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Could myocardial ^{99m}Tc -mibi washout rate be the savior in patients with ischemic cardiomyopathy in limited resources countries?!

Zainab Ahmed Mohamed Zaki

Assistant lecturer of Nuclear Medicine Department, faculty of medicine, Beni-Suef University, Egypt +201094982749

Corresponding Author: email: Drzaynabsinger@gmail.com

Hosna Mohamed Moustafa

Emeritus Professor of Oncology and Nuclear Medicine Department (NEMROCK), Kasr-El-Ainy Hospital, Cairo University, Egypt

Email: drhosna1947@gmail.com

Mahasen AbouGabal

Professor of Oncology and Nuclear Medicine Department (NEMROCK), Kasr-El-Ainy Hospital, Cairo University, Egypt

Email: kodomojanai20@yahoo.com

Dalia Rifaat Elremisy

Lecturer of cardiology, cardiology department, Cairo University

Email: Man.hamza@yahoo.com

ElShaymaa Hussein

Assistant professor of Oncology and Nuclear Medicine Department (NEMROCK), Kasr-El-Ainy Hospital, Cairo University, Egypt

Email: elshaymaahussein@cu.edu.eg

Abstract---Background: proper assessment of patients with ischemic cardiomyopathy is a key determinant for management with other investigations, improving the patient's quality of life and reducing future cardiac events. This study was conducted to evaluate the value of myocardial MIBI washout rate using delayed resting myocardial perfusion imaging in patients with ischemic cardiomyopathy in limited resources countries. Patients and Methods: this prospective study included 86 patients (64 males (74.4%) & 22 females (25.6%) with ejection fraction less than 35%. The mean age was 56.7 ± 9.4 years, all patients underwent ECG-gated single-photon emission computed

tomography (SPECT) technetium-^{99m} MIBI myocardial perfusion imaging (^{99m}Tc MIBI).

Keywords---Ischemic cardiomyopathy, MIBI, Washout Rate, Delayed imaging, Dobutamine echocardiography.

Introduction

Ischemic cardiomyopathy(ICM) is one of the most common cardiac diseases, it is increasing worldwide based on risk factors of coronary artery disease[1]. The vast majority of cardiovascular deaths occurs in developing countries [2]. Proper diagnosis and management of ICM has a crucial role in preventing future cardiac events especially in countries with limited resources. MIBI Myocardial perfusion imaging (MPI) is one of the most commonly used fundamental investigations in ICM, being a solid, highly validated technique, widely available, physiologic, and noninvasive[3]. In addition to the routine stress-rest MPI imaging, delayed (post 4 hours) imaging could be acquired to calculate Myocardial MIBI Washout rate which in turn could be used as an indicator for myocardial viability.

Dobutamine stress echocardiography is a combination of the conventional 2D echocardiography with a pharmacologic stress based on induction of a temporary change in regional function during stress [4]. It is a highly specific test used for assessment of myocardial ischemia, as well as hibernating viable myocardium which could benefit from revascularization.

Methods

This prospective study was performed in Nuclear Medicine Unit (faculty of Medicine, Cairo University, after being approved by the ethical committee during the period from February 2019 till May 2021. It included 86 patients [64 males (74.4%) & 22 females (25.6%)] with mean age 56.7 ± 9.4 years. All the patients underwent ECG-gated single-photon emission computed tomography (SPECT) technetium-^{99m} MIBI myocardial perfusion imaging (^{99m}Tc MIBI). An additional rest MPI images were acquired for each patient at 4 hours post tracer injection.

Thorough clinical history of patients was checked and only patients meeting inclusion criteria (Ejection fraction less than or equal 35%), were included, we excluded patients with ejection fraction more than 35% and patients with recent history of myocardial infarction or recent ICU admission.

Patients were instructed for preparation according to the SNMMI procedure guidelines for myocardial perfusion imaging: version 3.3 [5]. Briefly, patients were required to fast for at least 4 hours before the examination. Certain cardiac medications were withheld, also caffeine containing products were not consumed for at least 12 hours before the examination. A dose of 15 -20 mCi (555 -740 MBq) of ^{99m}Tc MIBI was injected intravenously for each study. then fatty foods (egg, milk or chocolate) were given 15 minutes after tracer injection to facilitate liver and biliary system clearance. In the rest study; the patient was imaged twice. Early imaging at one hour post injection and delayed imaging at 4 hours after the

same injection. While in stress study imaging was done at 30 minutes post injection.

ECG gated SPECT images were acquired, patients were supine with raised left arm using dual-head SPECT gamma camera with the detectors at 90 degrees rotating counterclockwise (180 degrees from right anterior oblique 45° to left posterior oblique position 135°), low-energy high-resolution parallel hole collimator was used, photon peak =140 keV, energy window of $\pm 20\%$, Zoom factor of 1.3, matrix: 128X128. Electrocardiogram synchronized data with R wave trigger, 8 frames / cardiac cycle to generate a total of 32 projections (40 s per projection).

Raw data were reconstructed using filtered back projection, then filtered using Butterworth filter. SPECT images were reformatted into Short-axis, vertical long-axis, and horizontal long-axis. All raw data sets were corrected with isotope decay factor and checked for patient motion by reviewing a rotating cine display.

MPI analysis:

For each SPECT MPI exam, images were interpreted by two nuclear medicine consultants both **qualitatively** and **semi-quantitatively**, qualitative interpretation included Perfusion defects in stress images in terms of its location, size and severity. Then reversibility was evaluated in rest images in terms of complete, partial or absent. Also, location of the defects was described in regard to the left ventricular walls and the coronary vascular territories likely to be involved. **Semi quantitative** evaluation was performed according to Bull's eye 17 segments model classifying segments according to degree of perfusion into 0-5 [6]. Also, **semi quantitative indices** including left ventricular ejection fraction, end systolic volume and end diastolic volume were calculated.

Calculation of **global myocardial washout rate** was done for each patient using the MIBI uptake counts per pixel within the polar map of perfusion images acquired at initial one hour as well as the polar map of delayed perfusion images at 4 hours as shown using Flotats et al. formula [7]. Normal washout rate percent is less than 12% [8].

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

Ce: myocardial counts in early imaging

Cd: myocardial counts in delayed imaging

Decay factor: = $1 / (1/2)^x$, x = (time difference)/6

DSE analysis:

During stress echocardiography, electrocardiographic leads were placed at standard limb and precordial sites with 12 lead ECG monitoring throughout the examination. Dobutamine was injected in 3-minute increments, starting with 5µg/kg and increasing to 10, 20, 30 and 40 µg/kg /min, data analysis were done

according to myocardial segments motion, including one or more than a diagnostic response(normal response, ischemic response, necrotic response and viability response) [9].

Statistical analysis

Data management and analysis was performed using Statistical Package for Social Sciences (SPSS) vs. 25. Numerical data were checked for normality and were statistically described in terms of mean (standard deviation) or median (range) as appropriate. Categorical data were described as numbers and percentages. Comparison between 2 numerical variables was done using Student t-test if normally distributed and Mann-Whitney U test if not normally. Comparison between more than 2 variables was done using Analysis of variance (ANOVA) with Bonferroni adjustment if the data was normally distributed and using Kruskal Wallis test if the data was not normally distributed or having unequal variance. Pearson's correlation coefficient (r) was calculated for normal data and Spearman rho correlation coefficient for non-normal data.

Results

The study included 86 patients, [64 males (74.4%) & 22 females (25.6%) with mean age 56.7 ± 9.4 years, maximum age was 86 years and minimum age was 36 years, with mean BMI 30.3 ± 5.9 . Regarding the prevalence of clinical risk factors, hypertension was present in 67.4% of patients, 52.3% were diabetic, smoking in 53.3%, and dyslipidemia was found in 45.3% .58.1% of patients had prior history of MI, 38.4% underwent PTCA and 12.8% of them had CABG (table 1).

Table (1): Patients' demographic and clinical data in the whole study group (n=86)

	Number	Percentage (%)
Age(years) Mean (SD)	86	56.7(± 9.4)
Gender: Male/ Female	64/22	74.4/25.6
BMI, Mean (SD)	86	30.3(± 5.9)
Hypertension	58	67.4
Diabetes	45	52.3
Smoking	46	53.3
Dyslipidemia	39	45.3
Previous MI	50	58.1
Previous PTCA	33	38.4
Previous CABG	11	12.8

Descriptive data of stress, early rest and delayed rest MPI images showed that the median number of affected segments per patient was 8 segments in the stress phase and it was equal in early and delayed rest phases (6 segments) and the most encountered severity score was score 5(absent perfusion) representing 88.2%, 76.7% and 81.4% respectively (table 2).

Table (2): Stress, early rest and delayed rest MPI parameters in the whole study group, (n=85 for stress and 86 for rest phases)

	Stress MPI	Early rest MPI	Delayed rest
No. of affected segments	8 (4-14)	6(3-13)	6 (3-13)
Severity score:			
Normal perfusion	0	0	0
Mild to moderate hypoperfusion	3(3.5%)	7(8.2%)	6(7%)
Severe hypoperfusion	7(8.2%)	13(15.1%)	10(11.6%)
Absent perfusion	75(88.2%)	66(76.7%)	70(81.4%)

We classified all segments in all patients according to bull's eye polar map (17 segments) into 4 categories based on degree of segmental perfusion (normal perfusion, mild to moderate hypoperfusion, severe hypoperfusion and absent perfusion) and compared stress, early rest and delayed rest MPI in each score, we found a statistically significant difference between the three studies regarding detection of **mild to moderate perfusion** defects, **P. value=0.038**, table (3).

Table (3): Stress, early rest and delayed rest MPS segmental classification using severity score

Severity score	Stress MPI No. of segments (N=1445)	Early rest MPI (N=1462)	Delayed rest MPI (N=1462)	P.value
0	8	6	6	0.804
1-3	106	145	136	0.038*
4	213	205	208	0.850
5	1118	1106	1112	0.523

*One patient missed stress MPI due to knee osteoarthritis.

Subsequent further classification of segments using early and delayed rest images included 2 categories based on whether segments showed washout or not (appearance of a new perfusion defect or worsening of an already present defect by more than 10%), we found that all normally perfused segments (6 segments) and infarcted segments (1106 segments) didn't show washout in delayed images. On the other hand, out of 350 ischemic segments, 9 segments only (2.5%) showed

washout while the remaining 341 segments (97.5%) didn't show washout, table (4).

Table (4): classification of segments in early and delayed rest phases according to presence or absence of washout(n=1462)

	Normally perfused segments	Ischemic segments	Infarcted segments
Washout (+)	--	9	--
Washout (-)	6	341	1106
Total	6	350	1106

By combining MPI images with wall motion and degree of functional improvement detected by DSE, 3 categories were evolved, table 5:

-Out of the 9 ischemic segments with washout, 8 segments (88.8%) showed wall motion abnormalities in low dose DSE, and functional improvement during high dose DSE occurred in 6 segments (75%).

-Out of the 341 ischemic segments without washout, 324 segments (95%) showed wall motion abnormalities in low dose DSE and functional improvement occurred in 107 segments (33%).

- In the 1106 infarcted segments, 1072 segments (97%) had motion abnormalities and only 215 segments (20%) showed functional improvement in high doses DSE with statistically significant difference between them, P.value<0.02.

Table (5): Comparison between MPI segments and DSE motion abnormalities and degree of improvement

	No. of segments washout	ischemic with	No of segments washout	ischemic without	No. of infarcted segments
	9		341		1106
Motion abnormalities in DSE	8(88.8%)		324(95%)		1072(97%)
Number of improved segments	6(75%)		107(33%)		215(20%)

left ventricular cardiac parameters:

By calculating left ventricular cardiac parameters derived from stress MPI and DSE, we found no statistically significant difference between both studies, P.value >0.5 as shown in table 6.

Table (6): Cardiac functional parameters in the whole study group in stress MPI(n=85) and DSE(n=79)

	MPI, median(range)	DSE, median(range)
LVEF%	27(15-38)	29(19-38)
ESV (ml)	127(63-190)	130(64-195)
EDV (ml)	192(96-287)	192(94-290)

Global washout rate % (GWR):

- Mean global washout rate was $16.1\% \pm 3.6$.

Univariate analytic statistics for global washout rate (GWR) %

Global washout rate was calculated for each patient and correlated to different demographic and clinical data and it showed a weak negative correlation with patient's age with correlation coefficient -0.022 and BMI with a weak negative correlation, correlation coefficient -0.029 yet no statistically significant difference with age or BMI.

Global washout rate showed **statistically significant difference with dyslipidemia (p. value=0.032)**, previous history of **myocardial infarction(P.value=0.002)** and previous **history of CABG(P.value=0.005)**, while no statistically significant difference was found with other demographic and clinical risk factors (gender, hypertension, diabetes, smoking, and previous PTCA) (table 7)

Table (7) GWR in relation to demographic and clinical data (n=86)

Global washout rate %			
	Mean (SD)	p-value	
Gender: Male	16.1(3.3)	0.904	
Female	16(4.4)		
Hypertension: Absent	15.5(3.6)	0.290	
Present	16.4(3.6)		

Diabetes: Absent	15.8(3.6)	0.495
Present	16.3(3.6)	
Smoking: Absent	15.8(3.9)	0.489
Present	16.4(3.3)	
Dyslipidemia: Absent	15.3(3.2)	0.032 *
Present	17.0(3.8)	
Previous MI: Absent	14.6(3.8)	0.002 *
Present	17.1(3.1)	
Previous PTCA: Absent	15.7(3.5)	0.245
Present	16.7(3.8)	
Previous CABG: Absent	15.7(3.5)	0.005 *
Present	18.9(3.0)	

Case presentation

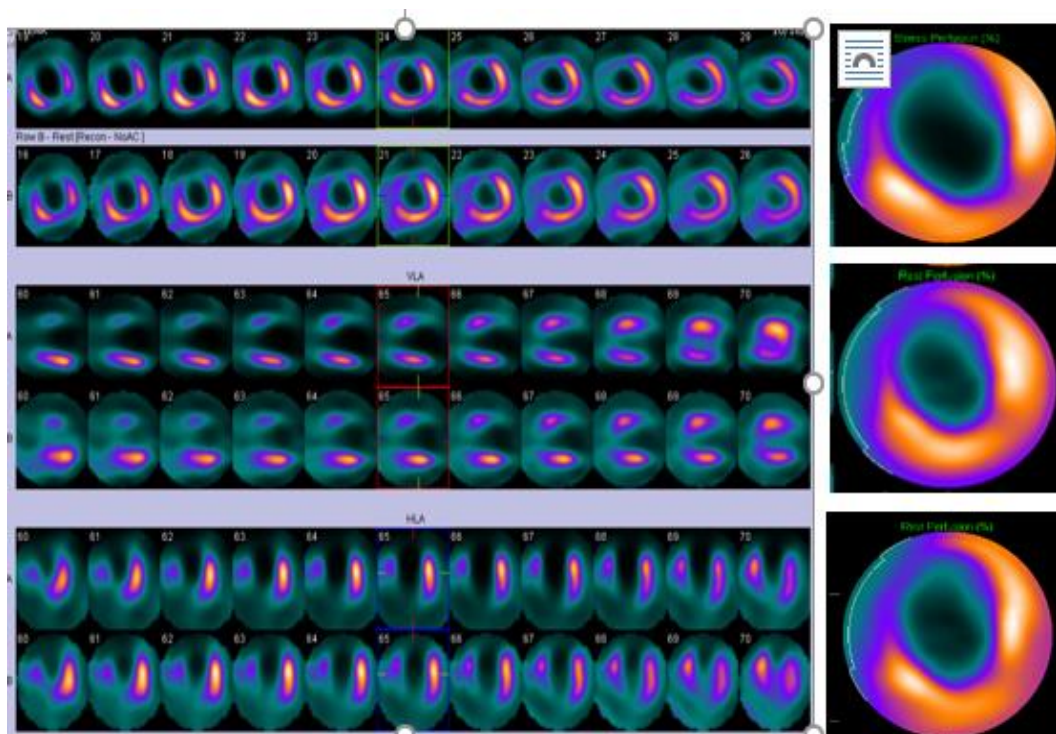
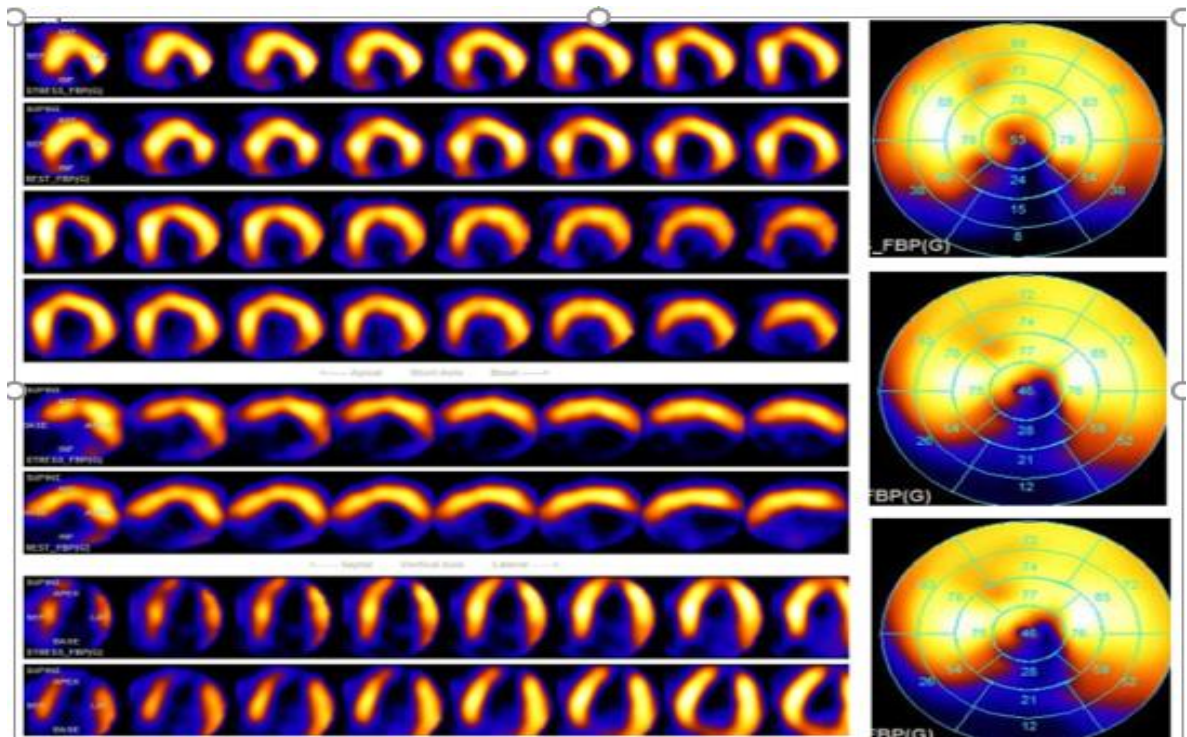


Figure1: representative example of a 66-year-old male patient, hypertensive and diabetic complaining of dyspnea on mild exertion with no previous history of MI or cardiac interventions. Upper polar map represents stress phase, mid one represents early rest imaging and lower one represents delayed rest phase, MPI showed a large fixed perfusion defect involving apex, apical anterior, septum, antero-septal, mid anterior wall, with severe hypoperfusion involving inferior wall, infero anterior and infero lateral walls with slight improvement of the infero lateral wall in rest study, no significant perfusion changes in the delayed phase, E.F.=28%, E.S.V.= 197 ml, E.D.V.=232 ml, GWR= 17%, DSE showed akinetic apex, apical anterior, septum, with hypokinesia of infero septal, infero lateral



walls improving in high dose DSE, E.F.= 32%, E.S.V.=187 ml, E.D.V.= 220 ml.

Figure 2: Representative example of a 64 -year-old male patient, hypertensive and chronic heavy smoker complaining of typical chest pain, with previous history of MI 2 years ago and RCA stenting, MPI showed large irreversible perfusion defects involving inferior and apico inferior walls, E.F.=16%, E.S.V.= 86 ml, E.D.V.= 154 ml, GWR= 11%, DSE showed akinesia of the whole inferior wall with severe hypokinesia of apical inferior and postero inferior walls with no improvement in high doses DSE, E.F.=20%, E.S.V.= 75 ml, E.D.V.= 162 ml

Discussion:

Ischemic cardiomyopathy (ICM) is a cardiac muscle disease due to ischemic insults with left ventricular systolic dysfunction [12] associated with reduced ejection fraction $\leq 35\%$ [10] [11]. It is increasing worldwide constituting a major

risk factor for heart failure and severe cardiac events [1]. Diagnosis and clinical work up of ICM include a variety of diagnostic modalities starting from full clinical examination, laboratory data, imaging and invasive techniques. One of the most commonly used imaging modalities in work up of ICM is 99m Tc-MIBI myocardial perfusion scintigraphy (MPI), 99m Tc-MIBI is a lipophilic univalent cationic myocardial perfusion imaging tracer, it is distributed along the blood flow and taken up by myocardial cells. It has been considered that MIBI bound to myocardium tends to remain for a relatively long period of time without redistribution as in Thallium-201[12]. However; it was observed that in certain circumstances, acceleration of myocardial MIBI washout which was called reverse redistribution pattern or MIBI washout pattern occurs. MIBI washout pattern could be simply defined as appearance of a new perfusion defect in the delayed rest images (4 hours post injection) or worsening of an already present defect in early rest images (1 hour post injection) by more than 10% [13]. It has been reported that delayed MIBI images within few hours after tracer injection can unmask enhanced washout rate in impaired myocardium as seen in ischemic cardiomyopathy [14] [15] [16]. A prior study conducted by Omar and Moustafa showed that the situations that MIBI accelerated washout rate is proved to be of clinical significance include ischemic heart disease, cardiomyopathy and prediction of cardiac events in patient with previous myocardial infarction [17].

The aim of this prospective study recruited from 86 patients referred with ischemic cardiomyopathy was to detect the added value of 99mTc- MIBI myocardial washout rate (GWR) in this group correlating with dobutamine echocardiography to detect residual jeopardized myocardium in this group. In our study, we compared early rest (ER) and delayed rest (DR)- MIBI images qualitatively regarding detection of the number of affected segments per patient, we found a statistical difference with a strong positive correlation between them, (p value <0.001, r=0.9). There are many prior studies that also compared early rest and delayed rest MIBI images in evaluating patients with ischemic heart disease. Tanaka et al. studied qualitatively the sensitivity of ER versus DR MIBI images in detecting uptake abnormalities consistent with ischemic heart disease, with referring to coronary angiography as a gold standard in all patients, they stated that there was a statistically significant difference between ER and DR images in patients with ischemic heart disease (p < 0.001) [18]. Using another detailed method, we classified all segments according to pattern of early and delayed washout pattern into normally perfused segments, ischemic segments with washout, ischemic segments without washout and infarcted segments. We found that washout occurred only in a small percent of the ischemic segments in 9/350 (2.5%), this small percentage could be attributed to homogeneity of the study group and predominance of infarcted segments (1106 segments) which didn't show any washout, we found also that normally perfused segments (6 segments) didn't show any washout. This was similar to a prior study conducted by Takeishi et al. who analyzed ER and DR MIBI images using segmental (regional) washout calculation in a group with ischemic heart disease, they showed that in segments with washout areas (from early rest to delayed rest), regional uptake of MIBI in DR images had decreased significantly (p < 0.01); this can be attributed to mixed infarcted and peri-infarct ischemia (jeopardized myocardium). While in normally perfused segments, and segments with fixed defects, tracer uptake was unchanged between the early and delayed images [19].

Further analysis of ischemic segments with washout, segments without washout and infarcted segments and comparing them with motion abnormalities detected by low dose DSE and degree of functional improvement in high doses DSE showed that the major percent of ischemic segments (75%) with washout showed functional improvement in high dose DSE compared to only 33% of ischemic segments without washout, p value <0.02 indicating high probability of residual viable myocardium in these segments, Also Fujiwara, et al. study analyzed segmental washout of patients following PTCA after AMI and correlated it to low dose dobutamine echocardiography, he found that washout of MIBI is evident in AMI after PTCA, also he found that 83% of ischemic segments with washout showed functional improvement (viable segments), during dobutamine infusion compared to only 54% of ischemic segments without washout, $P<0.02$, so they concluded that after coronary revascularization for AMI, the pattern of washout of MIBI indicates presence of dysfunctional but viable myocardium with preserved contractile response to dobutamine stimulation[20]. Moustafa.et al. also showed that GWR is higher in abnormally perfused mycoradium than in normally perfused myocrdium [21]

There are limitations in our study;

First, we have a relatively low number of the study population, second, lack of a viability study as FDG PET-CT as a reference tool.

We concluded that myocardial segments showing washout in the delayed rest images may have a potential to have a residual viable tissue and those patients- in turn- could get benefit form revascularization thus reducing future cardiac events and cardiac mortality.

List of Abbreviations

ECG: Electrocardiogram

MIBI: Methoxy Isobutyl Isonitrile

MPI: Myocardial perfusion Imaging

ICM: Ischemic Cardiomyopathy

ICU: Intensive Care Unit

SNMMI: Society of Nuclear Medicine and Molecular Imaging

DSE: Dobutamine Stress Echocardiography

MI: Myocardial Infarction

PTCA: Percutaneous Transluminal Coronary Angioplasty

CABG: Coronary Artery Bypass Graft

BMI: Body Mass Index

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Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethical Committee, Faculty of Medicine, Cairo University, Egypt. We obtained informed consents from the patients prior to the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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