

**Editorial, Cardiology.**

## **Is Still Myocardial MIBI washout can be applied in Ischemic Cardiomyopathy?**

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### **ABSTRACT:**

Myocardial perfusion with  $^{99m}\text{Tc}$ -labeled tracers is clinical standard method to assess ischemic heart diseases. Mitochondria are responsible for ATP production to ensure myocardial function and contractility under the normal circumstances. MIBI retention in myocytes is strongly related to normal mitochondrial function to maintain the electrochemical potential on the outer surface of mitochondria. In a damaged myocardium, the impaired function of energy-production and transfer in mitochondria can result in rapid release of MIBI, which is called reverse redistribution. It has been reported that delayed MIBI images within few hours can detect enhanced washout rate (WR) in impaired myocardium associated with Cardiomyopathy. 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. Cardiomyopathy is a myocardial disease characterized by left ventricular or biventricular dilatation and impaired myocardial contractility and causes substantial morbidity and mortality, despite major therapeutic achievements. It was identified that some patients with ischemic cardio myopathy (IDCM) had pathologic mutations in mitochondrial DNA. The mutations may be a sign of increasing stress to the heart, promoting consecutive damage to mitochondrial DNA, such defects may constitute the basis for the development of DCM and CHF. As 90% of  $^{99m}\text{Tc}$ -MIBI is contained inside myocardial cells mitochondria and cytochrome c oxidase inhibitor sodium cyanide and sarcolemma membrane detergent resulted in an increase in the  $^{99m}\text{Tc}$  MIBI clearance;

it is suggested that the clearance of  $^{99m}\text{Tc}$  MIBI can be used to assess ongoing

myocardial damage in patients with ischemic cardiomyopathy.

**Key Words:** ischemic cardiomyopathy -  $^{99m}\text{Tc}$  MIBI Washout - reverses redistribution.

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The situations that MIBI reverse redistribution i.e. accelerated MIBI washout, is proved to be of clinical significance in detection of ischemic heart disease, spastic angina, cardiomyopathy, heart failure and prediction of cardiac events in patient with previous myocardial infarction <sup>(1)</sup>.

Impairment in myocardial contractile reserves has been reported to be an important predictor for prognosis or detecting responders to medical therapy in cardiomyopathy patients <sup>(2,3)</sup>.

It has been reported that delayed MIBI images within few hours can detect enhanced washout rate (WR) in impaired myocardium associated with cardiomyopathy <sup>(4, 5 and 6)</sup>. However, the interval of early or delayed image acquisition, the visual evaluation criteria and the calculation method for washout rate (WR) are not standardized, and the washout evaluation method is still debated <sup>(7)</sup>.

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, it is difficult to evaluate the washout using global washout GWR in the whole myocardium. Therefore, the method for assessing washout of MIBI by visual evaluation using short-axis, horizontal long-axis and vertical long-axis slice images after reconstruction is adopted in patients with ischemic heart disease <sup>(7)</sup>.

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 <sup>(8)</sup>.

Global MIBI myocardial uptake is quantified by calculating the heart (H)-to-mediastinum (M) ratio, after drawing regions of interest over the myocardium and the mediastinum

in the anterior planar images. After the correction of physical decay of  $^{99m}\text{Tc}$ -, the global washout rate is calculated using the following *Flotats et al.* formula

$$WR = \frac{H_e - (H_d/DF)}{H_e} \times 100$$

$H_e$ : is Heart early count, DF is Decay factor time;  $H_d$  Cardiac delayed count <sup>(9)</sup>.

In ischemic heart disease, the fast washout of MIBI from the myocardium is noted following direct percutaneous coronary angioplasty (PCA) in patients with acute myocardial infarction <sup>(10, 11)</sup>. It could be attributed to inability of myocytes to retain the tracer due to stunned myocardium <sup>(12)</sup>. Several reports have shown the correlations between the increase in Tc MIBI washout rate and mitochondrial depolarization, cardiac dysfunction and higher cardiac event rates. It is expected that MIBI WOR can be a marker of myocardial damage or dysfunction in cardiomyopathy patients <sup>(12, 13 and 14)</sup>.

In *Omar and Moustafa*, they included 50 patients. Out of these 50 patients undergoing myocardial perfusion SPECT imaging; 22 patients had normal perfusion (SSS <4) and 28 patients had abnormal perfusion (SSS

$\geq 4$ ). The abnormal group includes 20 patients with reversible induced perfusion defects (SDS >2) and 8 patients fixed perfusion defect in both stress and rest studies (SDS < 2). The analysis of global washout rate was not significant in normal perfusion group as well as patients with irreversible perfusion defects (MIBI washout rate mean value was  $7 \pm 5$ ). While in patient with reversible perfusion defects significant MIBI washout rate was noted (with mean value of  $22 \pm 3$ ). So, in such study it was concluded that patients with reversible perfusion defects had significantly higher rate of washout compared to patients with normal perfusion and patients with irreversible perfusion defects. And this higher washout rate is directly correlated to the degree of reversibility <sup>(15)</sup>.

MIBI reverse redistribution was observed in a high percentage of patients with coronary artery stenosis, and MIBI delayed SPECT was more sensitive to evaluate myocardial damage patients with greater than 75% but less than 90% stenosis. Similarly reverse redistribution frequently occurs in salvaged regions in patients subjected to successful revascularization for AMI at an early stage which could be attributed to mitochondrial disorder due to ischemia/reperfusion injury (16).

In *Takeishi et al*, Myocardial SPECT with  $^{99m}\text{Tc}$ -MIBI was performed in 27 patients with acute myocardial infarction within 1 week after the onset. 23 patients underwent PTCA and 4 patients did not. Out of 22 patients with successful PTCA, RR of  $^{99m}\text{Tc}$ -sestamibi was observed in 15 patients (68%). Persistent defects (PD) were seen in 12 patients (7 patients with successful PTCA, 1 patient with unsuccessful PTCA, and 4 patients who did not receive angioplasty).

In patients with RR, regional uptake of  $^{99m}\text{Tc}$ -sestamibi around myocardial infarction decreased from 54% +/- 10% in the early images to 43% +/- 8% in the delayed images ( $p < 0.01$ ). Technetium- $^{99m}$ -sestamibi clearance from the myocardium was faster in the infarct area

than in the normal area (26% +/- 7% versus 9% +/- 6%,  $p < 0.01$ ).

Coronary arteriography performed 1 month later revealed that the patency of the infarct related artery was 100% (15/15) in patients with RR and 50% (6/12) in those with PD ( $p < 0.01$ ). The extent and severity of a wall motion abnormality were less in patients with RR than in those with PD (extent: 24 +/- 10 versus 36 +/- 9 chord,  $p < 0.01$ ; severity: -2.7 +/- 0.4 versus -3.4 +/- 0.6 S. D /chord,  $p < 0.01$ ) (17).

It is known that MIBI stress SPECT uncovered coronary stenosis by the fact of difference in myocardial perfusion in stress compared to rest status, while MIBI delayed SPECT was believed to reveal ischemia by detection disorder of mitochondrial function, accumulation of  $\text{Ca}^{2+}$  in the mitochondria of the ischemic myocardial cells leads to significant dilatation of the mitochondria, decreasing mitochondrial activity and ATP-synthesis ability that cause acceleration of MIBI washout. However, myocardial mitochondrial membrane disorder does not necessarily correlate with coronary stenosis, and MIBI washout could be accelerated by coronary artery spasm in reversible ischemia.

This study suggested that the severity of coronary stenosis and the time course strongly contribute to the occurrence of mitochondrial disorder. In other words, at a regional myocardial perfusion of less than 20 ml/min/100 gm of tissue, the amount of ATP decreased 10 minutes after ischemia, while at a regional perfusion of 20 to 40 ml/min/100 gm of tissue, the decrease in ATP was observed only after 60 minutes. These results revealed that ATP production depends on the volume of blood supplied to the myocardium, and also that the decrease of mitochondrial membrane potential was coupled with the decrease of ATP synthesis (18). Reverse redistribution of  $^{99m}\text{Tc}$ -MIBI is evident in patients with coronary artery disease resulting from coronaries stenosis,  $^{99m}\text{Tc}$ -MIBI redistribution is also reported in myocardial segments with coronary spasm, i.e. enhanced washout of  $^{99m}\text{Tc}$ -MIBI was observed in coronary spastic angina and might suggest that the ability of myocyte to retain the tracer was impaired in viable but damaged myocardium, it is often associated with left ventricular wall motion abnormalities, it may be attributed to the

close relation between repetitive brief ischemia and myocardial stunning in patients with coronary spastic angina (19).

Cardiomyopathy is a myocardial disease characterized by left ventricular or biventricular dilatation and impaired myocardial contractility and causes substantial morbidity and mortality, despite major therapeutic achievements. As the heart is exclusively dependent on the mitochondrial respiratory chain for its energy demand, it has been observed that cardiomyopathy is a common feature in patients with mitochondrial diseases. It was identified that some patients with IDCM had pathologic mutations in mitochondrial DNA. The mutations may be a sign of increasing stress to the heart, promoting consecutive damage to mitochondrial DNA. Oxidative stress may mediate tumor necrosis factor  $\alpha$  induced mitochondrial DNA damage and dysfunction in cardiac myocytes. Mitochondrial DNA defects may constitute the basis for the development of DCM and CHF. The evaluation of respiratory chain failure is clinically important in patients with mitochondrial cardiomyopathy.

Since that 90% of  $^{99m}\text{Tc}$ -MIBI is contained inside myocardial cells mitochondria and cytochrome c oxidase inhibitor sodium cyanide and sarcolemma membrane detergent resulted in an increase in the  $^{99m}\text{Tc}$  MIBI clearance; it is suggested that the clearance of  $^{99m}\text{Tc}$ -MIBI can be used to assess ongoing myocardial damage in patients with congestive heart failure (CHF) due to any cause including IDCM <sup>(19)</sup>.

*Kumita et al.*, study included seventeen patients in different stages of cardiomyopathy and six healthy control subjects were studied. The myocardial washout rate of  $^{99m}\text{Tc}$ -sestamibi was calculated in patients with non-ischemic CHF and compared with biventricular parameters obtained from first pass and ECG-gated myocardial perfusion SPECT data. The WOR was positively correlated with the end diastolic volume (EDV) index ( $r_2 = 0.216$ ;  $b = 0.464$ ;  $P = 0.02$  [ml/m<sup>2</sup>]), the end-systolic volume (ESV) index ( $r_2 = 0.234$ ;  $b = 0.484$ ;  $P = 0.01$ [ml/m<sup>2</sup>]), the summed motion score (SMS) ( $r_2 = 0.544$ ;  $b = 0.738$ ;  $P = 0.00$ ), and the summed

thickening score (STS) ( $r_2 = 0.656$ ;  $b = 0.810$ ;  $P = 0.00$ ); it was negatively correlated with the left ventricular ejection fraction (LVEF) ( $r_2 = 0.679$ ;  $b = -0.824$ ;  $P = 0.00$ ). This study concluded that myocardial washout rates in CHF patients were significantly higher than those in normal controls.

The myocardial washout rate of  $^{99m}\text{Tc}$ -MIBI was thought to be a novel marker for the diagnosis of myocardial damage. It is also demonstrated that the  $^{99m}\text{Tc}$ -MIBI WOR correlated inversely with functional cardiac parameters using myocardial perfusion imaging (MPI) in patients with idiopathic dilated cardiomyopathy. As a result,  $^{99m}\text{Tc}$ -MIBI scintigraphy might be a valuable molecular imaging tool for the diagnosis and evaluation of myocardial damage or dysfunction severity. Regarding the prognosis of congestive heart failure (CHF) patients with a higher washout of MIBI, it is suggested that the evaluation of MIBI washout rate may be useful for predicting the outcomes of CHF <sup>(12)</sup>.

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