: 20patients [40%] had stress induced perfusion

defects but still reversible in rest phase (SSS \geq 4 and SDS >2) and *Subgroup B*: 8 patients [16%] had either stress induced perfusion defects with minimal reversibility or fixed perfusion defect (SSS \geq 4 and SDS < 2). Regarding the analysis of gated quantitative indices; ejection fraction, end systolic volume and end diastolic volume were estimated in normal and abnormal groups as shown in *Table 1*.

		Norı gro	Subgrou	Subgrou	P valu
Figetion f	R	50 -	32 -	10 – 3	D * – 0 (
Ejection	Mea	58 :	39 ±	28 ±	P**< 0.0
End sy	R	22 -	62 - 8	90 - 1	P* < 0.0
volu	Mea	32 :	70 ±	120 ±	P**< 0.
End dia	R	65 -	125 - 1	150 - 2	P** < 0.
volu	Mea	70 :	150 :	190 ±	P***< 0

Table 1: Gated quantitative indices in the different groups.

2. The ejection fraction of normal perfusion group ranged from 50 to 65 % with mean value of 58 ± 5 while that for subgroup A of abnormal patients ranged from 32 - 45 % with mean value of 39 ± 3 and subgroup B ranged from 10 - 38 % with mean value of 28 ± 5 . Regarding ejection fraction for subgroup B, it shows marked difference but not statistically significant.

The end systolic volume of normal perfusion group ranged from 22 - 45 ml with mean value of 32 ± 7 , while that for subgroup A of

abnormal patients ranged from 62 - 80 ml with mean value of 70 ± 2 and subgroup B ranged from 90 - 130 ml with mean 120 ± 9 . The end diastolic volume of normal perfusion group ranged from 65 - 80 ml with mean value of 70 \pm 3 while that for subgroup A of abnormal patients ranged from 125 - 170 ml with mean value of 150 ± 7 and subgroup B ranged from 150 - 220 ml with mean value of 190 ± 19 . There were significant differences in subgroups B compared with normal group as regarding EDV & ESV. **Perfusion analysis in terms of vascular territories:** Within the 28 positive patients for myocardial ischemia, 52 stress induced perfusion defects were detected. 25 perfusion defects (48%) in the segments supplied by LAD vascular territory, 20 perfusion defects (38%) in segments supplied by RCA vascular territory

and 7 perfusion defects (14%) in segments supplied by LCx vascular territory.

3. Analysis of reversibility: The percentages of Reversibility of stress induced perfusion defects were estimated in normal perfusion and abnormal perfusion subgroups as shown in *Table 2*.

 Table 2: Percentage of reversibility in normal perfusion and abnormal perfusion subgroups

		Normal gro	Abnormal group		
			Subgroup	Subgroup B	
Percentage reversibilit	Ran	0 –2%	10 – 21 4	2-4%	
	Mean	1 ± 1	14 ± 3	3 ± 1	
P value			<0.01	0.86	

The analysis of perfusion defect reversibility showed that; in normal perfusion group as well as subgroup B; there were no significant differences in perfusion between stress and rest studies with mean value of 1 ± 1 , $3 \pm$ 1respectively. While in abnormal perfusion subgroup A; there were significant differences

in perfusion between stress and rest studies with mean value of 14 ± 3 , with significant difference if compared with normal perfusion group (P value < 0.01 respectively). **4.** Analysis of washout rate: The percentages of myocardial global washout rate were estimated in normal perfusion and abnormal perfusion subgroups as shown in *Table 3.*

 Table 3: Percentage of myocardial global washout ratein normal perfusion and abnormal perfusion subgroups.

		Normal gro	Subgroup	Subgroup
Global wasl rate	Rang	6 – 12 %	17 – 27 %	3-6 %
	Mean ±	9 ± 2	22 ± 3	5 ± 1
P value			<0.001	0.79

The analysis of global washout rate showed that; in normal perfusion group as well as subgroup B; there were no significant differences in MIBI washout rate with mean value of 9 ± 2 , 5 ± 1 respectively.

While in abnormal perfusion subgroup A, there was a significant difference in MIBI washout rate with mean value of 22 ± 3 if compared to

washout rate in normal perfusion group (P value < 0.001 respectively).

5. Correlation of perfusion defects with vascular territories: Correlation of reversibility and washout rate within the positive patients in relation to possible vascular territories is seen in *Table4.*

		LAI	LCx	RCA
Reversibilit	Rang	5 – 17	6 – 15	6-17 %
percentage	Mean ±	11.7 ±	9.02 ± 3	11.8 ± 4.9
Washout rate per-	Rang	13 – 30	14 – 22	13 – 27 %
	Mean ±	21.18 ±	17.02 ±	19.17 ± 3.86

Table 4: Percentage of Reversibility and Washout Rate in terms of vascular territories.

The percentage of stress induced perfusion defect reversibility was ranging from 5 - 17% with mean value of 11.7 ± 4.2 in region of LAD vascular territory, for the region of LCx; it was ranging from 6 - 15% with mean value of 9.02 ± 3.95 , and for the region supplied by RCA vascular territory was ranging from 6 - 17% with mean value of 11.8 ± 4.9 .

The percentage of washout rate in the region of LAD vascular territory ranged from 13 - 30 % with mean value of 21.18 ± 7.2 , and for LCx vascular territory ranged from 14 - 22 % 6.

with mean value of 17.02 ± 2.6 , while in the region supplied by RCA vascular territory ranged from 13 - 27 % with mean value of 19.17 ± 3.86 (*Table 4*).

5. Correlation between Reversibility and Washout Rate: Regarding the correlation between the percentages of reversibility and the percentage of washout rate for each vascular territory; the reversibility percentage was plotted on the X- axis and washout rate was plotted on the Y- axis in *Fig 1, Fig 2 and Fig 3* for LAD, LCx and RCA respectively.



Fig 1. Correlation between Reversibility and of Washout Rate in LAD vascular territory



Fig 2. Correlation between Reversibility and Washout Rate in LCx vascular territory.



Fig 3. Correlation between Reversibility and Washout Rate in RCA vascular territory

There was a significant positive linear correlation between the rate of washout and the percentage of reversibility of stress induced perfusion lesions in three vascular territories such that for LAD vascular territory; r = 0.695, for LCx vascular territory; r = 0.666 and for LAD vascular territory; r = 0.774.



Figure (4 A): Moderate reversible ischemic changes involves the apex and apical andmid part of anterior walls showed higher washout rate (17 %), while the LCx & RCA washout rate (6 % & 8% respectively. EF 49%, SSS =



Figure (4 B): Fixed perfusion defect in both stress and rest studies involving the inferior wall. with no significant washout rate (6%).Normal EF, SSS = 21%, SDS = 2.

DISCUSSION:

Searching for additive, non-invasive and accurate methods for early detection of Coronary artery disease (CAD) is a continuous process. Over the past 20 years; the mortality rate owing to CAD has significantly decreased because of the earlier and better detection of patients with known or suspected CAD and better subsequent treatment. The development and widespread use of noninvasive cardiac imaging techniques have contributed significantly to the improvement in evaluation of patients with known or suspected coronary artery disease.²

Regarding prevalence of the CAD risk factors within the patients; especially hypertension, diabetes and smoking, it was reported in our study as 46 %, 30 % and 22 % respectively. These same risk factors match those of previous researches that studied prevalence of risk factors in CAD. Zeinaet al¹⁶stated that CAD is more prevalent and severe in hypertensive patients. Also Vargheseet al¹⁷ showed the prevalence of coronary artery disease between diabetic and non-diabetic patients (67% vs. 55%). Regarding smoking **Shinton et al**¹⁸ suggested that smoking 20 or more cigarettes per day have a 2-3 times greater risk of developing a major coronary event than the general population. However, the percentage of patients in our study was diminished as compared to such

controlled study with large number of patients. The analysis of myocardial perfusion SPECT results in the present studied that included 50 patients showed that; 22 patients of them had normal perfusion study, 20 patients had reversible stress induced perfusion defects and 8 patients had irreversible perfusion defects.

Depaceet al 1983¹⁹ hypothesized that it is not the magnitude of change in global left ventricular function during exercise but the absolute level of global function at exercise that correlates best with the extent of coronary artery disease. Because it is affected by many factors such as age, exercise heart rate, medications, exercise duration and extent of coronary disease.

In this study, end systolic & diastolic volumes of normal perfusion patients were 32 ± 7 ml & $70 \pm$ 3ml respectively, while in patients with reversible perfusion defects were 62 - 80 ml & 150 ± 7 ml and patients with irreversible perfusion defects was 120 ± 9 & 190 ± 19 respectively. Also, ejection fraction in patients with normal perfusion was $58 \% \pm 5$, while patients with reversible perfusion defects it was $39 \% \pm 3$ and in patients with irreversible perfusion defects it was $28 \% \pm 5$. Although, EF in subgroup B were evidently lower, yet this was not statistically significant if compared with those of normal perfusion group.

Such findings reflect good correlations between the severity of perfusion defects and the quantitative indices of gated map. Okadaet al²⁰ reported that MIBI bound to myocardium tends to remain for a relatively long period of time without redistribution as in 201 thallium which is called reverse *redistribution*. The retention of MIBI in myocyte is highly related to normal mitochondrial function to maintain the electrochemical potential on the exterior surface of mitochondria. In ischemic myocardium, because of decrease in oxygen supply, the aerobic metabolism of ATP generation is deactivated and the mitochondrial membrane eventually becomes depolarized and could not any longer preserve the electronegative potential, leading to fast clearance of MIBI. The phenomenon of reverse redistribution of MIBI (MIBI washout) was first reported in 1995 by **Richter et al**²¹. They studied 36 patients with coronary artery disease and global myocardial MIBI washout was estimated after 120 minutes, to assess whether a clinically relevant change in myocardial MIBI activity could be documented after 2 hours following injection.

The interval of early or delayed image acquisition, the visual evaluation criteria and the calculation method for washout rate (WR) are not standardized in institutions, and the washout evaluation method is still debated. WR using a planar image may be an effective index when the washout is determined in the whole myocardium in patients with myocardial disease. However, since the washout of MIBI is increased only in a region that is subject to a coronary artery occlusion in patients with ischemic heart disease associated with a coronary stenosis, it is difficult to evaluate the washout rate in the whole myocardium. Therefore, the method for assessing washout of MIBI by visual evaluation using short-axis, horizontal long-axis and vertical longaxis slice images after reconstruction is adopted in patients with ischemic heart disease associated with a coronary stenosis ²².

In a different method, a polar map for short-axis images is used to prepare a coronary artery dominance map based on the myocardial maximum counts from the apex to the basal area, and a region with decreased tracer accumulation is regarded as an abnormal region in comparison with a normal area with enhanced washout.

In the present study, our quantification indices showed that patients with reversible perfusion defects had significantly higher rate of washout compared to patients with normal perfusion and patients with irreversible perfusion defects. Our results were similar with the fore mentioned literature investigating the washout rate; **Richter et al** who first concluded that rapid tracer washout was detected in patients with chronic coronary artery disease. However, the major drawback of their study was using planar imaging for semi-quantitative assessment which made his result not very accurate.

At present; we used SPECT with 3D reconstruction, *Bull's-eye* display was generated with circumferential slice count profiles which were divided into 17 segments representing the

whole LV myocardium and each group of segments represents the coronary artery supplying blood to that region and permits visual estimation of the degree and extent of the perfusion abnormality for each vascular territory. Global mean washout rate in normal perfusion patients was = 7 ± 5 % (less than 12%), which are similar.

In 2003, a study by **Souichiet al** ²³ was performed on 30 patients diagnosed to have coronary spastic angina in order to assess the washout rate in patients with coronary spastic angina. This study used quantitative methods and calculated segmental uptake and washout of 99mTc-MIBI by placing region of interest (ROI) on each myocardial segment of the slice, and then it was analyzed and expressed as a percent of the maximal counts in the left ventricle. Although that study didn't include ischemic coronary patients but its qualitative methods reported normal washout rate of 10.1.

In 2006, **Tanaka et al**²⁴ estimated the value of 99mTc-MIBI delayed imaging in 43 patients with CAD for assessment of the severity of myocardial ischemia in patients with coronary artery stenosis. The myocardial perfusion images at rest were obtained 1 hour and 6 hours after injection 740 MBq of MIBI and the myocardial perfusion stress images were obtained 1 hour after injection. Also, In 2010, **Tanaka et al**²² enhanced their study by studying 10 healthy volunteers to be compared to the selected patient group in his earlier study in 2006 in order to estimate a standard index for regional washout of a myocardialperfusion agent based on data obtained from the 17-segment polar map, the washout rate (WR) and the washout index (WO INDx) were calculated from early and delayed images.

The mean washout rate in normal myocardium was **35.**59 % \pm 6.97 and that of ischemic myocardium was (55.42 % \pm 10.68). Although we used the same quantitative methods but variation in mean washout rate in **Tanaka** study likely attributed to difference in late imaging time, in their study was at 6 hrs as compared to 4 hours from tracer injection in our study that may be associated with higher myocardial washout rate.

The most recent study that dealt with myocardial MIBI washout rate is that study of **Bulin et al** in **2014**¹⁴. They compared the resting MIBI WR obtained from MIBI uptake at 90 min and 4 h post MIBI injection for healthy normal volunteers (HNV) and 3 vessels CAD patients in order to reveal the concealed balanced ischemia . They reported that significantly higher GWR was observed in the 3VCAD group $(21.1 \pm 4.6 \%)$ than the HNV group $(9.5 \pm 4.9 \%)$. RWR values in LAD, RCA and LCX in the 3V-CAD group were 20.7 ± 5.9 %, 21.3 ± 4.8 % and 20.5 ± 7.2 % respectively, which were higher than those of the HNV group 9.4 \pm 5.6 %, 9.2 \pm 5.8 % and 10.1 ± 4.4 %. Additionally, the linear correlation of GWR and total CAD severity scores utilizing degree and location of obstructive lesions (stenosis C50 %) for quantification for the whole myocardium was strong and statistically significant ($r^2 = 0.73$). In the present study, our results were quite similar to those of **Bulin et al** such that the analysis of global washout rate in normal perfusion patients as well as patients with irreversible perfusions defects was = 7 ± 5 % (less than 12%), while patients with reversible perfusions defects had global washout rate 22 ± 3 %. Furthermore, the percentage of regional washout rate in patients with reversible stress induced perfusion defects in the region of LAD, LCx and RCA vascular territories were 21.18 \pm 7.2 %, 17.02 \pm 2.6 %, and 19.17 \pm 3.86 % respectively. Moreover, we added correlation of regional washout value with the degree of reversibility in terms of vascular territories that reflect significant linear correlation with

REFRENCES:

- Thom T, Kannel W, Silbershatz H, et al. Incidence, prevalence, and mortality of cardiovascular diseases in the United States. Hurst's the Heart, 9th ed. McGraw-Hill 1998: 3-17.
- Ford S, Ajani U, Croft J et al. explaining the decrease in US deaths from coronary disease, 1980–2000. New England Journal of Medicine, 2007: 2388-2398.

correlation coefficient (r) for LAD, LCx and RCA vascular territories was 0.695, 0.666 and 0.774respectively.

The main limitations of our study:

The small sample size of the patients. Absence of correlation of our results with coronary angiography as it is still the standard for diagnosis of CAD.

CONCLUSIONS:

The rate of MIBI washout in ischemic myocardium is higher than that of normal myocardium with value greater than 12 % which may be significant for presence of ischemia.Significant linear correlation was found between the rate of MIBI washout and degree of reversibility of stress induced perfusion defect in relation to different vascular territories.

- DeBono D, Investigation and management of stable angina: revised guidelines. Heart 1999:546–555.
- Klocke J, Baird M, Lorell B, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging. 2003: 342–356.
- Beanlands R, Dawood F, McLaughlin R, et al. Are the kinetics of 99mtechnetium MIBI

affected by cell metabolism and viability? Circulation. 1990:1802–14.

- Carvalho P, Chiu M, Kronauge J, et al. Subcellular distribution and analysis of technetium-99m-MIBI in isolated perfused rat hearts. J Nucl Med1992:1516–22.
- Piwnica D, Kronauge J, Chiu M. Uptake and retention 99mtechnetium MIBI in cultured chick myocardial mitochondria and plasma membrane potential dependence. Circulation. 1990:1826–38.
- Fujiwara S, Takeishi Y, Atsumi H, et al. Prediction of functional recovery in acute myocardial infarction: comparison between MIBI reverse redistribution and MIBI/BMIPP mismatch. J Nucl Cardiol 1998: 119–127.
- Souichi O, Yasuchika T, Hiroyuki Y, et al. Enhanced regional washout of technetium-99m-MIBIin patients unstable angina, Annals of Nuclear Medicine 2003: Vol. 17, 393–398.
- 10. Cerqueira M.D., Weissman N.J., Dilsizian V.; Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of Heart the American Association. Circulation. 2002:539-542.

- 11. Yoshioka J, Hasegawa S, Yamaguchi H, et
 al. Left ventricular volumes and ejection fraction calculated from quantitative electrocardiographic-gated 99mTc-MIBImyocardial SPECT. J Nucl Med. 1999:1693-8.
- Sabharwal N, Lahiri, A Role of myocardial perfusion imaging for risk stratification in suspected or known coronary artery disease Heart. 2003: 1291–1297.
- Ahmed Fathala, Myocardial Perfusion Scintigraphy: Techniques, Interpretation, Indications and Reporting Ann Saudi Med. 2011: 625–634.
- 14. **Bulin Du, Na Li, Xuena Li, et al.** Myocardial washout rate of resting 99mTc-MIBIuptake to differentiate between normal perfusion and severe three-vessel coronary artery disease documented with invasive coronary angiography Ann Nucl Med . 2014: 285–292.
- Souichi O, Yasuchika T, Hiroyuki Y, et al. Enhanced regional washout of technetium-99m-MIBIin patients with coronary spastic angina Annals of Nuclear Medicine. Vol. 17, 2003: 393–398
- 16. Zeina A. R., Barmeir, E., Zaid, G., et al. Coronary artery disease among hypertensive patients undergoing coronary computed

tomography angiography. Journal of Cardiovascular Medicine, 2009:252-256.

- 17. Varghese M, Kiron O. Coronary artery disease among diabetic and non-diabetic patients with end stage renal disease. Renal failure 2001: 669-677.
- Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and CAD. BMJ. 1989:789-794.
- DePace, Nicholas L.. "Value of left ventricular ejection fraction during exercise in predicting the extent of coronary artery disease." Journal of the American College of Cardiology 1.4 1983: 1002-1010.
- 20. Okada RD, Glover D, Gaffney T et al. Myocardial kinetics of technetium-99mhexakis-2-methoxy-2-methylpropyl isonitrile. Circulation 1988 : 491–498.

- 21. Richter WS, Cordes M, Calder D, et al. Washout and redistribution between immediate and two-hour myocardial images using technetium-99m MIBI. Eur J Nucl Med. 1995:49-55.
- 22. **Tanaka R, Katuhiko S,** Approach to establishment of a standard index for regional washout of a myocardial perfusion agent, Ann Nucl Med. 2010:713–719.
- Souichi O, Yasuchika T, Hiroyuki Y, et al. Enhanced regional washout of technetium-99m-MIBIin patients with coronary spastic angina Annals of Nuclear Medicine. Vol. 17, 2003 393–398.
- 24. Tanaka R , Tomoharu N, Satoru C, et al. Clinical implication of reverse redistribution on 99mTc-MIBIimages for evaluating ischemic heart disease, Annals of Nuclear Medicine. Vol. 20, 2006: 349–356.