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REVIEW ARTICLE

Underrecognized Utility of ^{123}I-BMIPP in CAD Diagnosis Outside of Japan

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Abstract

^{123}I-BMIPP (Iodine-123 labeled beta-methyl-p-iodophenyl-pentadecanoic acid) is a radiotracer that facilitates non-invasive assessment of myocardial fatty acid metabolism through single photon emission computed tomography imaging. Given that fatty acids serve as one of the primary energy sources for cardiac muscle, reduced uptake of ^{123}I-BMIPP offers valuable insights into the pathophysiology of various cardiac conditions, particularly in coronary artery disease (CAD). Despite its reported efficacy, the use of ^{123}I-BMIPP remains limited outside Japan, primarily due to regulatory and supply challenges. However, in Japan, ^{123}I-BMIPP is clinically utilized for CAD patients with various ischemic conditions as the protocol does not require stress tests or contrast iodine and has a relatively short acquisition time. This review highlights the clinical applications of ^{123}I-BMIPP across various conditions and aims to promote its broader adoption in clinical practice, both in Japan and internationally.

Keywords: ^{123}I-BMIPP, Myocardial fatty acid metabolism, Myocardial ischemia, Perfusion-metabolism mismatch

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Iodine-123 labeled Beta-Methyl-p-Iodophenyl-Pentadecanoic Acid (^{123}I-BMIPP) is a radiopharmaceutical tracer widely used in nuclear cardiology in Japan. Labeled with Iodine-123 (I-123), it allows for the non-invasive evaluation of myocardial fatty acid metabolism via single photon emission computed tomography (SPECT). Since fatty acids are a key energy source for the heart, reduced uptake can reveal important insights, particularly in coronary artery disease (CAD) (1).

^{123}I-BMIPP helps identify myocardial regions with impaired fatty acid metabolism due to ischemia, making it valuable for diagnosing various cardiac conditions, including unstable angina, acute coronary syndrome (ACS), myocardial infarction (MI), and heart failure. However, its use outside Japan is limited by regulatory and supply issues. This review aims to introduce ^{123}I-BMIPP's clinical utility to physicians in Japan and globally.

Mechanism of ^{123}I-BMIPP and protocol

The myocardium primarily uses fatty acids and glucose as energy sources. Under normal conditions, it predominantly relies on fatty acid metabolism during fasting and rest, however, in situations such as myocardial ischemia, energy metabolism shifts from fatty acids to glucose metabolism. ^{123}I-BMIPP exhibits the pharmacokinetics similar to endogenous fatty acids and, once taken up by cells, migrates into triglyceride pool and mitochondria. Due to the presence of a methyl group at the β-position as a side chain, it is resistant to β-oxidation and remains in the myocardium for a longer duration. By evaluating ^{123}I-BMIPP uptake, localized disturbances in myocardial fatty acid metabolism can be detected (2, 3).

The feasibility of ^{123}I-BMIPP myocardial SPECT as a metabolic imaging tool for detecting ischemia was initially demonstrated in canine models by Schebelt et al. They observed impaired fatty acid metabolism accompanied by increased glucose utilization in ischemic regions using C-11 palmitic acid and fluorodeoxyglucose positron emission tomography (FDG PET) imaging. (4). Schwaiger et al. further showed that fatty acid metabolic disturbances could persist for several weeks following a 3-hour coronary occlusion (5). These foundational studies paved the way for the clinical use

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Table 1 Perfusion–metabolism mismatch pattern

	^{123}I-BMIPP	Rest perfusion	Stress perfusion	Perfusion–metabolism mismatch
Normal	Normal	Normal	Normal	No
Ischemia	Normal or reduced uptake	Normal	Hypoperfusion	Yes
Stunning	Reduced uptake	Normal	Normal or hypoperfusion	Yes
Hibernation	Reduced uptake	Normal or hypoperfusion	Hypoperfusion	Yes
Infarction	Severely reduced uptake	Severe hypoperfusion	Severe hypoperfusion	Yes/no

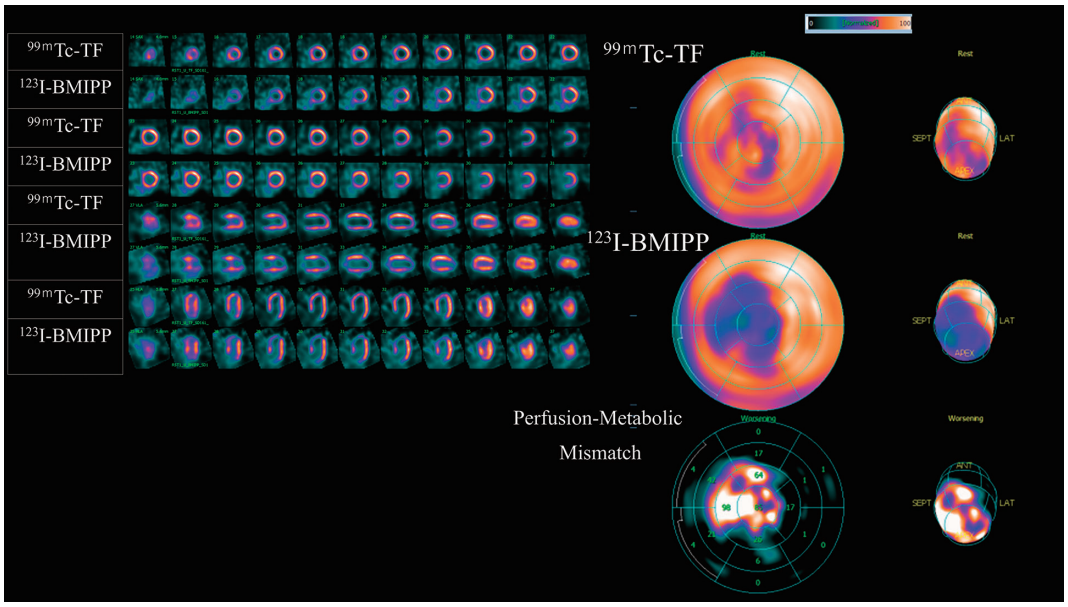

Figure 1 ACS example.
An 80-year-old male with ST-elevation myocardial infarction underwent PCI on the left anterior descending artery. Five days post-onset, dual-isotope SPECT with ^{99m}Tc-tetrofosmin and ^{123}I-BMIPP was performed to assess the effect of revascularization. The SPECT images showed a perfusion defect of ^{99m}Tc and reduced uptake of BMIPP in the anterior wall and septum. There was a significant perfusion–metabolism mismatch showing a larger reduced uptake of BMIPP than the perfusion defect of ^{99m}Tc.

of ^{123}I-BMIPP metabolic imaging to identify past myocardial ischemia in humans (6, 7).

The current ^{123}I-BMIPP SPECT protocol involves administering ^{123}I-BMIPP at rest, followed by SPECT imaging approximately 30 minutes later (8). In some cases, delayed imaging is also performed 3–4 hours post-administration to evaluate discrepancies between early and delayed images, although further evidence is needed to validate this approach. Additionally, dual-isotope simultaneous acquisition SPECT, which combines myocardial perfusion imaging with ^{123}I-BMIPP, is widely used in Japan to evaluate perfusion-metabolism mismatch (9). This technique allows for the concurrent assessment of fatty acid metabolism and myocardial perfusion, providing valuable insights into myocardial pathology by comparing metabolism and perfusion images. Table 1 details the interpretation of perfusion–metabolism mismatch in dual-isotope SPECT compared to stress and rest myocardial perfusion SPECT.

The capacity of ^{123}I-BMIPP to evaluate reduced myocardial uptake plays a crucial role in diagnosing various aspects of CAD. However, accurately interpreting decreased ^{123}I-BMIPP uptake necessitates careful consideration of both the severity of ischemia and the timing of imaging relative to ischemic episodes. In the following sections, I explore the utility of ^{123}I-BMIPP in different ischemic conditions.

Significance in ACS diagnosis

ACS, including unstable angina and acute myocardial infarction (AMI), involves severe myocardial ischemia, reducing fatty acid uptake. Revascularization restores blood flow, but delayed uptake causes perfusion–metabolism mismatches (10, 11). Mild ischemia can resolve within 2 weeks, but persistent reduction indicates infarction. These mismatches typically resolve 6–12 months post-revascularization (12), except in infarcted regions. In previous studies, ^{123}I-BMIPP showed 74% (7) sensitivity for detecting significant coronary stenosis and 81% (8) sensitivity for diagnosing ACS. An example of ^{99m}Tc-TF/^{123}I-BMIPP dual SPECT images from

a patient with AMI is shown in Figure 1. Another benefit of reduced ^{123}I-BMIPP uptake is its ability to pinpoint the exact lesions responsible for recent ischemia. This is especially valuable for patients with ACS who have multivessel disease or a history of coronary artery bypass grafting. By localizing the culprit lesions, ^{123}I-BMIPP aids in clinical decision-making, allowing for more targeted treatment strategies in complex cases.

Diagnosis of MINOCA

One of the greatest challenges in ACS diagnosis is identifying myocardial infarction with non-obstructive coronary arteries (MINOCA) (13). MINOCA can result from various mechanisms, including plaque rupture, thrombosis, microvascular dysfunction, coronary spasm, or spontaneous coronary artery dissection.

The sensitivity of ^{123}I-BMIPP for detecting vasospastic angina (VSA) is 72.5% (14), but a negative result does not exclude VSA as it cannot differentiate from obstructive angina. In exercise-induced VSA, the sensitivity drops to 56.6% due to episodic spasms rather than stenosis (14). The reduction in ^{123}I-BMIPP uptake in VSA is thought to result from recurrent ischemic episodes, including silent ischemia, reflecting the severity of the spasms. While large-scale MINOCA data on ^{123}I-BMIPP abnormalities are lacking, ^{123}I-BMIPP is useful for detecting recent ischemic events in MINOCA non-invasively.

Prediction of functional recovery

Previous studies have demonstrated that the extent of perfusion–metabolism mismatch between ^{123}I-BMIPP and ^{201}Tl or ^{99m}Tc in the acute stage correlates with improvements in left ventricular wall motion as observed through echocardiography or SPECT (11, 15, 16). Nishimura et al. reported a stronger correlation between the extent of the ^{123}I-BMIPP defect and ejection fraction at discharge and follow-up, compared to ^{201}Tl (17). Additionally, Nakata et al. found that the ratio of ^{201}Tl to ^{123}I-BMIPP severity in the acute stage was associated with improved regional wall motion (10).

In cases of AMI without percutaneous coronary intervention (PCI), matching defects in ^{123}I-BMIPP and perfusion tracers suggest extensive necrosis. However, after PCI, early imaging often reveals a larger ^{123}I-BMIPP defect, indicating a perfusion–metabolism mismatch that may decrease over time. This mismatch provides valuable insights into potential cardiac function recovery, although large-scale confirmation of these findings is still necessary. The presence of a significant mismatch suggests that a larger amount of myocardium has been salvaged within the risk area, correlating with a greater likelihood of subsequent cardiac function recovery. This makes perfusion–metabolism mismatch an important tool for evaluating therapeutic effects and predicting improvements in cardiac function.

The mismatch region is believed to identify stunned myocardium—tissue that has avoided necrosis due to early ischemia relief via reperfusion therapy but has suffered transient ischemic effects that impair fatty acid metabolism. Although this region may exhibit reduced wall motion in the acute phase, it is expected to normalize during the recovery phase. Figure 2 illustrates the concept of interpreting perfusion–metabolism mismatches in ACS for predicting functional recovery.

The utility of ^{123}I-BMIPP in chronic CAD and viability

In stable CAD, delayed recovery of fatty acid metabolism can help detect recent ischemic episodes, making ^{123}I-BMIPP a useful indicator of ischemic memory (18, 19). A previous study assessed patients with suspected CAD angina by comparing ^{123}I-BMIPP SPECT with stress ^{201}Tl after excluding those with prior myocardial infarction and unstable conditions. The patients were categorized into four groups: [1] negative BMIPP and negative Tl, [2] negative BMIPP and positive Tl, [3] positive BMIPP and negative Tl, and [4] positive BMIPP and positive Tl (20). In this study, concordant results indicated either no ischemic heart disease or CAD with ischemic memory. Negative BMIPP and positive Tl suggested significant CAD with stress-induced ischemia but no ischemic memory. Positive BMIPP and negative Tl was a unique combination, indicating ischemic memory despite normal stress perfusion imaging, which may imply false-negative stress perfusion imaging, multivessel disease, or insufficient stress. Even if stress-induced blood flow imaging is negative, reduced ^{123}I-BMIPP uptake suggests a high likelihood of CAD. However, the diagnostic accuracy of BMIPP is higher in acute, severe cases and lower in chronic, mild cases. Additionally, if multiple ^{123}I-BMIPP uptake abnormalities are observed, multivessel disease is possible (18, 20).

In chronic infarction, reduced ^{123}I-BMIPP uptake and myocardial perfusion defects may be similar in size, indicating complete necrosis. However, ^{123}I-BMIPP uptake often appears larger than perfusion images. When this discrepancy occurs in the chronic phase, hibernating myocardium is characterized by reduced contraction in chronically hypoperfused myocardial regions that have escaped necrosis (21). Hibernation is considered a self-protective response of the myocardium to reduced blood flow, and successful reperfusion can lead to improved cardiac function.

In stable CAD patients with a perfusion-metabolism mismatch, severe ischemic episodes or hibernation are suspected, suggesting myocardial viability (22). However, in patients with decreased blood flow uptake and no mismatch with metabolism, necrosis is likely, though the possibility of

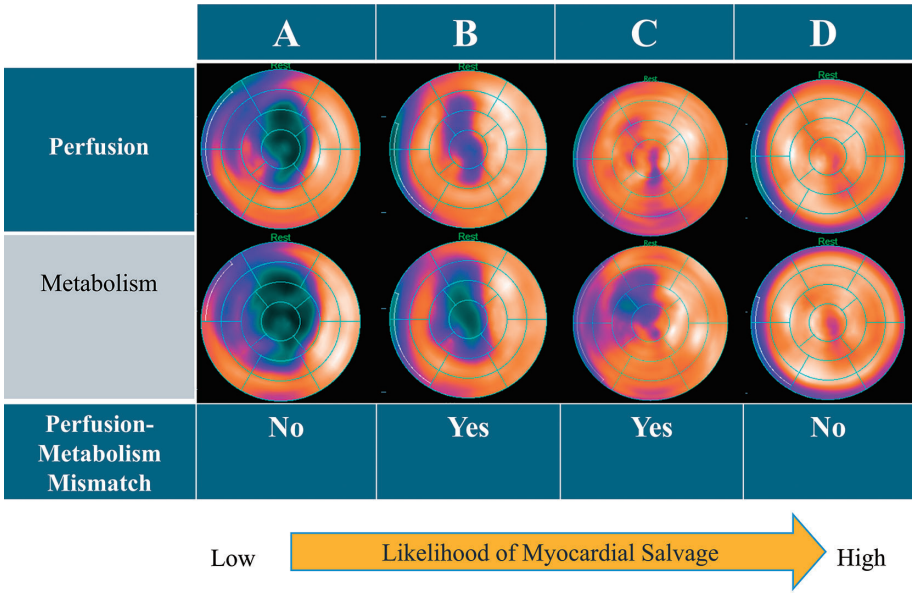

Figure 2 A proposed framework for interpreting perfusion–metabolism mismatch in ACS patients to predict functional recovery.
^{123}I-BMIPP exhibits "memory imaging" characteristics, allowing identification of stunned myocardium salvaged from a recent ischemic event. After PCI for ACS, dual-isotope SPECT results can be classified into four groups:

Group A: Both perfusion and BMIPP imaging show significant reductions without a perfusion–metabolism mismatch, potentially suggesting insufficient salvageable myocardium despite PCI. In such cases, an early introduction of remodeling prevention therapy is crucial to mitigate adverse cardiac remodeling and improve long-term outcomes.
Group B: Mild perfusion–metabolism mismatch, with BMIPP showing a slightly wider reduction. The mismatch area may indicate salvaged myocardium with preserved viability, suggesting potential functional recovery.
Group C: Significant perfusion–metabolism mismatch, with BMIPP showing a larger reduction. The salvaged myocardium is viable, with good prospects for functional improvement during recovery.
Group D: No perfusion abnormality and normal BMIPP, indicating a favorable prognosis.

viable myocardium without an ischemic episode causing mismatch cannot be ruled out. Although more evidence is needed to confirm the ability of this mismatch to predict viability, ^{123}I-BMIPP offers a valuable alternative for viability assessment in patients who cannot undergo stress myocardial perfusion imaging, ^{18}F-FDG PET or late gadolinium enhancement MRI. Ideally, viability assessment with other modalities is necessary, but when other modalities are difficult to use, evaluating fatty acid metabolism can help guide treatment strategies.

Conclusions

Although ^{123}I-BMIPP is not widely used outside of Japan, it is an extremely valuable tracer for the diagnosis of CAD and is widely utilized within Japan. This review has highlighted the unique characteristics of ^{123}I-BMIPP in assessing CAD patients with various ischemic conditions. It is hoped that this information will be helpful to physicians both in Japan and internationally.

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Conflicts of interest

The author has no disclosure.

Abbreviations

ACS: acute coronary syndrome
AMI: acute myocardial infarction
CAD: coronary artery disease
MINOCA: myocardial infarction with non-obstructive coronary arteries
PCI: percutaneous coronary intervention
STEMI: ST-elevation myocardial infarction
VSA: vasospastic angina

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References

1. Knapp FF, Jr., Goodman MM, Kabalka GW, Sastry KA. Synthesis and evaluation of radioiodinated (E)-18-iodo-17-octadecenoic acid as a model iodoalkenyl fatty acid for myocardial imaging. J Med Chem 1984; 27: 94–7.
2. Hosokawa R, Nohara R, Fujibayashi Y, et al. Myocardial kinetics of iodine-123-BMIPP in canine myocardium after regional ischemia and reperfusion: implications for clinical SPECT. J Nucl Med 1997; 38: 1857–63.
3. Fujibayashi Y, Yonekura Y, Takemura Y, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analogue, iodine-125-15-(p-iodophenyl) -3-(R, S) methylpentadecanoic acid (BMIPP), in relation to ATP concentration. J Nucl Med 1990; 31: 1818–22.
4. Schelbert HR, Henze E, Phelps ME, Kuhl DE. Assessment of regional myocardial ischemia by positron-emission computed tomography. Am Heart J 1982; 103: 588–97.
5. Schwaiger M, Schelbert HR, Ellison D, et al. Sustained regional abnormalities in cardiac metabolism after transient ischemia in the chronic dog model. J Am Coll Cardiol 1985; 6: 336–47.
6. Dilsizian V, Bateman TM, Bergmann SR, et al. Metabolic imaging with β-methyl-*p*-[^{123}I]-iodophenyl-pentadecanoic acid identifies ischemic memory after demand ischemia. Circulation 2005; 112: 2169–74.
7. Kawai Y, Tsukamoto E, Nozaki Y, Morita K, Sakurai M, Tamaki N. Significance of reduced uptake of iodinated fatty acid analogue for the evaluation of patients with acute chest pain. J Am Coll Cardiol 2001; 38: 1888–94.
8. Kontos MC, Dilsizian V, Weiland F, et al. Iodofiltic acid I 123 (BMIPP) fatty acid imaging improves initial diagnosis in emergency department patients with suspected acute coronary syndromes: A multicenter trial. J Am Coll Cardiol 2010; 56: 290–9.
9. Nanasato M, Hirayama H, Ando A, et al. Incremental predictive value of myocardial scintigraphy with ^{123}I-BMIPP in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. Eur J Nucl Med Mol Imaging 2004; 31: 1512–21.
10. Nakata T, Hashimoto A, Kobayashi H, et al. Outcome significance of thallium-201 and iodine-123-BMIPP perfusion-metabolism mismatch in preinfarction angina. J Nucl Med 1998; 39: 1492–9.
11. Franken PR, Dendale P, De Geeter F, Demoor D, Bossuyt A, Block P. Prediction of functional outcome after myocardial infarction using BMIPP and sestamibi scintigraphy. J Nucl Med 1996; 37: 718–22.
12. Fukuoka R, Horita Y, Namura M, et al. Serial changes in glucose-loaded ^{18}F-fluoro-2-deoxyglucose positron emission tomography, ^{99m}Tc-tetrofosmin and ^{123}I-beta-methyl-p-iodophenyl-penta-decanoic acid myocardial single-photon emission computed tomography images in patients with anterior acute myocardial infarction. Circ J 2013; 77: 137–45.
13. Tamis-Holland JE, Jneid H, Reynolds HR, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: A scientific statement from the American Heart Association. Circulation 2019; 139: e891–e908.
14. Sueda S. Clinical usefulness of myocardial scintigraphy in patients with vasospastic angina. J Cardiol 2020; 75: 494–9.
15. Ito T, Tanouchi J, Kato J, et al. Recovery of impaired left ventricular function in patients with acute myocardial infarction is predicted by the discordance in defect size on ^{123}I-BMIPP and ^{201}Tl SPET images. Eur J Nucl Med 1996; 23: 917–23.
16. Seki H, Toyama T, Higuchi K, et al. Prediction of functional improvement of ischemic myocardium with ^{123}I-BMIPP SPECT and ^{99m}Tc-tetrofosmin SPECT imaging: A study of patients with large acute myocardial infarction and receiving revascularization therapy. Circ J 2005; 69: 311–9.
17. Nishimura T, Nishimura S, Kajiya T, et al. Prediction of functional recovery and prognosis in patients with acute myocardial infarction by ^{123}I-BMIPP and ^{201}Tl myocardial single photon emission computed tomography: A multicenter trial. Ann Nucl Med 1998; 12: 237–48.
18. Yamabe H, Abe H, Yokoyama M, et al. Resting ^{123}I-BMIPP scintigraphy in diagnosis of effort angina pectoris with reference to subsets of the disease. Ann Nucl Med 1998; 12: 139–44.
19. Takeishi Y, Sukekawa H, Saito H, et al. Clinical significance of decreased myocardial uptake of ^{123}I-BMIPP in patients with stable effort angina pectoris. Nucl Med Commun 1995; 16: 1002–8.
20. Hatano T, Chikamori T, Usui Y, Morishima T, Hida S, Yamashina A. Diagnostic significance of positive I-123 BMIPP despite negative stress Tl-201 myocardial imaging in patients with suspected coronary artery disease. Circ J 2006; 70: 184–9.
21. Elsässer A, Schlepper M, Klövekorn WP, et al. Hibernating myocardium: An incomplete adaptation to ischemia. Circulation 1997; 96: 2920–31.
22. Fukuzawa S, Ozawa S, Shimada K, Sugioka J, Inagaki M. Prognostic values of perfusion-metabolic mismatch in Tl-201 and BMIPP scintigraphic imaging in patients with chronic coronary artery disease and left ventricular dysfunction undergoing revascularization. Ann Nucl Med 2002; 16: 109–15.