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ORIGINAL PAPER

99 mTc-MIBI washout as a complementary factor in the evaluation of idiopathic dilated cardiomyopathy (IDCM) using myocardial perfusion imaging

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Abstract Rapid technetium-99 m methoxyisobutylisonitrile (99 mTc-MIBI) washout has been shown to occur in impaired myocardia. This study is based on the hypothesis that scintigraphy can be applied to calculate the myocardial 99 mTc-MIBI washout rate (WR) to diagnose and evaluate heart failure severity and other left ventricular functional parameters specifically in idiopathic dilated cardiomyopathy (IDCM) patients. Patients with IDCMP ($n = 17$; 52.65 ± 11.47 years) and normal subjects ($n = 6$; 49.67 ± 10.15 years) were intravenously administered 99 mTc-hexakis-2-methoxyisobutylisonitrile (99 mTc-MIBI). Next, early and delayed planar data were acquired (at 3.5-h intervals), and electrocardiogram (ECG)-gated myocardial perfusion single photon emission computed tomography (SPECT) was performed. The 99 mTc-MIBI WR was calculated using early and delayed planar images. Left ventricular functional parameters were also analyzed using quantitative gated SPECT (QGS) data. In target group, myocardial WRs (29.13 ± 6.68%) were significantly higher than those of control subjects (14.17 ± 3.31%; $P < 0.001$). The 99 mTc-MIBI WR increased with the increasing severity of the NYHA functional class (23.16 ± 1.72% for class I, 30.25 ± 0.95% for class II, 32.60 ± 6.73% for class III, and 37.50 ± 7.77% for class IV; $P = 0.02$). The WR was positively correlated with the end-diastolic volume (EDV) index ($r^2 = 0.216$; $\beta = 0.464$; $P = 0.02$ [ml/m^2], the end-systolic volume (ESV) index ($r^2 = 0.234$; $\beta = 0.484$; $P = 0.01$ [ml/m^2]), the summed motion score (SMS) ($r^2 = 0.544$; $\beta = 0.738$; $P = 0.00$), and the summed thickening score (STS) ($r^2 = 0.656$; $\beta = 0.810$; $P = 0.00$); it was negatively correlated with the left ventricular ejection fraction (LVEF) ($r^2 = 0.679$; $\beta = –0.824$; $P = 0.00$). It can be concluded that 99 mTc-MIBI scintigraphy might be a valuable molecular imaging tool for the diagnosis and evaluation of myocardial damage or dysfunction severity.

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Introduction

Idiopathic dilated cardiomyopathy (IDCM) is a primary myocardial disease of unknown cause characterized by left ventricular or biventricular dilatation and impaired myocardial contractility and it consisting of 50% of total dilated cardiomyopathy [1–3] and causes substantial morbidity and mortality, despite major therapeutic achievements [3, 4]. The heart is exclusively dependent on the mitochondrial respiratory chain for its energy demand and cardiomyopathy has been observed as a common feature in patients with mitochondrial diseases [5–8]. Myocardial metabolic failure (cytopathy) and ischemia caused by arterial mitochondrial dysfunction (angiopathy) are among possible pathogeneses for mitochondrial cardiomyopathy [5].

The evaluation of respiratory chain failure is clinically important in patients with mitochondrial cardiomyopathy; however, there is no useful tool available for in vivo evaluation. Almost 90% of technetium 99 m methoxyisobutyl isonitrile (99 mTc-MIBI) inside myocardial cells is contained within the mitochondria [9] and is retained for a relatively long time without any considerable change in distribution [10]. Observation has suggested that the clearance of 99 mTc-MIBI can be used to assess ongoing myocardial damage in patients with congestive heart failure (CHF) due to any cause [11, 12]. However, previous reports have mainly assessed the 99 mTc-MIBI washout rate (WR) in subjects with heart failure resulting from known causes. In this study, we aimed to evaluate whether the severity of CHF resulting from IDCM can be evaluated using the 99 mTc-MIBI WR.

Materials and methods

Participants and study design

Seventeen patients in different stages of dilated cardiomyopathy (DCM) (New York Heart Association class I to IV and decreased left ventricular ejection fraction (LVEF) (target) and six healthy control subjects were studied. The DCM diagnosis was based on increased left ventricular dimensions, a globally decreased contraction pattern as determined by echocardiography, and the absence of ischemic heart disease (IHD) assessed by scintigraphy and/or angiography. Patients were excluded if there was evidence of prior myocardial infarction, underlying valvular pathology according to echocardiography, uncontrolled systemic hypertension, or any other systemic disease. Physical examination, electrocardiography, echocardiography, and laboratory analysis confirmed that the six healthy controls included in the study had no history of ischemia or abnormality. All healthy controls were in the low-risk category of pretest likelihood of coronary artery disease (CAD) estimated by means of nomograms [13].

The study complies with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Shaheed Beheshti University of Medical Science in Tehran. All patients gave written informed consent.

Study protocol

Gated 99 mTc-MIBI SPECT

Thirty minutes after administration of 740 MBq 99 mTc-MIBI and early planar imaging, gated single photon emission computed tomography (SPECT) was performed using a prefixed RR interval at a rate of eight frames per cardiac cycle and a rotating, single head gamma camera (Solus, ADAC, Milpitas, CA) equipped with a low-energy, all purpose parallel-hole collimator. A 20% window around the photo-peak energy of 99 mTc-MIBI (140 keV) was used. Patients were in a supine position during imaging. Thirty-two projections (35 s/projection) were obtained in a 180-degree circular orbit, beginning from 45 degrees right anterior oblique to 135 degrees left posterior oblique with step/shoot acquisition. A 64 × 64 × 16 matrix was used. Cine-display images of the rotating planar projections were reviewed on screen to assess the subdiaphragmatic activities, attenuations, and patient motion. The LVEF (%), end-diastolic volume (LVEDV, ml), and end-systolic volume (LVESV, ml) were automatically calculated from the ECG-gated SPECT data with 99 mTc-sestamibi using the

Table 1 The basic data in two target and control groups

	Target	Control	P value
Age (year)	52.65 ± 11.47	49.67 ± 10.15	0.609
Sex (M/F)	9/8	1/5	0.12
BMI (kg/m^2)	25.07 ± 4.1	25.03 ± 2.09	0.973
SBP (mm Hg	122.06 ± 19.93	115.83 ± 4.45	0.708
HR (beat/min)	81.59 ± 13.87	73.83 ± 4.45	0.052
LVEF (%)	28.82 ± 11.39	65.50 ± 5.26	0.00
NYHA (I/II/III/IV)	6/4/5/2	NA	NA

BMI Body mass index; *SBP* Systolic blood pressure; *HR* Heart rate; *LVEF* Left ventricle ejection fraction according to echocardiography; *NYHA* New York heart association; *NA* Not applicable

quantitative gated SPECT (QGS) program (Cedars-Sinai Medical Center) Table 1.

Parametric analysis

Thirty minutes and 3.5 h after 99 m Tc-MIBI injection, cardiac uptake was quantified in planar anterior views in a 256 × 256 matrix for 5 min. As shown in Fig. 1, the regions of interest on the planar images were the mediastinum and the heart in order to quantify cardiac 99 m Tc-MIBI uptake in terms of the heart-mediastinum (*H*/*M*) count ratio in the early (e) and delayed (d) views. The mean count per pixel was considered. The 99 m Tc-MIBI WR (%) was calculated based on the Flotats et al. formula [14]:

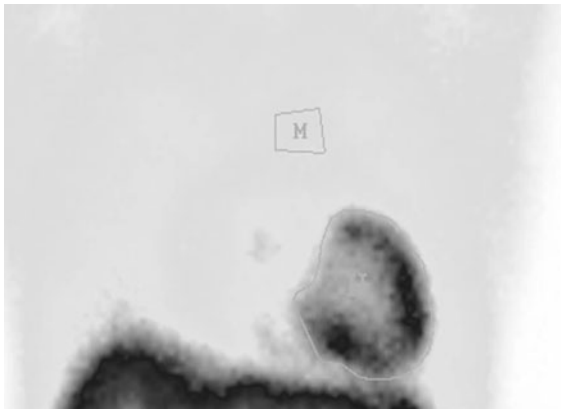

Fig. 1 Calculation of myocardial washout rate using planar 99mTc-MIBI imaging

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

H_e Heart early count; M Upper mediastinum count; D_f Decay factor time; H_d Cardiac delayed count.

In addition, the raw EDV and ESV data were divided by body surface area (BSA), and the end-diastolic volume (EDV) index and the end-systolic volume (ESV) index were acquired. The BSA was calculated using the following formula [15]:

$$\text{Body Surface area} = \sqrt{\frac{\text{weight(kg)} \times \text{height(cm)}}{3600}}$$

$$\text{EDVI (ml/m}^2) = \text{EDV/BSA}$$
$$\text{ESVI (ml/m}^2) = \text{ESV/BSA}$$

Statistical analysis

The data were expressed as mean ± SD, Man–Whitney U test and Kruskal–Wallis test were used for quantitative comparison, and differences in proportion (categorical variables) were examined using chi-square test. Linear regression was used to analyze the relationship between the WR and the gated SPECT findings. A P value of < 0.05 was considered statistically significant. Statistical analysis was performed using an IBM computer and PASW software, version 18.0 (SPSS, Inc., Chicago, USA).

Results

Twenty-three patients, 17 with IDC (CHF group; 9 men and 8 women; mean age of 52.65 ± 11.47 years; New York Heart Association [NYHA] functional class I to IV) (target) and six normal controls (NC group; 1 man and 5 women; mean age of 49.67 ± 10.15 years) were included in this study.

According to the echocardiography results, the ejection fraction (EF) of the patients was 28.82 ± 11.39% and it was 65.50 ± 5.26% for the control group ($P = 0.00$). The LVEDV and LVESV indices were significantly greater and LVEF was lower in patients with CHF than in healthy volunteers (Table 2). The 99 mTc-MIBI WR was significantly higher in target (29.13 ± 6.68%) than in the control group (14.17 ± 3.31%) ($P = 0.001$), whereas H/M ratios according to early and delayed images did not

Table 2 The scintigraphic findings in two target and control groups

	Target	Control	P value
H/M (e)	2.72 ± 0.4	2.47 ± 0.14	0.286
H/M (d)	3.00 ± 0.38	3.04 ± 0.31	0.658
WR (%)	29.13 ± 6.68	14.17 ± 3.31	0.001
LVEF (%)	28.12 ± 11.96	71.17 ± 4.36	0.001
EDVI (ml/m$^{2)}$	111.82 ± 69.5	40.50 ± 6.05	0.000
ESVI (ml/m^2)	86.00 ± 68.98	12.00 ± 2.89	0.000
SV (ml)	44.35 ± 10.97	49.17 ± 3.31	0.074
SMS	40.94 ± 19.28	0.5 ± 0.84	0.001
STS	29.35 ± 11.54	0.33 ± 0.52	0.001

H/M(e) Heart/mediastinum count ratio in early image; *H/M(d)* Heart/mediastinum count ratio in delay image; *WR* Washout rate; *LVEF* (%) Left ejection fraction according to gated myocardial perfusion imaging; *EDVI* End-diastolic volume index; *ESVI* End-systolic volume index; *SV* Stroke volume; *SMS* Sum motion score; *STS* Sum thickening score

differ in either group (P values of 0.286 and 0.658, respectively).

The WR was positively correlated with the end-diastolic volume (EDV) index ($r^2 = 0.216$; $\beta = 0.464$; $P = 0.02$ [ml/m^2], the end-systolic volume (ESV) index ($r^2 = 0.234$; $\beta = 0.484$; $P = 0.01$ [ml/m^2]), the summed motion score (SMS) ($r^2 = 0.544$; $\beta = 0.738$; $P = 0.00$), and the summed thickening score (STS) ($r^2 = 0.656$;$\beta = 0.810$; $P = 0.00$); it was negatively correlated with the left ventricular ejection fraction (LVEF) ($r^2 = 0.679$; $\beta = -0.824$; $P = 0.00$). The association between cardiac function parameters using gated SPECT and WRs is shown in Figs. 2, 3, 4, 5, 6. The mean WR across four classes was compared using Kruskal–Wallis test; it was 23.16 ± 1.72% for class I; 30.25 ± 0.95% for class II; 32.60 ± 6.73% for class III, and 37.50 ± 7.77% for class IV, which had significant differences (P value = 0.02) [Fig. 7].

Discussion

Myocardial uptake and retention of 99 m Tc-MIBI involve passive diffusion across the plasma and mitochondrial membranes [9]. Mitochondrial membrane integrity is required for the intracellular binding of 99 m Tc-MIBI, and mitochondrial injury results in extracellular leakage of the tracer [5, 16, 17].

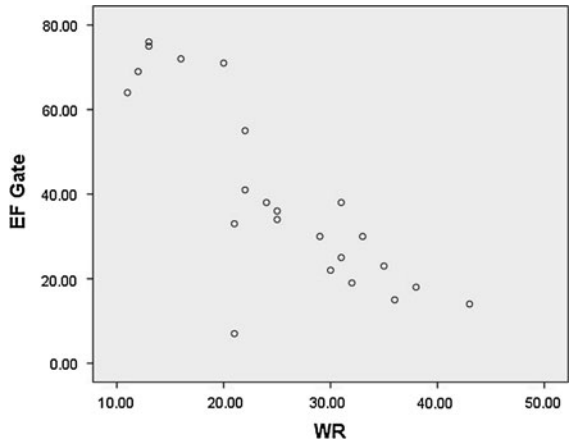

Fig. 2 The association between the 99mTc-MIBI washout rate and ejection fraction using gated SPECT

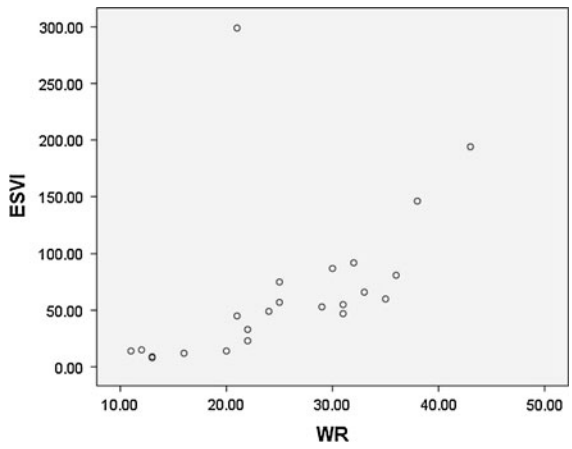

Fig. 3 The association between the 99mTc-MIBI washout rate and end-systolic volume index (ESVI) parameters using gated SPECT

Beanlands et al. showed that irreversible cellular injury caused by cytochrome c oxidase inhibitor sodium cyanide and sarcolemmal membrane detergent Triton X-100 resulted in an increase in the 99 mTc-sestamibi clearance [10]. Markers of oxidative stress are shown to increase in CHF patients and have been correlated with myocardial dysfunction and overall severity of heart failure [4]. In mitochondrial respiratory chain failure, energy production shifts from the aerobic to the glycolytic pathway result in augmented lactic acid production and increased uptake of 123I-beta-methyl-iodophenyl pentadecanoic acid (BMIPP) [5]. Thus, the 99 mTc-MIBI/123I-BMIPP mismatch, together with the increased 99 mTc-MIBI WR, appears to be a sign of mitochondrial respiratory

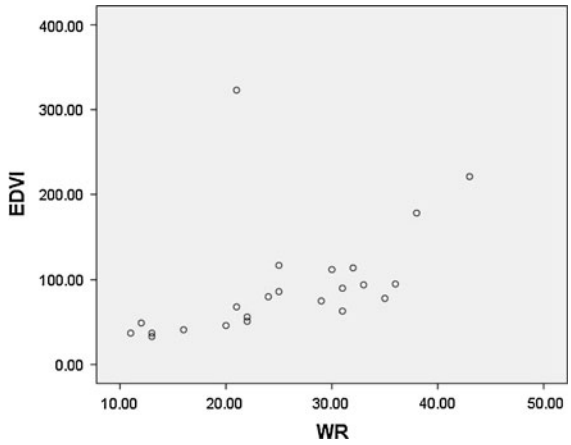

Fig. 4 The association between the 99mTc-MIBI washout rate and end-diastolic volume index (EDVI) parameters using gated SPECT

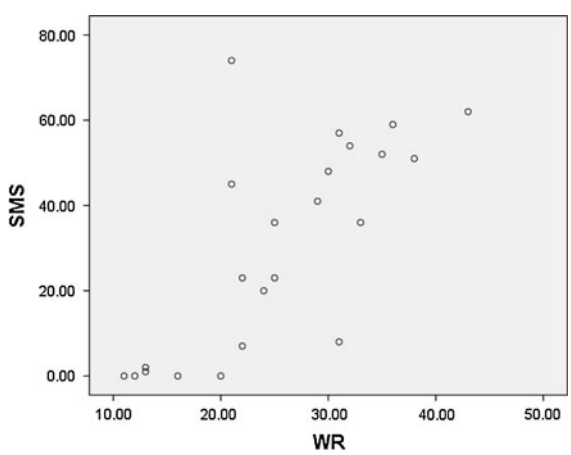

Fig. 5 The association between the 99mTc-MIBI washout rate and sum motion score (SMS) parameters using gated SPECT

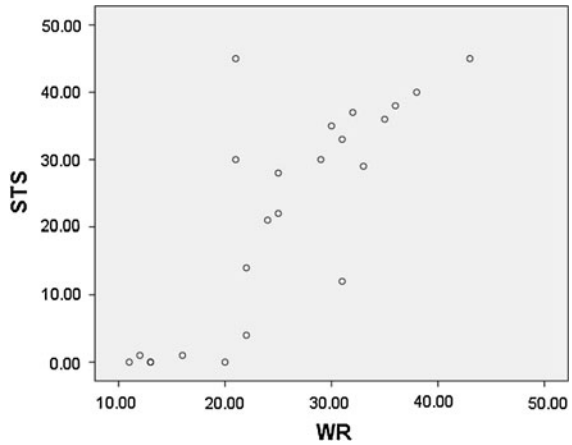

Fig. 6 The association between the 99mTc-MIBI washout rate and sum thickening score (STS) parameters using gated SPECT

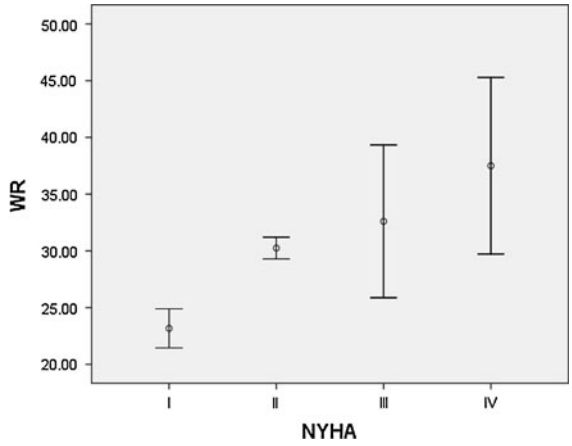

Fig. 7 The mean 99mTc-MIBI washout rate in patients with different functional classes according to New York Heart Association [NYHA] classification

failure and may reflect the severity of cardiac involvement.

The 99 mTc-MIBI WR increased in target and reached the maximum in class IV patients who showed severe cardiac failure reflecting respiratory chain failure (Table 2). This is in accordance with previous reports [16, 18, 19]. In this study, although differences in the early and delayed *H*/*M* ratio were not statistically significant between the two groups, the myocardial 99 mTc-sestamibi WR in the target group ($29.13 \pm 6.68\%$) were significantly higher than those in the control group ($P \leq 0.01$). This is consistent with a previous report stating that the initial 99 m Tc-MIBI uptake rate (at 40–60 min) was higher in cultured chick embryo cardiac myocytes with mild to moderate metabolic injury than in those without such injury [20].

In addition, the myocardial WRs of all subjects correlated well with left ventricular function in the current investigation. Insufficient adenosine triphosphate (ATP) production caused by mitochondrial dysfunction in damaged myocardia may be related to concordant findings of 99 mTc-sestamibi rapid washout and left ventricular dysfunction [5].

In a study by Kumit et al., the myocardial WRs for 25 CHF patients were significantly higher than for

those in the control group (39.6 + 5.2% vs. 31.2 + 5.5%; $P < 0.01$) and they correlated with functional cardiac parameters. Myocardial WRs did not demonstrate a statistically significant difference between patients with and without hypoperfused areas on myocardial perfusion SPECT, and it is suggested that washout of the hypoperfused areas did not necessarily contribute to the rapid washout in the CHF group [18]. In another study by Sugiura et al., the 99 mTc-MIBI WR was higher in CHF patients (31.2% ± 6.3%) than in healthy controls (25.2% ± 4.7%; $P < 0.05$). There were positive correlations between the 99 mTc-MIBI WR and brain natriuretic peptide levels ($r = 0.723$; $P < 0.0001$) and a negative correlation between the 99 m Tc-MIBI WR and the LVEF ($r = -0.545$; $P < 0.01$). The 99 mTc-MIBI WR correlated with that of metaiodobenzylguanidine(MIBG) ($r = 0.603$; $P < 0.01$). They also demonstrated that 99 mTc-MIBI scintigraphy is useful in evaluating the severity of CHF [16].

Recently, Matsuo and et al. showed that the myocardial 99 mTc-MIBI WR is a novel marker for the diagnosis of myocardial damage or dysfunction, providing prognostic information for patients with CHF [19].

There were good correlation between the WR of 99 mTc-MIBI and the LVEF on 99 mTc-MIBI gated SPECT, possibly due to impaired mitochondria in the myocardium that accumulated in the heart wall to compensate for the energy decline due to respiratory chain failure [5]. P-glycoprotein (P-gp) might also influence the uptake and WR of 99 mTc-MIBI [21].

In addition, several studies revealed a variable degree of interstitial and perivascular fibrosis in IDCMP that leads to decreased myocardial tissue perfusion in this subgroup as fibrotic tissue is unable to rapidly exchange water across the barriers. This also might explain the higher WR in this subgroup [2].

Patients with ischemic heart failure (IHF) have a worse prognosis [22], but may benefit from revascularization, lipid-lowering drugs, and neurohormonal blockades [23, 24]. Conversely, in patients with IDCM, genetic screening of family and exclusion of IHD by noninvasive methods are becoming more important in diagnosing and managing the disease [25]. Assessment of myocardial perfusion and regional ventricular function using exercise technetium-99 m sestamibi gated SPECT imaging can reliably distinguish between patients with ischemic cardiomyopathy and patients with nonischemic dilated cardiomyopathy [26, 27]. Likewise, addition of the WR value to usual SPECT data may help to determine prognosis with more accuracy.

It may be helpful to compare the myocardial WRs with several biomarkers, such as TNF and O_2^-, and to prove myocardial damage in the CHF group and the correlation with scintigraphic findings. Follow-up studies are also required to clarify the relationship between the 99 mTc-sestamibi myocardial washout and patient outcome, including left ventricular functional outcome and prognosis for CHF patients.

This study had a few limitations. We did not test the role of permeability glycoprotein (P-gp) in 99 mTc-MIBI washout. Overexpression of P-gp would enhance WRs. This hypothesis could be tested by enrollment of patients with CHF after treatment with specific P-gp inhibitors. In addition, the calculation of WRs at different times following 99 mTc-MIBI administration (earlier than 3.5 h) is recommended in order to implementation of a study during the shorter time.

Conclusion

The study demonstrated that the 99 mTc-MIBI WR correlated with functional cardiac parameters using myocardial perfusion imaging (MPI) in patients with idiopathic dilated cardiomyopathy. As a result, 99 mTc-MIBI scintigraphy might be a valuable molecular imaging tool for the diagnosis and evaluation of myocardial damage or dysfunction severity.

Conflicts of interest The author(s) declare that they have no conflict of interests.

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