DOI: https://doi.org/10.17816/DD568668

# Скорость вымывания 99mTc-метокси-изобутил-изонитрила как маркёр митохондриальной дисфункции миокарда: систематический обзор и метаанализ

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**АННОТАЦИЯ**

**Обоснование.** В обзоре изложены особенности фармакокинетики перфузионного радиофармпрепарата 99mTc-MIBI, которые позволяют оценить митохондриальную дисфункцию миокарда, а также показаны основные клинические точки приложения феномена ускоренного вымывания данного индикатора.

**Цель.** Систематизация данных фундаментальных (экспериментальных) и клинических исследований в области изучения и оценки митохондриальной дисфункции по результатам перфузионной сцинтиграфии миокарда; проведение метаанализа клинических исследований в данной области.

**Материалы и методы.** Поиск проводился в базах данных Pubmed, Scopus, Google Scholar и eLibrary до середины 2023. Были использованы ключевые слова, их комбинации и англоязычные аналоги: митохондриальная дисфункция, 99mTc-МИБИ, 99mTc-Тетрофосмин, перфузионная сцинтиграфия миокарда, обратное перераспределение, вымывание, скорость вымывания. При выполнении метаанализа для расчёта средней оценки разницы была использована модель случайных эффектов.

**Результаты.** Для систематического анализа было отобрано 40 статей: 13 — экспериментальные, 24 — оригинальные клинические работы, 2 — клинические случаи, 1 обзор. Для выполнения метаанализа было отобрано 6 исследований по дизайну «случай–контроль». Общее число пациентов, составивших основу систематического обзора, — 551; число пациентов, составивших основу метаанализа — 196. Анализ литературы показал, что выраженность феномена обратного перераспределения и скорость вымывания 99mTc-MIBI взаимосвязаны с микроструктурой митохондрий и миокарда, сократимостью и гемодинамикой левого желудочка, уровнем натрийуретических пептидов, толерантностью к физическим нагрузкам, тяжестью коронарного атеросклероза, окислительным метаболизмом миокарда, уровнем риска сердечно-сосудистых событий. Метаанализ показал, что скорость вымывания статистически значимо повышена у лиц с патологией сердца, по отношению к контролю (средняя оценка разницы 9,5771 (95% доверительный интервал: от 6,6001 до 12,5540; z=6,3053; $p$ <0,0001).

**Заключение.** Оценка функции митохондрий по данным оценки вымывания 99mTc-MIBI может предоставить дополнительные сведения о функциональном состоянии сердечной мышцы.

**Ключевые слова:** митохондриальная дисфункция; 99mTc-МИБИ; 99mTc-Тетрофосмин; перфузионная сцинтиграфия миокарда; обратное перераспределение; скорость вымывания; кардиомиопатии; хроническая сердечная недостаточность; ишемическая болезнь сердца

**Как цитировать:**
Гуля М.О., Завадовский К.В. Скорость вымывания 99mTc-метокси-изобутил-изонитрила как маркёр митохондриальной дисфункции миокарда: систематический обзор и метаанализ // Digital Diagnostics. 2023. Т. 4, № 4. С. 509–528. DOI: https://doi.org/10.17816/DD568668

**Рукопись получена:** 22.08.2023 **Рукопись одобрена:** 11.09.2023 **Опубликована online:** 10.10.2023

DOI: https://doi.org/10.17816/DD568668

# 99mTc-MIBI washout rate as a marker of myocardial mitochondrial dysfunction: A systematic review and meta-analysis

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**ABSTRACT**

***BACKGROUND:*** This review outlines the features of the pharmacokinetics of the perfusion radiopharmaceutical 99mTc-MIBI, which allows the assessment of myocardial mitochondrial dysfunction, and shows the main clinical applications of the phenomenon of increased 99mTc-MIBI washout rate.

***AIM:*** To systematize the data of fundamental (experimental) and clinical studies evaluating and estimating mitochondrial dysfunction according to myocardial perfusion scintigraphy data and perform meta-analysis of clinical studies in this field.

***MATERIALS AND METHODS:*** PubMed, Scopus, Google Scholar, and eLibrary databases were searched until mid-2023. The following keywords, their combinations, and Russian-language counterparts were used: mitochondrial dysfunction, 99mTc-MIBI, 99mTc-Tetrofosmin, myocardial perfusion scintigraphy, reverse redistribution, washout, and washout rate. In the meta-analysis, a random-effects model was used to calculate the mean difference estimate.

***RESULTS:*** Forty articles were selected for systematic analysis: 13 were experimental, 24 were original clinical papers, 2 were clinical cases, and 1 was a review. Six studies using a case–control design were selected for the meta-analyses. The total number of patients in the systematic review and meta-analysis were 551 and 196, respectively. In the analysis of the literature, the severity of the reverse redistribution phenomenon and 99mTc-MIBI washout rate correlated with mitochondrial and myocardial microstructure, left ventricular contractility and hemodynamics, natriuretic peptide levels, exercise tolerance, coronary atherosclerosis severity, myocardial oxidative metabolism, and risk of cardiovascular events. The meta-analysis showed that the washout rate was statistically significantly accelerated in individuals with cardiac pathologies, relative to controls (mean difference score, 9.5771 [95%]; confidence interval, 6.6001–12.5540; z=6.3053, $p$ <0.0001).

***CONCLUSION:*** The assessment of mitochondrial function by 99mTc-MIBI washout evaluation may provide additional insights into the functional status of cardiac muscles.

**Keywords:** mitochondrial dysfunction; 99mTc-MIBI: 99mTc-Tetrofosmin; myocardial perfusion scintigraphy; reverse redistribution; washout rate; cardiomyopathies; congestive heart failure; ischemic heart disease

**To cite this article:**
Gulya MO, Zavadovsky KV. 99mTc-MIBI washout rate as a marker of myocardial mitochondrial dysfunction: A systematic review and meta-analysis. *Digital Diagnostics.* 2023;4(4):509–528. DOI: https://doi.org/10.17816/DD568668

**Received:** 22.08.2023 **Accepted:** 11.09.2023 **Published online:** 10.10.2023

DOI: https://doi.org/10.17816/DD568668

# 99m锝-甲氧基异丁基异腈（99mTc-MIBI）洗脱率作为心肌线粒体功能障碍的标志物；系统综述和荟萃分析

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**简评**

**论证。**本综述概述了灌注放射性药物99mTc-MIBI的药代动力学特征。这些特征可被用于评估心肌线粒体功能障碍。综述还说明了该指标加速洗脱现象的临床应用要点。

**该研究的目的**是系统整理关于通过心肌灌注闪烁成像研究和评估线粒体功能障碍领域的基础（实验）和临床研究数据；对该领域的临床研究进行荟萃分析。

**材料与方法。**检索是在Pubmed、Scopus、Google Scholar和eLibrary数据库中进行的，检索期截至2023年年中。使用的关键词及其组合和英文对应词包括：线粒体功能障碍、99mTc-MIBI、99m锝-替曲膦、心肌灌注闪烁成像、反向再分布、洗脱、洗脱率。在进行荟萃分析时，采用了随机效应模型来计算平均差异估计值。

**结果。**我们一共选中了40篇文章，以进行系统分析：其中13篇为实验性文章，24篇为临床医学论文，2篇为临床病例，1篇为综述。我们一共选中了6项研究，以进行病例对照模型的荟萃分析。系统综述中的患者总人数为551人；荟萃分析中的患者人数为196人。文献分析显示了，反向再分布现象的严重程度和99mTc-MIBI洗脱率与线粒体和心肌微结构、左室收缩力和血流动力、利尿钠肽水平、运动耐量、冠状动脉粥样硬化严重程度、心肌氧化代谢和心血管事件风险水平相关。荟萃分析表明了，与对照组相比，心脏病变受试者的洗脱率在统计学上显著较高。平均差异估计值为9.5771（95%置信区间：6.6001至12.5540；z=6.3053；p<0.0001）。

**结论。**通过99mTc-MIBI洗脱评估对线粒体功能进行评估，可为了解心肌功能状态提供更多信息。

**关键词：**线粒体功能障碍；99mTc-MIBI；99m锝-替曲膦；心肌灌注闪烁成像；反向再分布；洗脱率；心肌病；慢性心力衰竭；缺血性心脏病。

**引用本文：**

Gulya MO, Zavadovsky KV. 99m锝-甲氧基异丁基异腈（99mTc-MIBI）洗脱率作为心肌线粒体功能障碍的标志物；系统综述和荟萃分析. *Digital Diagnostics*. 2023;4(4):509–528. DOI: https://doi.org/10.17816/DD568668

**收到：**22.08.2023 **接受：**11.09.2023 **发布日期：**10.10.2023

**Abbreviations**

$^{123}$I-BMIPP: iodine-123 labeled β-methyl iodophenyl pentadecanoic acid
$^{123}$I-MIBG: $^{123}$I-metaiodobenzylguanidine
99mTc-MIBI: iodine-123-labeled metaiodobenzylguanidine
ACS: acute coronary syndrome
AMI: acute myocardial infarction
CAD: coronary artery disease
CHF: chronic heart failure
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LV: left ventricular
MD: mitochondrial dysfunction
MPS: myocardial perfusion scintigraphy
RR: reverse redistribution
SPECT: single-photon emission computed tomography
WR: washout rate

## BACKGROUND

Cardiovascular diseases are the leading cause of morbidity and mortality [1]. Among cardiovascular diseases, acute and chronic coronary syndromes and chronic heart failure (CHF) are the leading causes of disability.

The pathophysiology of coronary artery disease (CAD) is influenced by coronary atherosclerosis, progressive lumen narrowing, and myocardial ischemia.

The pathogenesis of CHF is more complex and is largely determined by etiology. The most common manifestation of CHF is reduced left ventricular (LV) contractility. The pathogenesis of both diseases is influenced by mitochondrial function. Mitochondria are vital organelles that control cell energy metabolism and overall homeostasis. A steady energy supply is required to maintain the contractile activity of the human heart. Myocardial mitochondria perform the most difficult task of producing approximately 30 kg of adenosine triphosphate per day to keep the heart pumping [2]. To meet this requirement, the following aspects are necessary:

- Continuous supply of the substrate to the mitochondria is ensured.
- Mitochondria have sufficient oxidative capacity.
- The cell has an effective system for transporting adenosine triphosphate from the mitochondria to the consumption sites [3].

The transmembrane potential is one of the main parameters representing mitochondrial function [4]. Under normal conditions, mitochondria have the largest negative charge (in absolute value) of all intracellular organelles and serve as a destination for charged lyophilic molecules entering the cell via the sarcolemma. Retention of these substances in the cell is proportional to the transmembrane potential of mitochondria. Consequently, a reduction in the transmembrane potential decreases the accumulation of these substances. Various diagnostic agents (mainly dyes) are available for assessing mitochondrial function in vitro. However, few diagnostic agents are used for assessing mitochondria in vivo.

The search for new tools for assessing mitochondrial function appears to be a pressing issue in modern cardiology and X-ray diagnosis. The monovalent lipophilic cation technetium-99m methoxy isobutyl isonitrile (also known as technetium (99mTc) sestamibi, or 99mTc-MIBI) is a widely used diagnostic agent for myocardial perfusion imaging. Unlike other in vivo diagnostic agents, this drug accumulates in cardiomyocyte mitochondria based on their membrane potential [5]. A decrease in mitochondrial function in cardiomyocytes results in a decrease in mitochondrial internal matrix potential, followed by an increase in radiopharmaceutical clearance. Thus, accelerated 99mTc-MIBI washout suggests mitochondrial functional abnormalities. In addition to 99mTc-MIBI, technetium tetrofosmin (99mTc-TF) can be used.

The mechanism of accumulation of various diagnostic agents in the myocardium is schematically depicted in Figure 1.

Moreover, no reviews exist in the Russian-language literature on the use of myocardial perfusion scintigraphy (MPS) with 99mTc-MIBI to identify and characterize mitochondrial dysfunction (MD, damage).

## PURPOSE

To systematize experimental and clinical findings in the examination and assessment of MD according to MPS and conduct a meta-analysis of clinical studies on this topic.

## LITERATURE SEARCH METHODS

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol [6]. To analyze available data on MD in cardiovascular diseases, a systematic literature search was performed in PubMed, Scopus, Google Scholar, and eLibrary databases using the following keywords, their combinations, and English-language analogs: mitochondrial dysfunction, 99mTc-MIBI, 99mTc-TF, myocardial perfusion scintigraphy, reverse redistribution, and washout rate (WR).

The search was performed from the database inception until the middle of 2023 and included all studies published

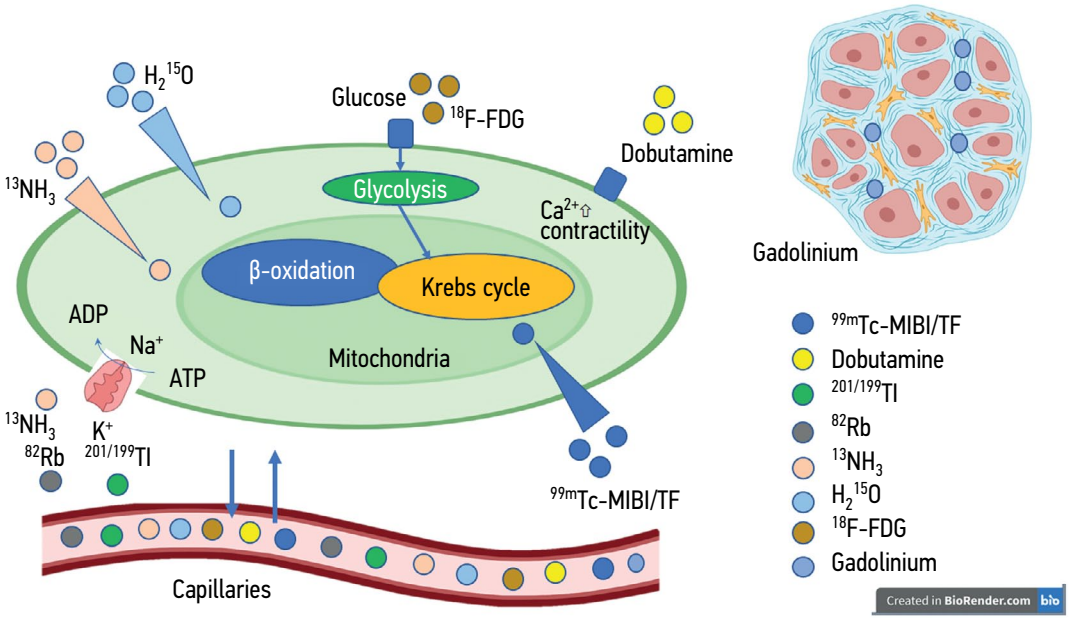


**Fig. 1.** Schematic depiction of the mechanism of the accumulation of various diagnostic agents in the cell and intercellular space. $^{201/199}$Tl: thallium-201 or thallium-199; its uptake is determined by membrane integrity and normal functioning of the $Na^+/K^+$ pump. $^{82}$Rb: rubidium-82; its uptake is also determined by the $Na^+/K^+$ pump. 99mTc-MIBI/TF-based tracers: lipophilic cations that freely pass through the mitochondrial membrane and are retained because of the transmembrane potential. Dobutamine stimulates β1 and β2 adrenergic receptors, increasing the intracellular calcium concentration and inotropic function of the heart. $^{18}$F-FDG: fluorodeoxyglucose accumulates in the cell via the glucose transporter protein. $^{13}NH_3$: ammonium is accumulated via passive diffusion and active transport of the $Na^+/K^+$ pump. $H_2{}^{15}O$: oxygen-15 labeled water readily diffuses into the cell, forming an equilibrium between the extracellular and intracellular pools. Gadolinium is an extracellular diagnostic agent that is retained in the intercellular space.

up to that date. Further analysis included studies in which MPS with 99mTc-MIBI or 99mTc-TF was used to assess MD in various cardiovascular diseases. The following articles were excluded: articles in which MD was mentioned in the references, articles in languages other than English and Russian, and articles examining the washout of 99mTc-MIBI (or 99mTc-TF) in cancer and other disorders not associated with cardiovascular diseases. In total, 40 articles were selected based on these criteria. These included 13 experimental studies, 24 original clinical studies, 2 clinical cases, and 1 review. A meta-analysis was performed for case–control studies using Jamovi v. 2.4.2 (The Jamovi Project, Australia) and the expansion module MAJOR v. 1.2.1. During the meta-analysis, a random-effects model was used to calculate the mean difference.

## EXPERIMENTAL STUDIES

The 99mTc-MIBI is used for noninvasive imaging of myocardial perfusion. This radiopharmaceutical is currently the most widely used diagnostic agent for MPS in Russia and worldwide [7, 8]. A tracer enters the cell via the cardiomyocyte sarcolemma and accumulates in negatively charged mitochondria in proportion to the transmembrane gradient [9]. In an experimental study on a culture of chicken heart cells, electron microscopy and electron microprobe analysis revealed that approximately 90% of the drug binds to the mitochondria as an energy-dependent free cationic complex [10].

In an experimental study in which cardiomyocyte cell cultures were exposed to various mitochondrial and plasma membrane potential inhibitors, the drug primarily accumulated in mitochondria and did not accumulate in the cytoplasm, owing to the significantly higher electrical potential of the mitochondrial membrane [9]. Further retention of the tracer depends on the membrane potential, as demonstrated in an experiment using an artificial respiratory chain uncoupler carbonyl cyanide m-chlorophenyl hydrazone, which causes a rapid decrease in 99mTc-MIBI concentration.

In an in vitro experiment on the subcellular fraction of mitochondria, P. Crane et al. revealed that increasing the concentration of calcium ions causes faster 99mTc-MIBI washout from the mitochondria [11]. In ischemia models with ischemic cardiomyocytes overloaded with calcium ions, 99mTc-MIBI washout is a marker of mitochondrial damage. In an ischemia–reperfusion model on isolated rat hearts, K. Fukushima et al. [12] demonstrated that 99mTc-MIBI washout increases during mild ischemia and is more pronounced during severe ischemia.

Thus, accelerated 99mTc-MIBI washout from the myocardium is associated with impaired mitochondrial function and cardiomyocyte damage.

## IN VIVO ASSESSMENT OF MD USING MYOCARDIAL PERFUSION SCINTIGRAPHY

For the in vivo detection of MD, early and delayed planar or tomographic perfusion imaging is used. Early imaging is performed for 30 min [13] to 1 h [14] after a radiopharmaceutical injection; delayed imaging is performed for 3–4 h [15]. Typically, imaging is performed at rest. The radiopharmaceutical dose is 370–470 MBq, which is similar to the dose used for conventional MPS [16]. The MD visual pattern is a defect in tracer uptake that occurs (or intensifies) during delayed perfusion single-photon emission computed tomography (SPECT) of the myocardium: the so-called reverse redistribution (RR) of a radiopharmaceutical occurs. Thus, a generally accepted technique is used to determine the size of the perfusion defect.

The second parameter of MD assessment is the heart-to-mediastinum ratio (HM). It is determined using the average number of pulses in the area of interest (heart and mediastinum, respectively) according to the anterior planar scintigraphy images.

Moreover, the global clearance or WR of 99mTc-MIBI was calculated as the ratio of radiotracer uptake in the heart area on early and delayed planar scintigraphy images. Some authors have used the number of pulses in the heart area minus the number of pulses in the mediastinum [14]. Furthermore, some authors consider the half-life of 99mTc (6.04 h) into account when determining WR. A few studies have examined the 99mTc-MIBI WR by LV regions [18].

The normal values for people aged 50 ± 13 years are as follows:

- WR: 11% ± 5%
- Early HM: 3.5 ± 0.3
- Delayed HM: 3.1 ± 0.3 [14, 19]

The pathological pattern was accelerated 99mTc-MIBI washout from the myocardium, similar to the study with 123I-metaiodobenzylguanidine (123I-MIBG, a marker of cardiac sympathetic activity). The main clinical studies of mitochondrial damage based on MPS with 99mTc-MIBI are presented in Table 1.

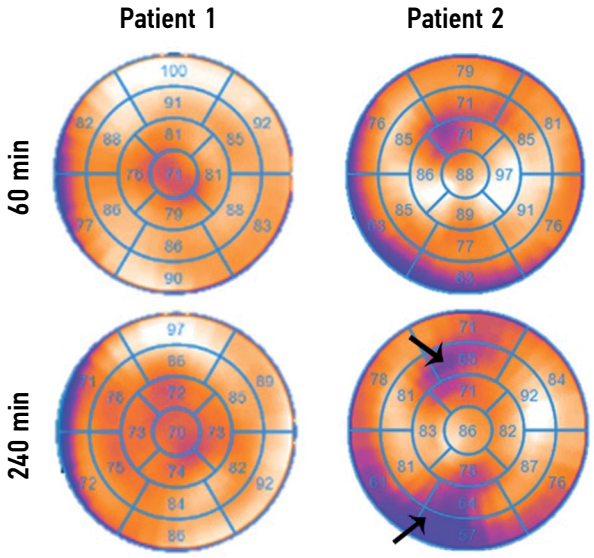


**Fig. 2.** An example of the absence and presence of 99mTc-MIBI reverse redistribution. Patient 1: female, 56 years old, CAD (grade II stable angina) secondary to nonobstructive coronary atherosclerosis; CHF, NYHA class II; LV ejection fraction, 64%; end-systolic volume, 42 mL; end-diastolic volume, 117 mL. Delayed imaging (240 min) revealed no perfusion defects. Patient 2: male, 58 years old; CAD (grade II stable angina); anterior descending artery stenosis, 75%; right coronary artery stenosis, 70%; CHF, NYHA class II; LV ejection fraction, 65%; end-systolic volume, 39 mL; end-diastolic volume, 112 mL. Delayed imaging (240 min) revealed perfusion defects (arrows) that were not detected during early imaging (60 min). Images were obtained at the Research Institute of Cardiology, Tomsk National Research Medical Center.

## MD ASSESSMENT IN CAD

### Acute coronary syndrome (ACS)

RR and accelerated washout of 99mTc-MIBI are observed in patients with ACS. Y. Takeishi et al. [20] quantified the regional patterns of 99mTc-MIBI distribution in patients with ACS 7 days after successful primary angioplasty. In symptom-related artery areas, 68% of patients had accelerated washout of the radiopharmaceutical, whereas the remaining had stable perfusion defects. Coronary angiography 1 month after ACS revealed patency of the symptom-related artery in accelerated washout areas in 100% of cases. The pathological mobility of the myocardial wall was less pronounced than that in patients with stable defects (–2.6 ± 0.4 and –3.4 ± 0.6, respectively; $P < 0.01$). The authors concluded that accelerated washout is a marker of postischemic myocardial stunning and, a predictor of myocardial contractility restoration within a month following reperfusion.

S. Fujiwara et al. [21] sought to detect viable myocardium in patients with ACS by identifying RR areas and accelerating regional washout of 99mTc-MIBI. We assessed the functional characteristics of myocardial segments with 99mTc-MIBI RR in 30 patients after percutaneous coronary intervention for acute myocardial infarction (AMI). The findings of myocardial perfusion SPECT were compared with those of low-dose dobutamine stress echocardiography: 5–10 mg/(kg × min).

In this sample of 250 myocardial segments, 41% were in the infarct-related artery zone, with only 22% demonstrating accelerated radiopharmaceutical washout. Accelerated washout was significantly more common in segments in the infarct-related artery zone. According to stress echocardiography findings, practically all RR segments (96%) and only 70% of non-RR segments had impaired contractility at rest. Dobutamine infusion improved contractility in 83%

DOI: https://doi.org/10.17816/DD58668

**Table 1.** Main clinical studies of mitochondrial damage based on myocardial perfusion scintigraphy using 99mTc-MIBI

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| **Authors** | **Underlying condition** | **Number of patients** | **LV ejection fraction (%)** | **Time of early and delayed imaging** | **Washout rate calculation formula** | **Washout rate (%)** | **Main conclusion** |
| S. Fujiwara et al., 2001 [21] | ACS | 30 | Acute phase: patients with RR: 55 ± 7 patients without RR: 54 ± 9 After 1 month: patients with RR: 59 ± 8 patients without RR: 58 ± 12 | Early: 60 minutes; Delayed: 3 h | Adjustment for the count in the mediastinum: no Adjustment for T1/2 of 99mTc: yes | Normal segments: 15; Ischemic segments without RR: 18; Ischemic segments with RR: 30 | RR suggests reversible functional disorders associated with dobutamine-induced contractile reserve preservation. Early and delayed imaging with 99mTc-MIBI provides useful information on the residual viability of dysfunctional myocardium in patients with AMI |
| A. Masuda et al., 2016 [13] | ACS | 19 | 56.5 ± 9.5 | Early: 30 min; Delayed: 3 h | Differences in perfusion defect scores were assessed | No data are available | In patients with ACS, myocardial segments with accelerated 99mTc-MIBI washout showed a decrease in oxidative metabolism. 99mTc-MIBI washout can be associated with MD |
| Y. Chen et al., 2022 [23] | ACS | 1 | 63 | A series of 7 images from injection to the 7th minute post-injection | No data are available | Up to 31 | Serial changes in 99mTc-MIBI WR during dynamic myocardial perfusion SPECT may help assess MD and severity of myocardial ischemia in ACS |
| T. Kato и et al., 2022 [24] | ACS | 165 | 54.5 ± 8.6 | Early: 60 minutes; Delayed: 4 h | Differences in TPD were assessed | No data are available | Accelerated 99mTc-MIBI washout can predict exercise tolerance in patients with ACS |
| B. Du et al., 2014 [18] | Stable CAD | CAD: 8 Control: 10 | – | Early: 90 minutes; Delayed: 4 h | Adjustment for the count in the mediastinum: no Adjustment for T1/2 of 99mTc: no | Three-vessel CAD: 21.1 ± 4.6 Control: 9.5 ± 4.9 $P < 0.001$ | In patients with impaired mitochondrial function due to three-vessel CAD, the global and regional 99mTc-MIBI WRs were consistently higher than those in healthy volunteers. Global 99mTc-MIBI WR is a sensitive parameter for severity stratification in patients with advanced coronary atherosclerosis |
| M.O.M. Othman et al., 2021 [15] | Stable CAD | 100 | No data are available | Early: 60–90 min; Delayed: 4 h | Adjustment for the count in the mediastinum: no Adjustment for T1/2 of 99mTc: yes | Low-risk group: 7.9 Intermediate-risk group: 15.1 High-risk group: 19.3 | The global 99mTc-MIBI WR positively correlated with the risk stratification in patients with stable CAD. It can be used as an additional parameter for risk assessment |

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**Table 1.** Continued

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| **Authors** | **Underlying condition** | **Number of patients** | **LV ejection fraction (%)** | **Time of early and delayed imaging** | **Washout rate calculation formula** | **Washout rate (%)** | **Main conclusion** |
| S. Kumita et al., 2002 [33] | Nonischemic CHF | CHF: 28<br>Control: 8 | CHF: 43.2 ± 15.7<br>Control: 67.0 ± 11.8 | Early: 30 min;<br>Delayed: 3 h | Adjustment for the count in the mediastinum: yes<br>Adjustment for T1/2 of 99mTc: no | CHF: 39.6 ± 5.2<br>Control: 31.2 ± 5.5<br>$P < 0.01$ | Myocardial 99mTc-MIBI WR is considered a new marker for the diagnosis of myocardial injury in patients with CHF |
| T. Sugiura et al., 2006 [34] | Dilated cardiomyopathy | DCM: 17<br>Control: 10 | DCM: 37.4 ± 11.1<br>Control: 61.3 ± 9.4 | Early: 60 minutes;<br>Delayed: 3 h | Adjustment for the count in the mediastinum: yes<br>Adjustment for T1/2 of 99mTc: no | DCM: 31.2 ± 6.3<br>Control: 25.2 ± 4.7<br>$P < 0.05$ | Scintigraphy using 99mTc-MIBI is a valuable tool for assessing the severity of congestive heart failure |
| S. Matsuo et al., 2007 [35] | Nonischemic CHF | CHF: 61<br>Control: 7 | CHF: 48 ± 15<br>Control: 73 ± 7 | Early: 30 min;<br>Delayed: 3 h | Adjustment for the count in the mediastinum: no<br>Adjustment for T1/2 of 99mTc: yes | CHF: 28.2 ± 5<br>Control: 22.9 ± 4.1<br>$P < 0.01$ | 99mTc-MIBI WR is a new diagnostic marker of myocardial injury that provides prognostic information for patients with heart failure |
| M.K. Shiroodi et al., 2010 [38] | DCM | DCM: 17<br>Control: 6 | DCM: 28.8 ± 11.3<br>Control: 65.5 ± 5.26 | Early: 30 min;<br>Delayed: 3.5 h | Adjustment for the count in the mediastinum: no<br>Adjustment for T1/2 of 99mTc: yes | DCM: 29.13 ± 6.68<br>Control: 14.17 ± 3.31<br>$P = 0.001$ | The 99mTc-MIBI WR correlates with the functional parameters of the heart during MPS in patients with DCM. Scintigraphy with 99mTc-MIBI is a valuable molecular imaging tool for the diagnosis and severity assessment of myocardial injury or dysfunction in DCM |
| E.V. Migunova et al., 2020 [47] | Patients after heart transplantation (DCM) | 2 | Patient 1: 60<br>Patient 2: 61 | Early: 60 minutes;<br>Delayed: 4 h | Adjustment for the count in the mediastinum: no<br>Adjustment for T1/2 of 99mTc: yes | Patient 1: 23.78–57.50;<br>Patient 2: < 23.0 | The washout rate can be a predictor of myocardial injury, which is important for follow-up in patients after heart transplantation |
| D. Hayashi et al., 2013 [14] | DCM | 20 | 34 ± 9 | Early: 60 minutes;<br>Delayed: 4 h | Adjustment for the count in the mediastinum: yes<br>Adjustment for T1/2 of 99mTc: yes | 24.4 ± 8.4 | In patients with DCM, accelerated 99mTc-MIBI washout can be a predictor of MD and myocardial contractile reserve impairment during a dobutamine stress test |

**Table 1.** Ending

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| **Authors** | **Underlying condition** | **Number of patients** | **LV ejection fraction (%)** | **Time of early and delayed imaging** | **Washout rate calculation formula** | **Washout rate (%)** | **Main conclusion** |
| M. Yamanaka et al., 2021 [36] | Nonischemic CHF | 25 | 49.4 ± 15.5 | Early: 45 minutes; Delayed: 4 h | Visual analysis of segments during early and delayed imaging (quantitative assessment of the WR was not performed) | No data are available | In nonischemic CHF, MD is manifested at early stages by the washout of 99mTc-MIBI; fibrotic changes in the myocardium are detected at later stages using time-delayed contrast-enhanced cardiac MRI |
| M. Sun et al., 2008 [41] | HCM | HCM: 15 Control: 12 | HCM: 54.47 ± 10.14 Control: 60.17 ± 4.0 | Early: 10 min; Second early: 90 minutes; Delayed: 4 h | Adjustment for the count in the mediastinum: no Adjustment for T1/2 of 99mTc: no | HCM: 42.66 ± 3.30 Control: 31.27 ± 4.04 $P < 0.01$ | The 99mTc-MIBI WR in the HCM group was significantly higher than that in the control group. 99mTc-MIBI WR correlates with hypertrophic LV wall thickness |
| S. Isobe et al., 2010 [42] | HCM | 24 | 74.5 ± 5.6 | Early: 40 min; Delayed: 4 h | Adjustment for the count in the mediastinum: yes Adjustment for T1/2 of 99mTc: yes | 23.8 ± 4.8 | Accelerated 99mTc-MIBI washout in HCM suggests myocardial degradation. The 99mTc-MIBI WR can be a valuable tool for the early detection of myocardial injury in HCM patients |
| M. Ikawa et al., 2006 [19] | Primary mitochondrial DNA mutation | 5 | 44.4 ± 10.9 | Early: 60 minutes; Delayed: 4 h | Adjustment for the count in the mediastinum: no Adjustment for T1/2 of 99mTc: no | 21.2 ± 6.18 | In mitochondrial cardiomyopathy, the combination of increased uptake of 123I-BMIPP with decreased uptake and accelerated 99mTc-MIBI washout may be a valuable tool for assessing the severity of MD and can be used for the differential diagnosis of mitochondrial cardiomyopathy. |
| M. Sarai et al., 2013 [43] | Cardiac sarcoidosis | 11 | Before therapy: 57 ± 19 After therapy: 58 ± 21 (NS) | Early: 60 minutes; Delayed: 4 h | Adjustment for the count in the mediastinum: no Adjustment for T1/2 of 99mTc: no | Before therapy: 25 ± 5 After therapy: 17 ± 5 $P < 0.0001$ | The 99mTc-MIBI WR can be used to assess heart function in patients with sarcoidosis during steroid therapy. When assessing disease activity in mild myocardial injury during steroid therapy, quantitative assessment of 99mTc-MIBI WR is more useful than semiquantitative assessment (in points) |

Note: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, chronic heart failure; DCM, dilated cardiomyopathy; DNA, deoxyribonucleic acid; HCM, hypertrophic cardiomyopathy;MD, mitochondrial dysfunction;

MPS, myocardial perfusion scintigraphy; NS, not significant; RR, reverse redistribution; T1/2, half-life; TPD, total perfusion deficit.

DOI: https://doi.org/10.17816/DD568668

of initially dysfunctional RR segments and 54% of non-RR segments. These findings suggest that accelerated 99mTc-MIBI washout is linked to the reversibility of functional myocardial contractility disorders. Early and delayed myocardial perfusion SPECT with 99mTc-MIBI can provide clinically valuable information on cardiomyocyte viability following AMI.

Accelerated 99mTc-MIBI washout was also observed in patients with vasospastic angina [22]. S. Ono et al. performed early and delayed myocardial perfusion SPECT with 99mTc-MIBI at rest in 39 patients with vasospastic angina confirmed by the ergometrine (ergonovine) test. Decreased uptake was found in 32 cases (82%), either on delayed images or on both early and delayed images. Furthermore, 23 (72%) of all ergometrine-induced vasospastic areas showed decreased uptake on delayed images. The tracer WR in the reduced accumulation area was significantly higher than that in the normal area, indicating a decline in the mitochondrial membrane's ability to retain MIBI. According to the authors, delayed SPECT with 99mTc-MIBI at rest is a viable tool for the diagnosis of coronary vasospastic angina.

In 2022, Y. Chen et al. [23] published a clinical case in which an accelerated 99mTc-MIBI washout (up to 31%) was observed in the anterior descending artery, with a spasm detected via invasive angiography. Unlike other studies, washout in this study was assessed by dynamic SPECT (using a gamma camera with cadmium-zinc-telluride detectors) from the radiopharmaceutical injection to the seventh minute. Myocardial flow reserve in the anterior descending artery was reduced to 1.26.

T. Kato et al. [24] performed total perfusion deficit (TPD) analysis in 165 patients with ACS and found an association between 99mTc-MIBI RR and cardiopulmonary exercise test parameters. Ergospirometry revealed that patients with a TPD difference of ⩾4 had a significantly lower anaerobic threshold than those without RR. Furthermore, the difference in TPD between early and delayed images, as well as the presence of diabetes mellitus, were independent predictors of exercise tolerance recovery during a 3-month follow-up.

A. Masuda et al. compared accelerated 99mTc-MIBI washout with the findings of echocardiography and positron emission tomography (PET) with 11C-acetate in 19 patients with ACS (unstable angina, AMI with and without ST elevation). PET with 11C-acetate enables noninvasive assessment of myocardial oxidative metabolism [25] and myocardial blood flow [26, 27]. The clearance of 11C-acetate is linked to Krebs cycle activity in mitochondria, where acetate is converted to acetyl-CoA and metabolized by acetyl-CoA synthetase-2 [28]. As a result, oxidative metabolism as measured by PET with 11C-acetate could be linked to mitochondrial function. Segments with accelerated 99mTc-MIBI washout were associated with decreased oxidative metabolism in the myocardium and impaired regional contractility. The authors concluded that accelerated 99mTc-MIBI washout is associated with MD and may serve as a predictor of myocardial contractility restoration in patients with ACS.

## Stable CAD

The presence of balanced ischemia, which implies an underestimation of the severity of the decrease in myocardial perfusion during visual analysis of scintigraphy data, makes identifying patients with stable CAD with multivessel CAD by MPS challenging [29, 30]. This issue could be resolved with quantitative blood flow assessment [31], determination of transient ischemic dilatation and/or stunning, or 99mTc-MIBI WR evaluation.

B. Du et al. investigated the 99mTc-MIBI WR in healthy individuals and patients with three-vessel CAD and the relationship with the clinician-administered dissociative states scale, using invasive coronary angiography data, to determine the potential use of this parameter in stratifying CAD severity [18]. The 99mTc-MIBI WR was significantly higher in patients with three-vessel CAD than in the control group (21.1%±4.6% and 9.5%±4.9%, respectively, $P < 0.001$). A positive correlation was found between the radiopharmaceutical WR and the severity index of coronary artery obstructive lesions ($r^2 = 0.73$, $P = 0.006$). Furthermore, the results of regional 99mTc-MIBI washout across vascular territories are presented in this study. The authors proposed incorporating delayed imaging into the protocol of routine perfusion scintigraphy with 99mTc-MIBI at rest and using WR as an additional indicator of balanced ischemia in three-vessel CAD when suspiciously normal perfusion does not match the clinical presentation.

M.O.M. Othman et al. [15] discovered that the global 9mTc-MIBI WR positively correlated with the risk of cardiovascular events as measured by the Framingham risk score and the Duke treadmill score (r = 0.4 and r = 0.6, respectively), as well as the risk as measured by MPS (r = 0.7). Moreover, WR negatively correlated with LV ejection fraction (r = –0.4). The authors concluded that the global 9mTc-MIBI WR can be used to stratify patients with stable CAD into high (annual mortality >3%) and low (annual mortality < 1%) risk groups [32].

## Nonischemic CHF

The majority of studies assessing MD by MPS were performed in patients with nonischemic CHF. In these studies, 99mTc-MIBI RR was assessed in isolated groups of patients with dilated and hypertrophic cardiomyopathies, as well as in mixed groups of patients with hypertrophic, hypertensive, valvular, and toxic cardiomyopathy, cardiac sarcoidosis, and Takotsubo cardiomyopathy.

S. Kumita et al. performed one of the first studies on the use of 99mTc-MIBI WR as a marker of myocardial injury in patients with CHF [33]. The following was observed in 25 patients with nonischemic cardiomyopathy compared with the control group:

- A significantly higher 99mTc-MIBI WR (39.6%±5.2% and 31.2%±5.5%, $P < 0.01$).

- A significant inverse correlation of WR with LV ejection fraction (r = –0.61) and peak ejection rate (r = –0.47).
- A positive correlation with end-systolic (r = 0.45) and end-diastolic (r = 0.48) LV volumes.

The authors concluded that this approach can be used to evaluate LV damage and contractile dysfunction.

T. Sugiura et al. [34] investigated the association of 99mTc-MIBI WR with brain natriuretic peptide (BNP) levels and the findings of myocardial scintigraphy with 123I-MIBG in patients with dilated cardiomyopathy (DCM).

The 99mTc-MIBI WR was significantly higher in the DCM group than in the control group. In the DCM group, WR significantly correlated with the following:

- BNP level (r = 0.72, $P < 0.0001$): positive correlation
- Indexed values of end-diastolic (r = 0.556, $P < 0.01$) and end-systolic (r = 0.567; $P < 0.01$) volumes: positive correlation
- LV ejection fraction (r = –0.545, $P < 0.01$): negative correlation

Furthermore, this study found a correlation (r = 0.603, $P < 0.01$) between the WRs of 99mTc-MIBI and 123I-MIBG.

Given that the 99mTc-MIBI WR correlates with well-known predictors of the CHF course (BNP level and cardiac scintigraphy with 123I-MIBG), the authors suggest that 99mTc-MIBI WRs can also be used for the prognosis and risk stratification of patients with CHF. This is especially relevant because 99mTc-MIBI is considerably cheaper, more readily available, and more widely used radiopharmaceutical than 123I-MIBG, which requires radioactive iodine to be produced in a cyclotron.

S. Matsuo et al. studied 61 patients and found an increase in the 99mTc-MIBI WR in the nonischemic cardiomyopathy group compared with the control group; however, no abnormalities were found in the heart-to-mediastinum ratio [35]. Furthermore, a correlation was found between 99mTc-MIBI WR and the following:

- BNP level (r = 0.31)
- End-systolic (r = 0.39) and end-diastolic (r = 0.49) volumes
- LV ejection fraction (r = 0.52)
- Peak LV filling velocity (r = 0.44)

According to the Kaplan–Meier analysis, WR >28% was a predictor of CHF progression. M. Yamanaka et al. [36] performed early (45 min) and delayed (4 h) MPS with 99mTc-MIBI at rest and contrast-enhanced cardiac magnetic resonance imaging in patients with clinical signs of nonischemic cardiomyopathy. Myocardial segments with normal radiopharmaceutical uptake during early imaging and perfusion defects detected during delayed imaging were significantly more frequently associated with delayed contrast enhancement on magnetic resonance imaging. This suggests impaired mitochondrial function in areas with even minor fibrotic changes, as seen in the early stages of cardiomyopathy. The authors advocate delayed scintigraphy for the early detection of myocardial injury in cardiomyopathies because it is straightforward and easy to perform and does not involve the additional administration of radiopharmaceuticals.

K. Takehana et al. [37] studied 20 patients with DCM (LV end-systolic volume, 177±78 mL; LV ejection fraction, 28.2%±12.4%). Three subgroups of myocardial segments were identified according to early (after 1 h) and delayed (after 3 h) MPS: with accelerated, normal, and delayed washout. Systolic thickening and systolic motion of the LV wall were significantly decreased in the accelerated washout group compared with the other two groups, where no significant differences were observed. A strong negative correlation was found between LV ejection fraction and the number of segments with accelerated washout (r = –0.65, $P < 0.01$) and global 99mTc-MIBI WR. Because 99mTc-MIBI WR is linked to mitochondrial membrane dysfunction, accelerated washout of radiopharmaceuticals may suggest that MD plays a major role in the pathogenesis of DCM.

M.K. Shiroodi et al. [38] reported similar findings when they investigated the relationship between the WR of radiopharmaceuticals, NYHA functional class of CHF, and LV functional parameters according to myocardial perfusion SPECT synchronized with the echocardiogram. A significant ($P < 0.05$) correlation was found between 99mTc-MIBI WR and the following:

- End-diastolic ($r^2 = 0.216$) and end-systolic ($r^2 = 0.23$) volumes: positive correlation
- LV wall kinesis ($r^2 = 0.54$): positive correlation
- LV ejection fraction ($r^2 = 0.679$): negative correlation

The authors concluded that this method is essential in determining the degree of myocardial injury, particularly in patients with idiopathic DCM, because the 99mTc-MIBI WR increased significantly as the functional class of CHF increased.

D. Hayashi et al. performed an intriguing study in terms of the methodology used [14]. They performed 99mTc-MIBI WR assessment, dobutamine stress echocardiography, and endomyocardial biopsy with quantitative analysis of mitochondrial RNA (mRNA) expression and mitochondrial microstructure analysis by electron microscopy in 20 patients with DCM. These patients showed a significant correlation of the 99mTc-MIBI WR with changes in the rate of increase in LV pressure with increasing dobutamine doses and severity of mitochondrial damage, in accordance with the severity of crista degeneration (r = 0.88; $P = 0.048$) and the presence of glycogen-positive zones (r = 0.90; $P = 0.044$) according to electron microscopy. Patients with accelerated 99mTc-MIBI washout (>24.3%) had higher rates of LV pressure increase than those with 99mTc-MIBI WR below the predefined threshold value. The mRNA level for mitochondrial electron transport enzymes was significantly reduced in the subgroup of patients with accelerated 99mTc-MIBI washout. To our knowledge, this is the first study to show a link between accelerated 99mTc-MIBI washout and decreased mRNA expression and impaired mitochondrial microstructure in patients with DCM.

### Hypertrophic cardiomyopathy (HCM)

The characteristics of 99mTc-MIBI WR have been studied in patients with HCM [39–42]. This pathology is characterized by primary damage to the cardiomyocyte mitochondria caused by genetic factors.

M. Sun et al. [41] examined 15 patients with HCM and discovered that the 99mTc-MIBI WR was significantly higher in this group than in the control group. The authors also discovered a link between WR and maximum LV wall thickness in the HCM group. Accelerated 99mTc-MIBI washout in the HCM group may be due to mitochondrial DNA mutations.

S. Isobe et al. [42] identified two subgroups of patients with HCM: those with accelerated (≥22.5%) and normal (<22.5%) washout of 99mTc-MIBI. The authors also performed direct pressure measurements in both ventricles and echocardiography with atrial electrical stimulation. The 99mTc-MIBI WR showed a significant positive correlation with peak and basal LV pressure ($r = 0.63$, $P < 0.005$; $r = 0.67$, $P < 0.0005$, respectively) and BNP level ($r = 0.57$, $P < 0.005$). A negative correlation was found between the WR and the rate of increase in LV pressure ($r = –0.63$, $P < 0.005$). The LV wall thickness and the ratio of the transmitral flow velocity to the mitral annular velocity were significantly higher in the group with accelerated 99mTc-MIBI washout than in the group without it. For the first time, this study showed a link between stress-induced changes in central hemodynamics and 99mTc-MIBI washout parameters in patients with HCM. The authors underlined the potential use of this method for noninvasive assessment of the severity of hemodynamic abnormalities and prognosis in these patients.

### Cardiac sarcoidosis

M. Sarai et al. demonstrated that the 99mTc-MIBI WR can be used for the functional assessment of the heart in cardiac sarcoidosis during steroid therapy [43]. Specifically, quantitative 99mTc-MIBI WR assessment (based on the difference in the number of pulses between early and delayed imaging) was superior to visual assessment of regional washout in predicting the restoration of LV diastolic function in sarcoidosis. Thus, visual analysis revealed no significant differences in the size of the perfusion defect before and after 6 months of therapy, whereas quantitative analysis revealed a significant decrease in the WR of radiopharmaceuticals after therapy (25% ± 5% vs. 17% ± 5%, respectively, $P$ <0.0001). The authors discovered a link between changes in WR and LV diastolic function restoration during long-term steroid therapy.

In 2022, M. Suzuki et al. [44] described more pronounced changes in the size of perfusion defects during delayed imaging with 99mTc-MIBI in patients with sarcoidosis compared with patients without it (3.0 [–1.0 to 5.0] vs. 0.0 [–0.5 to 1.0], $P = 0.010$). Furthermore, according to early and delayed PET findings, patients with sarcoidosis had a more pronounced decrease in 18F-fluorodeoxyglucose uptake than patients without sarcoidosis. These findings show that metabolic disorders reduce the ability of the myocardium to retain the tracer.

### Systemic mitochondrial heart disease

A few studies have reported accelerated 99mTc-MIBI washout in patients with mitochondrial encephalomyopathy, with a simultaneous increase in 123I-phenyl-methyl-pentadecanoic acid (123I-BMIPP, an analog of free fatty acids) uptake, indicating an imbalance in the energy state of cardiomyocytes [45], including genetic damage to mitochondrial DNA [46].

M. Ikawa et al. [19] used cardiac scintigraphy with 99mTc-MIBI and 123I-BMIPP to assess damage to the mitochondrial respiratory chain in patients with a primary mitochondrial DNA mutation. The authors present the findings for five patients. Pronounced involvement of the heart muscle in the pathological process was associated with significantly decreased 99mTc-MIBI uptake and accelerated washout, in combination with increased 123I-BMIPP (perfusion–metabolism mismatch). The authors explain the first phenomenon by impaired mitochondrial transmembrane potential and the second by high blood triglyceride levels. As a result, detecting a perfusion–metabolism mismatch can be used to determine the severity of mitochondrial respiratory chain disruption. An important aspect of this study was the increased 123I-BMIPP uptake in the myocardium in contrast to hypertrophic and congestive heart failure, which can be used to differentiate primary mitochondrial DNA mutation from other types of cardiomyopathies.

### Heart transplantation

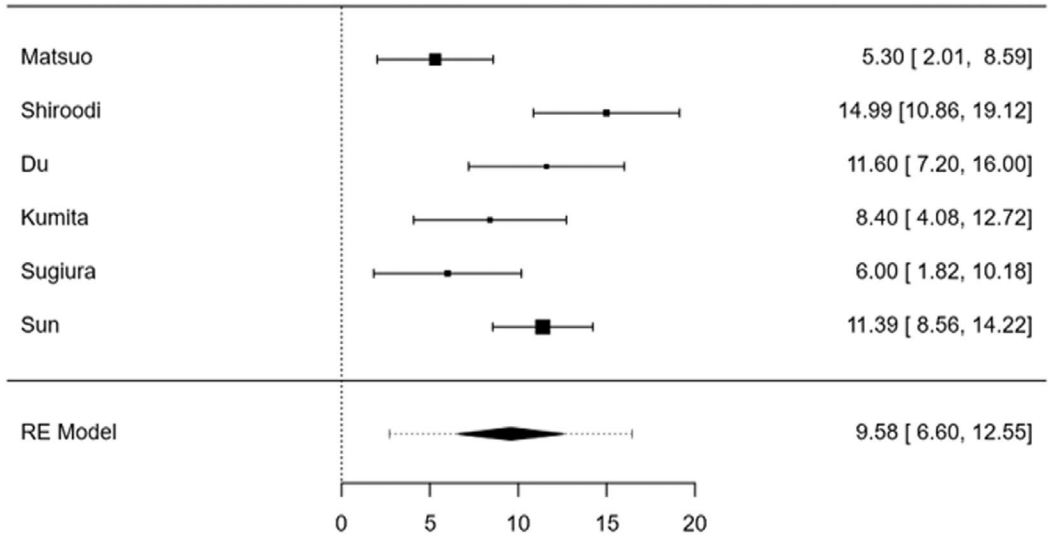
E.V. Migunova et al. [47] discovered that accelerated tracer washout in patients who had undergone heart transplantation is associated with histochemical signs of mild acute rejection, such as localized perivascular and interstitial mononuclear cell infiltrates. The authors concluded that calculating the radiopharmaceutical WR allows the identification of segments with impaired mitochondrial function, which can aid clinicians in the differential diagnosis of a transplanted heart rejection crisis with CAD.

## META-ANALYSIS FINDINGS

The hypothesis that WR in the pathology group was significantly higher than that in the control group was tested during the meta-analysis. Six case–control studies were selected for the meta-analysis [18, 33, 34, 38, 41, 46]. The results are presented in Fig. 3.

## PERSPECTIVES AND LIMITATIONS OF THE PROPOSED METHOD

The 99mTc-MIBI washout assessment method is applicable to areas of cardiology not covered in this review. For example, it appears promising to assess MD in patients




Random-Effects Model (k=6)

| | Estimate | se | Z | p | CI Lower Bound | CI Upper Bound |
|---|---|---|---|---|---|---|
| Intercept | 9,58 | 1,52 | 6,31 | <0,001 | 6,600 | 12,554 |

Note. Tau² Estimator: Restricted Maximum-Likelihood

Heterogeneity Statistics

| Tau | Tau² | I² | H² | R² | df | Q | p |
|---|---|---|---|---|---|---|---|
| 3,158 | 9,9697 (SE=8,7429 ) | 73,13% | 3.721 | . | 5,000 | 18,575 | 0,002 |

**Fig. 3.** Meta-analysis findings (k=6 studies). The mean differences ranged from 5.3000 to 14.9900; most estimates were positive (100%). The mean difference based on the random-effects model was 9.5771 (95% confidence interval: 6.6001–12.5540); the mean result was significantly different from zero (z = 6.3053; $P < 0.0001$).

with preserved CHF (HFpEF) and reduced LV ejection fraction and assess cardiotoxicity when using doxorubicin-based drugs.

An experimental study on isolated rat hearts revealed that adding doxorubicin to the perfusion mixture decreased 99mTc-MIBI uptake, and increasing the doxorubicin concentration caused a dose-dependent progressive decrease in radiopharmaceutical uptake. Furthermore, the ability of the myocardium to retain 99mTc-MIBI was compromised after 5 min of doxorubicin infusion, and not only was the administered dose lost, but the tracer that had previously entered the heart was washed out to the baseline level [48]. In continuation of the experiment, in vivo studies were performed 14 days after the intraperitoneal injection of doxorubicin in rats. It was found that increasing the doxorubicin dose resulted in a significant decrease in 99mTc-MIBI uptake (from 2.3% ± 0.3% to 0.9% ± 0.2% of the injected dose/g when using doxorubicin at a dose of 10 mg/kg, $P < 0.05$). Doxorubicin 10 mg/kg induced a threefold increase in the number of visibly damaged mitochondria per field of view.

In Russia, patients with HFpEF account for 53% of the CHF population, whereas in Europe and the United States, they account for 51%–63%. The phenotypic diversity of HFpEF is associated with several risk factors that activate one or more pathophysiological mechanisms, including MD. The identification of patients with HFpEF and accelerated 99mTc-MIBI washout may contribute to better risk stratification in this cohort [49]. Furthermore, the proposed method can be used to assess the efficacy of potential CHF therapies and predict the efficacy of cardiac resynchronization therapy and the use of cardioverter defibrillators.

Despite the fundamental and clinical findings presented in the review, studies of 99mTc-MIBI WR are limited. The analyzed literature contained no systematic reviews or meta-analyses. Furthermore, no randomized studies have used 99mTc-MIBI washout to guide treatment. This is most likely due to factors affecting washout parameters, such as patient age, sex, and underlying pathology. The data collection protocol and methods for determining 99mTc-MIBI WR are not standardized. The threshold values for normal

and pathological clearance of this radiopharmaceutical have not been determined. This primarily applies to normal clearance values (Table 1), which are highly variable. The formulas used to calculate the WR vary: some studies apply an adjustment to the half-life of 99mTc and/or consider the scintillation count in the mediastinum, whereas others do not. Most studies used small patient samples. Only one study found a link between radiological findings that characterize MD and organelle microscopy data [14].

## CONCLUSION

The reverse redistribution of 99mTc-MIBI and its accelerated washout represent a universal nonspecific scintigraphy pattern of myocardial injury caused by MD. According to the literature review, the most extensive evidence base for the use of this method has been accumulated for nonischemic CHF.

In vivo studies have demonstrated a link between the accelerated 99mTc-MIBI washout and the following:

- Findings of mitochondrial microscopy and myocardial histological examination
- LV contractility and hemodynamics
- Natriuretic peptide levels
- Exercise tolerance
- Severity of coronary atherosclerosis
- Myocardial oxidative metabolism
- Risk of cardiovascular events

The correlation with the findings of cardiac scintigraphy with 123I-MIBG is significant because 99mTc-MIBI is considerably cheaper, more readily available, and more widely used radiopharmaceutical than 123I-MIBG, which requires 123-iodine to be produced in a cyclotron. The cardiac 99mTc-MIBI WR is a valuable tool for assessing and monitoring mitochondrial damage in vivo in clinical practice. More research is required to verify the method for noninvasive assessment of mitochondrial function.

## ADDITIONAL INFORMATION

**Funding source.** This study was not supported by any external sources of funding.

**Competing interests.** The authors declare that they have no competing interests.

**Authors' contribution.** All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. M.O. Gulya — selection and analysis of publications, writing the manuscript, preparing tables and illustrations; K.V. Zavadovsky — concept and design of the article, writing the text of the manuscript.

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