REVIEW ARTICLE

Clinical Implications of the Washout Phenomenon in Technetium-99m (^{99m}Tc-) Labeled Compounds for Myocardial Perfusion Imaging

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Abstract

The technetium (Tc) labeled myocardial perfusion compounds are tracers that have been taken up into myocytes and retained in mitochondria several times, thus reflecting the activity of myocytes at the time of injection. However, under certain conditions, "reversed redistribution" is known to occur. This review summarized the unique properties of imaging with the Tc myocardial perfusion tracers.
Keywords: Reversed redistribution, Technetium (Tc) labeled compounds, Washout
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Technetium labeled compound and kinetics in myocyte

It has been reported that both the myocardial uptake and retention of technetium-99m (^{99m}Tc-) labeled compounds depend principally upon the mitochondrial function of the myocardium (1). These lipophilic monovalent cationic myocardial perfusion imaging tracers are distributed dependent on the mitochondrial membrane potentials and tend to remain for a relatively long period without redistribution (2). In severely damaged myocardium, mitochondrial dysfunction leads to faster clearance of ^{99m}Tc-labeled compounds, due to inadequate myocyte capacity to retain the compound. That results in a faster washout (WO) of ^{99m}Tc-labeled compounds and that decreases over time (2, 3). As commercialized myocardial perfusion imaging with Tc-labeled agents, Tc-Sestamibi (Tc sestamibi) and Tc-Tetrofosmin (TcTF) are available. Although they have similar kinetics, TcTF has a small renal clearance and is more rapidly washed from liver, allowing better image quality from an earlier after injection (4). Accelerated myocardial WO is defined as a reversed redistribution (RR), and it occurs in both of them. Mitochondria produce adenosine triphosphate (ATP) by oxidative phosphorylation as an energy-producing source and maintain normal myocardial function and contractility (5, 6).

In ischemic myocardium, the aerobic metabolism of ATP production is impaired due to reduced oxygen supply, and mitochondrial membranes are depolarized, unable to maintain surface electronegative potentials. This mechanism leads to an inability to retain Tc sestamibi, increasing WO (7).

Evaluation of WO in cardiac myocytes

In evaluation of the WO, many studies reported that the elapsed time between initial and delayed images is 3–4 hours; the initial image is acquired at 30 minutes after tracer administration, and the delayed image is acquired 3–4 hours later (6–9). For assessing WO of ^{99m}Tc-labeled compounds, the visual evaluation using 17 segments model from short-axis, horizontal long-axis, and vertical long-axis slice images is adopted with four or five point scoring system (from 0; normal to 4; no activity) in patients with ischemic heart disease (8). A polar map from reconstructed short-axis mages was used to prepare a coronary artery dominance map based on the myocardial maximum counts from the apex to the basal area. It was divided into 3 segments corresponding to the three major coronary territories and was calculated with proper software (8–10).

Several situations of accelerated WO of Tc ^{99m}Tc-labeled compounds

It has been reported that MIBI is reversed redistribution, i.e., accelerated disappearance of MIBI, in the following

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clinical conditions: vasospastic angina (11), cardiac sarcoidosis (12–14), heart failure (15–16) including non-ischemic cardiomyopathy, reperfusion after acute myocardial infarction (8, 9, 17, 18).

Vasospastic angina

Ono et al has demonstrated that the delayed imaging after a single injection of ^{99m}Tc-sestamibi was useful in detecting myocardial functional abnormalities associated with coronary spastic angina (11). They showed that the WO rate in spastic segments was higher than that in nonspastic segments. After medical treatment, the WO rate from spastic segments decreased (11). Patients with coronary spastic angina often demonstrate abnormal left ventricular regional wall motion in culprit artery. Although transient myocardial stunning was originally defined as abnormal contractility of impaired myocardium after reperfusion in AMI (19), it may also be the result of repetitive myocardial ischemia in vasospastic angina.

Their data of improved left ventricular ejection fraction after medication suggested that myocardial segments with reverse redistribution may indicate stunned myocardium with reversible dysfunction by coronary spasm.

RR in reperfused myocardium after acute myocardial infarction

In patients with acute myocardial infarction, ^{99m}Tc-labeled compounds RR is a well-known phenomenon early after reperfusion (7–9, 17, 18, 20). It was observed early, at 5 days after reperfusion, and continued for a relatively long period, 6 months in some cases (18). They report that regional wall motion abnormalities were less frequent with RR than in cases with fixed defects, and that the disappearance of RR resulted in an earlier recovery of contractility.

In other words, RR may reflect rescued myocardium, and the disappearance of RR may indicate earlier recovery of myocardium.

Viable stunned myocardium cannot retain ^{99m}Tc-labeled compounds as long as normal cells, generating the faster wash-out phenomenon which is reduced over time. In this case, the magnitude of the RR will be proportional to the magnitude of the stunning (17, 18). Recently, the volume of ^{99m}Tc-sestamibi RR in patients with ACS early after reperfusion could help to predict improvement in exercise capacity in the chronic phase (21).

Cardiac sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown cause. Cardiac sarcoidosis (CS) is a serious long-standing malignant disease with the possibility of causing life-threatening arrhythmias and severe heart failure. For early diagnosis, both myocardial perfusion scintigraphy and ^{18}F-fuorodeoxyglucose positron emission tomography (FDG PET) are useful for the diagnosis of CS (22). While FDG PET for monitoring CS and determining treatment efficacy, there is a positive relationship between ^{99m}Tc-labeled compounds WO and LV functional recovery after steroid therapy in patients with CS (12, 13).

Regardless of whether the initial uptakes of the ^{99m}Tc-labeled compound are normal or abnormal, it has been reported that FDG uptake is increased at regions of WO elevation (14). The region with WO enhancement of ^{99m}Tc-compound without perfusion defects in the initial imaging is thought to reflect early inflammation and such cases are expected to be effective steroid therapy. On the other hand, the regions with perfusion defects in the initial image without WO are thought to be fibrotic scar and such cases are suggested the possibility of inadequate therapeutic response. From these data based on both of the extent of myocardial damage and the degree of WO (12–14), the following concepts may be useful in diagnostic staging and treatment; 1) the segments of normal or mildly reduced initial perfusion with increased WO and FDG uptake is considered to be an early stage with active inflammation, 2) the segments of moderately reduced initial perfusion with increased WO and FDG uptake is considered to continued inflammation with granulomatous changes, and 3) severely reduced or perfusion defects without WO and FDG uptake is considered to be an advanced stage with replacement fibrosis.

Other cardiac disease

The WO of ^{99m}Tc-labeled compounds have also been observed in non-ischemic cardiac diseases such as left bundle branch block (23), hypertrophic cardiomyopathy (24).

In CLBBB, WO of ^{99m}Tc-labeled compounds was observed in the septal wall similar to Tl-201 perfusion imaging during exercise (23). The precise mechanism is unclear, but the hemodynamic impairments that occurred in the septal wall such as asynchronous construction, a decrease in systolic thickening, or intramyocardial pressure increase in the diastolic phase could play an important role in a decrease in regional blood flow to the septum and a reduction in ^{99m}Tc-labeled compounds diffusion across the sarcomere and mitochondrial membrane.

In hypertrophic cardiomyopathy (HCM), the degree of ^{99m}Tc-labeled compounds WO corresponded well with the left ventricular wall thickness (24). The mechanism of fast washout of ^{99m}Tc-labeled compounds in hypertrophic myocardium of HCM patients is unknown. The impaired electrical gradient of mitochondrial and cellular membrane potentials might contribute to an increased washout of ^{99m}Tc-labeled compounds.

In non-ischemic cardiomyopathy, cardiac MRI and Tc

labeled compounds can evaluate the severity of tissue damage (16). Normal or mild perfusion reduction with enhanced WO of Tc-labeled compound reflects ongoing myocardial damage with inflammation, on the other hand, myocardial defects in myocardial perfusion imaging and severe late gadolinium enhancement reflect scar image.

Finally, in stress myocardial imaging with ^{99m}Tc-labeled compounds, sometimes RR also has been observed. Irrespective of the reperfusion strategy, the history of myocardial infarction itself has been reported to play a role in RR (25).

Conclusion

The unique washout phenomenon of ^{99m}Tc-labeled compounds, which are essentially retained stably in cardiomyocytes, is thought to indicate unstable mitochondrial function, an additional parameter that has implications for myocardial viability after reperfusion after infarction and for recovery capacity after myocardial damage.

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Conflicts of interest

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