

**Original Article, Cardiology****Myocardial Viability Assessment: Role of Dobutamine Echocardiography and Tetrofosmin Gated SPECT****Zaher, A<sup>\*</sup> . El-Bedweihy, M<sup>\*</sup> . Amin, A<sup>\*\*</sup> . Salama, S<sup>\*\*\*</sup>***<sup>\*</sup>Nuclear Medicine department, National Cancer Institute and Kasr El-Aini**<sup>\*\*</sup>Cairo University & Cardiology Department <sup>\*\*\*</sup> Kasr El-Aini Cairo University***ABSTRACT:**

**Objective:** Myocardial viability assessment is an essential step to identify patients who may improve after revascularization. **The aim of this study** is evaluation of dobutamine echocardiography and Tc-99m tetrofosmin gated SPECT in the assessment of myocardial viability compared to the current gold standard; thallium-201 gated SPECT. **Patients and Methods:** This prospective study included 35 consecutive patients with asynergy or low ejection fraction (EF) < 50% on resting echocardiography. The myocardial viability of all patients was tested with threetechniques; Dobutamine Echocardiography, Tetrofosmin SPECT and the gold standard; 201-Tl SPECT (rest-redistribution study).

**Results:** The mean age of the studied group was 53.4±9.1 years. (1 female and 34 males) Dobutamine Echo identified 156 viable segments. Its Sensitivity and specificity were 30.1% and 83.5%, respectively. <sup>99m</sup>Tc-tetrofosmin gated SPECT detected 484 viable segments.

Sensitivity and specificity were 96.6% and 94.9, respectively. There was no agreement between dobutamine echo and <sup>201</sup>Tl SPECT ( $\kappa = 0.057$ ) or <sup>99m</sup>Tc-tetrofosmin gated SPECT ( $\kappa = 0.055$ ). Tetrofosmin SPECT and 201-Tl SPECT showed outstanding agreement in assessment of myocardial viability ( $\kappa = 0.890$ ). Echo-measured EF was significantly higher than EF estimated by Tetrofosmin SPECT ( $p = 0.01$ ) and <sup>201</sup>Tl SPECT ( $p = 0.02$ ). The latter two methods were not significantly different in estimation of EF ( $p = 1.000$ ).

**Conclusion:** For evaluation of myocardial viability, dobutamine echocardiography is a good positive test; <sup>99m</sup>Tc tetrofosmin is a better sensitive marker of myocardial viability compared to <sup>201</sup>Tl SPECT. We recommend starting with dobutamine echo (no radiation exposure) with PPV of 90% to detect viability. For negative dobutamine results we can proceed to <sup>99m</sup>Tc-sestamibi or tetrofosmin SPECT with 97% sensitivity.

## INTRODUCTION:

Myocardial contractile abnormalities may be reversible after acute myocardial infarction spontaneously or following coronary revascularization. It has been proposed that post-ischemia, the myocardium can be either stunned or hibernating<sup>[1,2]</sup>. Stunning refers to contractile abnormalities with preserved blood supply of non-infarcted myocardium presenting what is called perfusion-contraction mismatch<sup>[3]</sup>. Hibernation is characterized by dysfunctional hypoperfused myocardium that demonstrates contractile recovery following revascularization. Further ischemia leads to myocardial scarring with irreversible function<sup>[4]</sup>.

Assessment of myocardial viability is a vital step in the evaluation of patients with ischemic heart disease for assessment of prognosis as well as response to coronary revascularization either by PTCA or surgery. Numerous noninvasive imaging procedures have been described to detect viable dysfunctional myocardium having the potential of functional recovery. Testing viability is no more an asset in patients' evaluation; it became an integral part of clinical practice. Several techniques are available for this purpose including radionuclide imaging, echocardiography, and positron emission tomography<sup>[5,6]</sup>.

The presence of inotropic reserve is a characteristic feature of viable myocardium which became the basis of contractile response to pharmacological stress with dobutamine as a valuable diagnostic tool<sup>[7,8]</sup>. The test has high specificity, but lacks reasonable sensitivity.

Some myocardial segments show functional recovery after revascularization without demonstration of contractile reserve<sup>[9]</sup>.

Perfusion imaging is a functional diagnostic tool that uses perfusion radiotracers and single-photon emission computed tomography (SPECT) or positron emission tomography (PET). The application of electrocardiographic gating to SPECT and PET allows simultaneous determination of perfusion and function in a single study. Theoretical basis of radionuclide imaging is that tracer uptake by myocytes with intact cellular and mitochondrial membranes reflects viability.<sup>[10]</sup>

Thallium-201 (<sup>201</sup>Tl) is a radionuclide tracer that assesses myocardial perfusion and myocyte cell membrane integrity. It is actively transported by intact cell membranes of hibernating myocytes. Bax and coworkers reported sensitivity of 86% and specificity of 59% for thallium imaging in predicting functional improvement following revascularization<sup>[11,12]</sup>.

Quantitative technetium-99m (<sup>99m</sup>Tc) sestamibi single-photon emission computed tomography (SPECT) is also a reliable method for the detection of myocardial viability. Contrary to <sup>201</sup>Tl, <sup>99m</sup>Tc tetrofosmin is similar to <sup>99m</sup>Tc sestamibi in evaluation of myocardial viability. It is easier to prepare as it does not need boiling. Tc-99m sestamibi and Tc-99m Tetrofosmin are readily available in kit form at all nuclear medicine departments, this makes their use for myocardial perfusion and viability

detection more convenient than thallium and ready to use 7 days a week. Both sestamibi and tetrofosmin were reported to correlate well with  $^{201}\text{Tl}$  and dobutamine echocardiography in the assessment of myocardial viability<sup>[14,15]</sup>. In the current study, we evaluated dobutamine echocardiography and gated SPECT with Tc-99m tetrofosmin (myoview) in comparison to thallium-201 gated SPECT (rest-redistribution study), being the current gold standard, in the assessment of myocardial viability.

## PATIENTS AND METHODS

**Study Population:** This is a prospective comparative study that included 35 consecutive patients, referred from the cardiology department, for evaluation of myocardial viability after myocardial infarction, between August 2010 and March 2012. Patients were enrolled according to two inclusion criteria; asynergy (hypokinesis, akinesis, or dyskinesis) on resting echocardiography and low ejection fraction (EF) < 50%. Patients with any evidence of current angina and risk to do dobutamine ECHO were excluded.

The myocardial viability of all patients was tested with three techniques; Dobutamine Echocardiography, Tetrofosmin SPECT and  $^{201}\text{Tl}$  SPECT. We considered  $^{201}\text{Tl}$  SPECT (rest-redistribution study) as the gold standard for the assessment of myocardial viability. We compared the results of dobutamine ECHO and Tetrofosmin SPECT with  $^{201}\text{Tl}$  SPECT to estimate the sensitivity of both techniques in the assessment of myocardial viability.

### Resting Tetrofosmin SPECT Protocol

All patients were given sublingual nitrates (GTN), 10 mg, followed 20 minutes later by IV injection of 600 MBq Tc-99m tetrofosmin. SPECT study was done after 60 min. The beneficial effects of nitrates are an increase in coronary flow reserve and decreased myocardial oxygen demand. The former effect is the desired one to increase tracer delivery to ischaemic myocardium, **Pavlovic et al, 2009**<sup>[35]</sup>

### SPECT Acquisition and Processing:

SPECT images were acquired using a rotating dual-head gamma camera with the detectors mounted at right angle and fitted with high-resolution collimators. The image acquisition variables included a 140-keV photopeak with a 20% energy window, 64 projections at 40 second per projection over 180 degrees (90 per detector) and a matrix size of 64 x 64. Acquisitions were gated for 8 frames per cardiac cycle. The 8-interval projection datasets were reconstructed with filtered back projection and no attenuation correction. Images were displayed in the standard short axis, horizontal and vertical long axes for qualitative interpretation. LVEF was automatically calculated (**Moore et al., 1990**)<sup>[16]</sup>.

### $^{201}\text{Tl}$ SPECT Protocol (rest-redistribution study):

The standard protocol for rest (15 min)--redistribution (3 hours) SPECT studies was done after IV injection of 111-185 MBq  $^{201}\text{Tl}$  with IV re-injection of 37 MBq  $^{201}\text{Tl}$  before the redistribution image (**Bax et al., 1996**)<sup>[17]</sup>.

**SPECT Image Interpretation:** For the analysis of wall motion, the left ventricle was divided into 18 segments. These

segments included the apex, anterior (apical, mid and basal segments), inferior (apical, mid and basal segment), lateral (apical, mid and basal segments), inferoseptal (apical, mid and basal segments), anteroseptal (apical, mid and basal segments) and finally the posterior (inferolateral; mid and basal segments) (Sinusaset al., 1989)<sup>[18]</sup>.

The gated image sets were read independently by 2 expert observers unaware of patients' condition. Wall motion was assessed visually and quantified using the QGS program by using a 5-point scoring system; 0: normal, 1: mild hypokinesia, 2: moderate hypokinesia, 3: severe hypokinesia, 4: akinesia, 5: dyskinesia. We considered grades from 0 to 3 to reflect the presence of viable myocardium and grades 4 and 5 to reflect non-viable myocardium.

Segmental perfusion was assessed using the count density by using the QPS program using 2-point scoring system; 1: normal viable myocardium (> 50% of the count density) and 2: non-viable (< 50% of the count density).

#### **Dobutamine Echocardiography Protocol**

Dobutamine echocardiography was performed using a standard protocol (Ostojic, 1994)<sup>[19]</sup>. First, resting echocardiography was performed with the patient lying in the left lateral recumbent position.

Echocardiographic imaging was then performed after intravenous infusion of dobutamine, starting at a dose of 5 microgram/kg/min, which was increased every 3 min to 7.5 and 10 microgram/kg/min. Images were obtained in the standard para-sternal long-axis and short-axis views, with particular attention for

determining regional function. During dobutamine infusion, the 12-lead ECG and blood pressure were monitored. The test was ended prematurely if the heart rate reached 85% of the predicted maximum or if any of the following developed: severe angina, a systolic blood pressure < 85 or > 180 mmHg, more than 2 mm of ST depression in more than 2 contiguous leads, or significant arrhythmia (16 beats of supraventricular tachycardia or > 3 beats of ventricular tachycardia) (Pierard et al., 1990)<sup>[20]</sup>. All studies were performed on a Sonos 1500 ultrasound system (Agilent Technologies, Palo Alto, CA) equipped with a 2.5 -MHz transducer.

#### **Echocardiographic Image Processing and Analysis:**

For the analysis of wall motion, the left ventricle was divided into 16 segments as anterior (apical, mid and basal segments), inferior (apical, mid and basal segment), lateral (apical, mid and basal segments), inferoseptal (apical, mid and basal segments), anteroseptal (mid and basal segments) and finally the posterior (inferolateral (mid and basal segments). Echo could not assess 2 segments (apex itself and apical anteroseptal) that were assessed by SPECT, so the end result in ECHO is to assess the 16 segments as mentioned before (La Canna, 1994)<sup>[21]</sup>. The dobutamine echocardiographic studies were interpreted randomly using all 7 digital images for each view displayed on 2 monitors placed side by side to allow simultaneous review of all stages of the test. All studies were read by a single experienced investigator who was unaware of the clinical information. All the results were revised again by another blind operator who revised the

radionuclide information, and the results of resting echocardiography. A wall motion score was assigned to each of the 16 segments for every stage of the test.

#### Statistical Methods:

Data was analyzed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Kendall rank correlation coefficient (Kendall's tau ( $\tau$ ) coefficient) was used to

measure the association between two methods for assessment of wall motion as ordinal data. Kappa test was used for inter-rater analysis of two tests assessing myocardial viability as nominal data.

#### RESULTS:

The studied sample included one female and 34 males (97.1%) with a mean age  $53.4 \pm 9.1$  years, ranging from 32 to 72 years. Table 1 shows the risk factor profile of the study cohort. All patients have within normal values of hemoglobin, renal function tests and fasting blood sugar.

**Table 1: Associated morbidity and history of the study population**

	Frequency	Percentage
Diabetes Mellitus	17	48.6
Hypertension	28	80.0
Hyperlipidemia	17	48.6
Current Smoker	20	57.1
Previous myocardial infarction	32	91.4
History of stenting	7	20
History of CABG	2	5.7

We compared the grade of each myocardial segment studied in the dobutamine ECHO and Tetrofosmin SPECT with the same segment in  $^{201}\text{Tl}$  SPECT to detect which of the two techniques (*Dobutamine echo vs. Tetrofosmin SPECT*) is more sensitive in the assessment of myocardial viability in comparison to  $^{201}\text{Tl}$  SPECT (rest-redistribution study); the current gold standard technique in the assessment of viability.

With Dobutamine Echo, 156 segments of the 560 studied segments (27.9%) showed

improvement of wall motion denoting viability. On the other hand,  $^{99\text{m}}\text{Tc}$ -tetrofosmin gated SPECT detected 484 viable segments (76.8%) and  $^{201}\text{Tl}$  SPECT detected 494 viable segments (78.4%). Table 2 shows the agreement between the three techniques. There was no agreement between dobutamine echo and  $^{201}\text{Tl}$  SPECT ( $kappa = 0.057$ ) or  $^{99\text{m}}\text{Tc}$ -tetrofosmin gated SPECT ( $kappa = 0.055$ ). However, Tetrofosmin SPECT and  $^{201}\text{Tl}$  SPECT showed outstanding agreement in assessment of myocardial viability ( $kappa = 0.890$ ) (Fig 1, Table 2).

**Table 2:** Agreement between dobutamine echo and <sup>201</sup>Tl SPECT or <sup>99m</sup>Tc – tetrofosmin gated SPECT in myocardial viability testing

	Thallium-201 SPECT		kappa
	Viable Segments	Non-viable Segments	
<b>Dobutamine Echo</b>			
Viable Segments	141 (30.1%)	15 (16.5%)	0.057
Non-viable Segments	328 (69.9%)	76 (83.5%)	
	Thallium-201 SPECT		kappa
	Viable Segments	Non-viable Segments	
<b>Tetrofosmin SPECT</b>			
Viable Segments	477 (96.6%)	7 (5.1%)	0.890
Non-viable Segments	17 (3.4%)	129 (94.9%)	
	Tetrofosmin SPECT		kappa
	Viable Segments	Non-viable Segments	
<b>Dobutamine Echo</b>			
Viable Segments	138 (30.0%)	18 (18.0%)	0.055
Non-viable Segments	322 (70.0%)	82 (82.0%)	

Table 3 shows the diagnostic reliability of Tetrofosmin SPECT and Dobutamine Echo compared to the gold standard; <sup>201</sup>Tl SPECT. Perfusion test with Tetrofosmin SPECT has the highest sensitivity, 96.6% and specificity 94.9%.

Its overall accuracy was 92.6%. On the other hand, Dobutamine echo was not sensitive in assessment of myocardial viability 30.1%, but it has a rather good specificity (83.5%) and accuracy of (38.8%). (Fig 2a,b,c)

**Table 3:** Sensitivity, specificity, PPV and NPV for Tetrofosmin SPECT and Dobutamine Echo for detection of myocardial viability

	Sensitivity	Specificity	PPV	NPV	Accuracy
Tetrofosmin SPECT	96.6%	94.9%	98.6%	88.4%	92.6%
Dobutamine Echo	30.1%	83.5%	90.4%	18.8%	38.8%

PPV = positive predictive value, NPV = negative predictive value

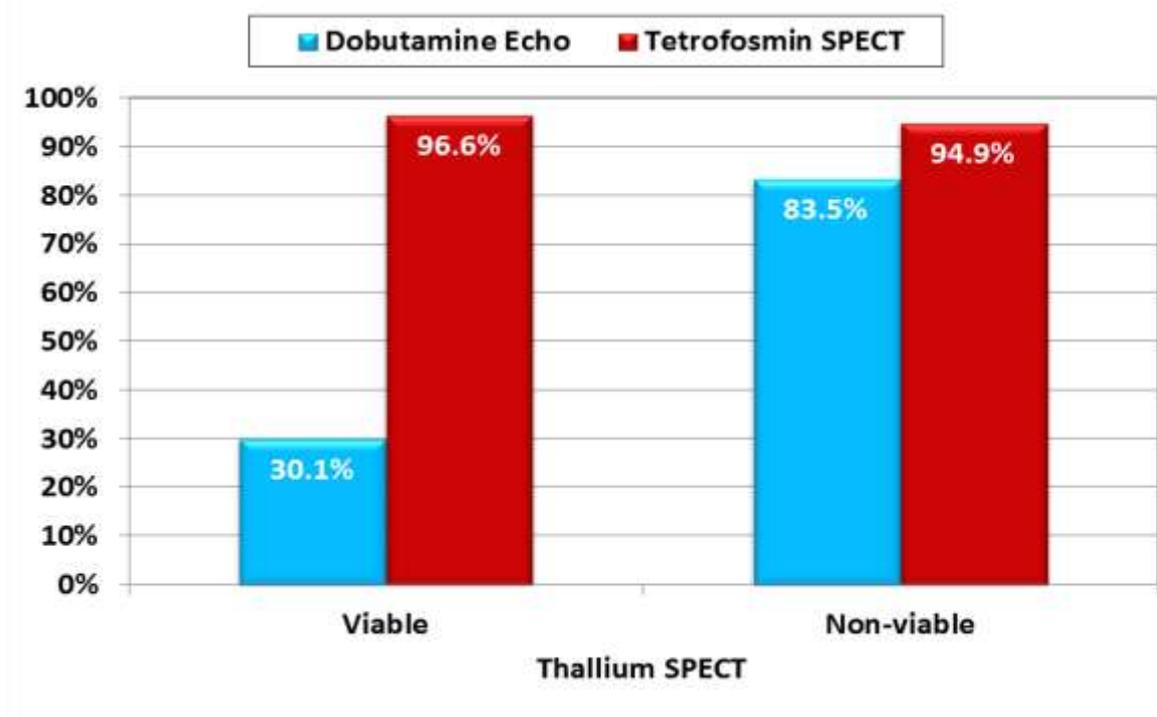
**Table 4:** Estimated ejection fraction (EF) by dobutamine echo, Tetrofosmin SPECT and 201-Tl SPECT

	Mean±SD	p value
Echo EF	34.9±12.7	
Tetrofosmin SPECT EF	29.3±9.4	0.010*
201-Tl SPECT EF	29.6±10.0	0.020**

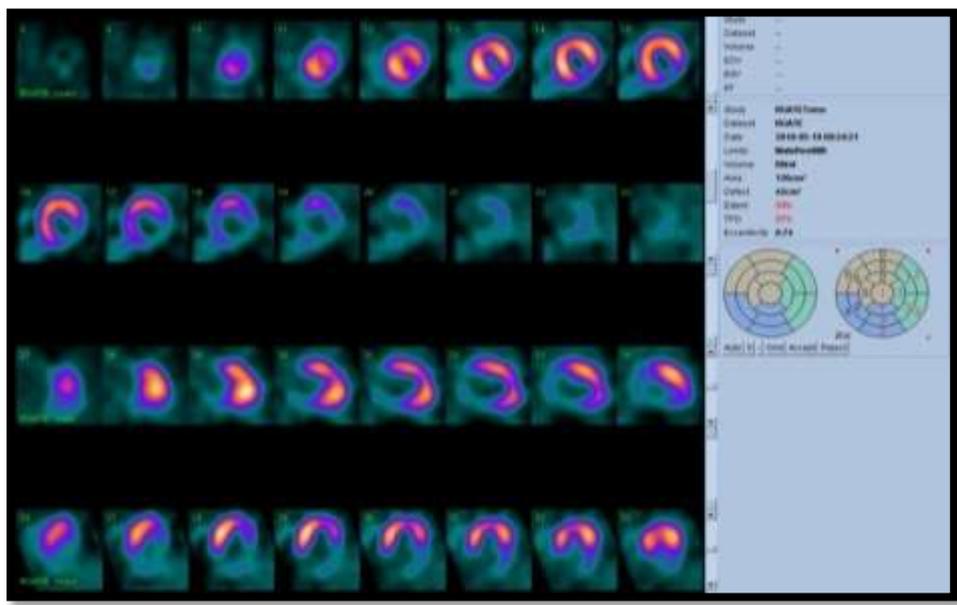
\* Echo vs. Tetrofosmin SPECT, \*\* Echo vs. 201-Tl SPECT

Echo-measured EF was significantly higher than EF estimated by Tetrofosmin SPECT (p= 0.01) and <sup>201</sup>Tl SPECT (p = 0.02). The latter two methods were not significantly different in estimation of EF (p = 1.000), and

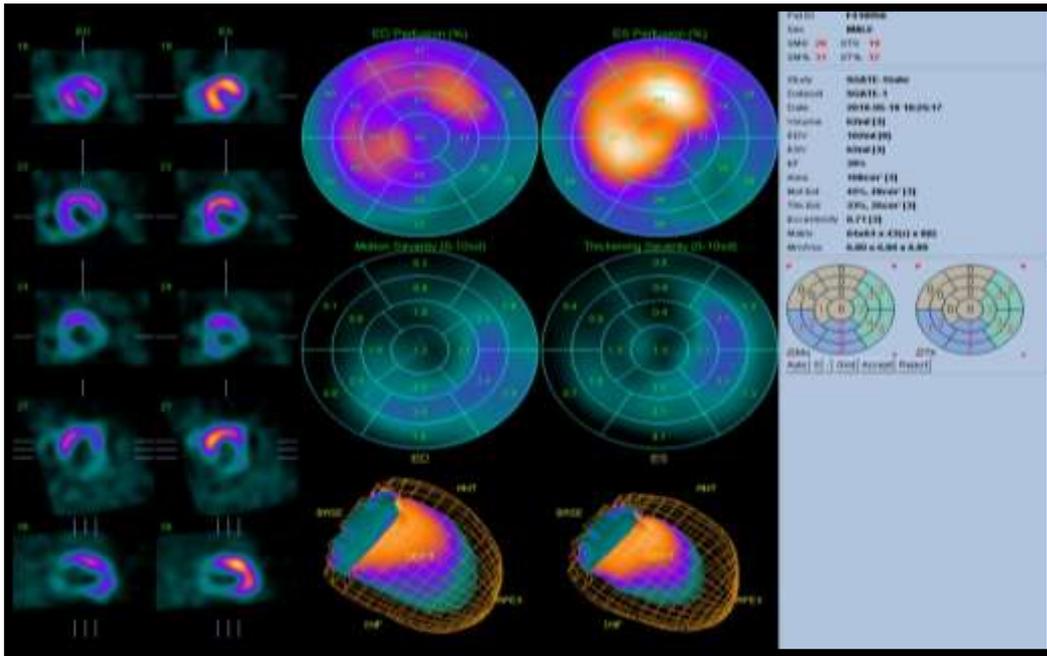
have an ICC coefficient of 0.894 (95% CI: 0.800-0.945). ICC coefficient of Echo with Tetrofosmin SPECT was 0.558 (95% CI: 0.281-0.750) and with 201-Tl SPECT was 0.550 (95% CI: 0.270-0.744) (Table 4).



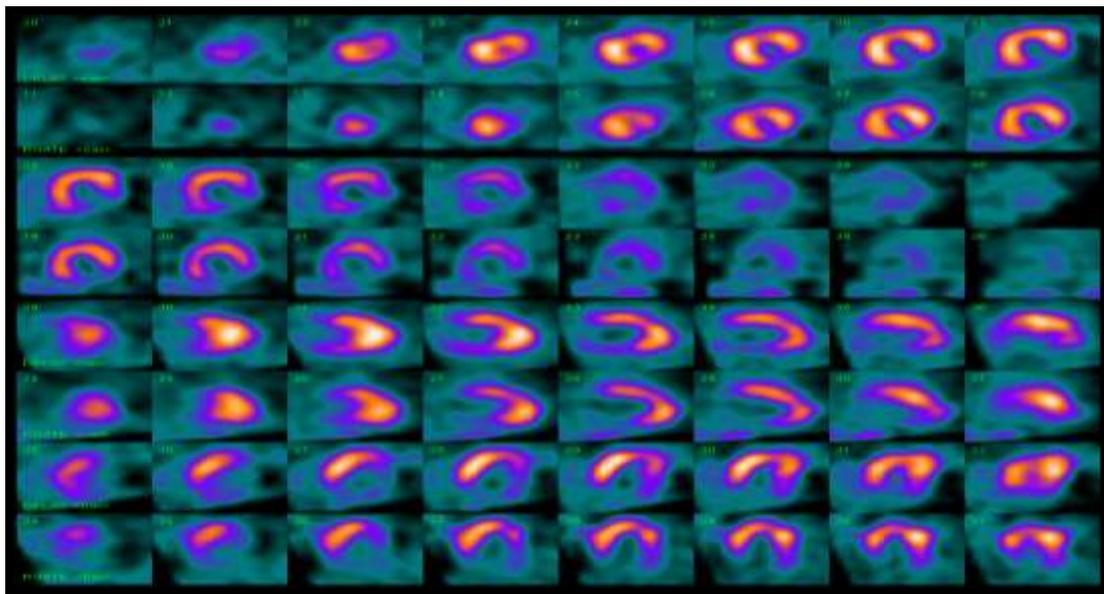
**Figure 1:** Viability assessment with dobutamine echo and <sup>99m</sup>Tc –tetrofosmin gated SPECT relative to <sup>201</sup>Tl SPECT



**Fig. 2 (A):** A 54 Y old male with history of MI. Tc-99m Tetrofosmin viability images revealed mild hypoperfusion (grade 1) of the apical anterior wall & severe hypoperfusion (grade 2) of most of the inferior & inferolateral walls.



**Fig. 2 (B):** QGS (wall motion) findings; revealed grade 1 hypokinesia of the apical anterior wall and grade 4 (akinetic) of the inferior & inferolateral walls



**Fig. 2 (C):** 201-Tl myocardial viability images showing the same findings as Tetrofosmin images. Low dose Dobutamine ECHO revealed Akinesia of the anterior, inferior and inferolateral segments.

## DISCUSSION:

This study demonstrates outstanding agreement between Tetrofosmin SPECT and  $^{201}\text{Tl}$  SPECT ( $kappa = 0.890$ ) in the assessment of myocardial viability. Sensitivity and specificity of tetrofosmin were 96.6% and 94.9%. On the other hand, dobutamine Echo did not show agreement with  $^{201}\text{Tl}$  SPECT ( $kappa = 0.057$ ); Echo sensitivity was 30%, however its specificity was rather good (83.5%). Ejection fraction was significantly underestimated by SPECT studies compared to echo, which is normally expected in cases with dilated LV cavity. Meanwhile there was no significant difference between Tetrofosmin and  $^{201}\text{Tl}$  SPECT in EF estimation. ICC coefficient of the two methods was 0.894. The primary objective of myocardial viability assessment is to identify patients whom symptoms may improve after revascularization. Recent investigations have shown that patients with viable myocardium will have poor prognosis if not referred for revascularization procedures in contrast to patients with myocardial scarring who do not appear to be helped with revascularization.  $^{201}\text{Tl}$  SPECT imaging is well established for estimation of myocardial viability. In the current study, we used  $^{201}\text{Tl}$  SPECT imaging as the gold standard method for evaluation of the role of Dobutamine Echo and Tetrofosmin SPECT in assessment of myocardial viability. We are trying to substitute thallium by  $^{99\text{m}}\text{Tc}$ -labelled agents as the latter are readily available on shelf at every nuclear medicine department, can be injected in higher doses, produce better quality SPECT images and give less radiation dose to the patient compared to

thallium which is not readily available. Tetrofosmin imaging in this study seems comparable to  $^{201}\text{Tl}$  SPECT with very high agreement and accuracy contrary to Dobutamine Echo which has much less sensitivity and accuracy. In addition tetrofosmin gated SPECT evaluates perfusion and wall motion in the same time with additional automated estimation of LVEF & is not operator dependent.  $^{99\text{m}}\text{Tc}$  sestamibi is widely used now in the United States.<sup>[22]</sup> A number of investigators have shown a higher specificity with  $^{99\text{m}}\text{Tc}$  sestamibi compared to  $^{201}\text{Tl}$ .<sup>[23,24]</sup> Early studies concluded that  $^{201}\text{Tl}$  imaging was superior to  $^{99\text{m}}\text{Tc}$  sestamibi for identifying myocardial viability.<sup>[25]</sup> Sestamibi imaging wrongly identified 36% of nonviable myocardial regions compared with thallium.<sup>[26]</sup> Ragosta et al.<sup>[27]</sup> reported sensitivity for sestamibi of 94% and low specificity of 76%. Other studies, however, found comparable results of Technetium-99m sestamibi and  $^{201}\text{Tl}$  in viability assessment.<sup>[28]</sup> In the present study, dobutamine Echo has high specificity (83.5%) and positive predictive value (90.4%) in detection of viable myocardium; it is a well-recognized method for detection of contractile reserve of the myocardium.<sup>[29,30]</sup> In a series of patients with recent MI, dobutamine Echo had specificity of 88% in the detection of myocardium capable of late mechanical recovery.<sup>[31]</sup> Despite high specificity of dobutamine stress echocardiography, its sensitivity tends to be lower than the other imaging modalities.<sup>[32]</sup> In contrast to our study, other studies reported higher accuracy and sensitivity in predicting recovery of dysfunctional myocardium.<sup>[33,34]</sup>

We can conclude that for evaluation of myocardial viability, dobutamine echocardiography is a good positive test; however, its sensitivity is unacceptably low. On the other hand,  $^{99m}\text{Tc}$  tetrofosmin is a sensitive marker of myocardial viability compared to  $^{201}\text{Tl}$  SPECT. Thus we recommend starting with dobutamine

echo (no radiation exposure) and PPV of 90% to detect viability. For negative dobutamine results we can proceed to  $^{99m}\text{Tc}$ -sestamibi or tetrofosmin SPECT that is nearly 97% sensitive for detection of viable myocardial segments and can better assess the apex that is not properly evaluated by dobutamine echo.

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