Metabolic Planar Imaging Using $^{123}$I-β-Methyl-Iodophenyl Pentadecanoic Acid Identifies Myocardial Ischemic Memory After Intracoronary Acetylcholine Provocation Tests in Patients With Vasospastic Angina

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**Summary**

The aim of this study was to determine the diagnostic accuracy of early/delayed $^{123}$I-β-methyl-iodophenyl pentadecanoic acid ($^{123}$I-BMIPP) planar images to detect disrupted fatty acid metabolism in patients with vasospastic angina (VSA). Heart-to-mediastinum (H/M) ratios and washout rates were calculated from early and late (15 minutes and 4 hours after tracer injection, respectively) planar $^{123}$I-BMIPP images from 13 hypertensive control individuals (mean age, 69.5 years) and 37 patients with VSA (mean age, 62.8 years) 10.5 (mean) days after administering the intracoronary acetylcholine provocation test. Patients with VSA had significantly lower early H/M and delayed H/M ratios (early; 2.2 ± 0.3 versus 2.7 ± 0.5, P = 0.007; delayed: 1.8 ± 0.3 versus 2.4 ± 0.4, P < 0.001) and significantly greater washout rates (39.8 ± 11.8% versus 29.3 ± 11.7%, P = 0.011) than controls. The overall area under the curve defining the accuracy of diagnostic performance was 0.76 (95% confidence interval (CI): 0.59-0.92) and 0.85 (95% CI, 0.73-0.98) for the early and delayed H/M ratios and 0.74 (95% CI, 0.73-0.90) for washout rates. Planar $^{123}$I-BMIPP imaging can diagnose coronary artery spasm with acceptable diagnostic performance and indicates that the delayed H/M ratio has a powerful ability to assess recent ischemia. This technique might be useful in the face of apparently normal coronary angiographic findings during the subacute and chronic phases after ischemic events. (Int Heart J 2014; 55: 113-118)

**Key words:** Acute coronary syndrome, Angina pectoris, Angiography, Cardiac catheterization, Cardiovascular disease, Coronary angiography, Heart, Ischemic heart disease, Myocardial ischemia, Variant angina

Fatty acid metabolism is a major pathway of energy production in the normally perfused myocardium. Ischemia caused by reduced coronary blood flow shifts the substrate, which elevates glucose uptake (anaerobic) while fatty acid uptake remains reduced (aerobic). The persistence of altered fatty acid metabolism even after the restoration of blood flow is termed ischemic memory. $^{12}$ $^{123}$I-β-methyl-iodophenyl pentadecanoic acid ($^{123}$I-BMIPP) is a useful tracer with which to identify myocardial ischemic memory because of its high myocardial uptake and prolonged retention. $^{12}$ Imaging using $^{123}$I-BMIPP single-photon emission computed tomography (SPECT) can detect vasospasm more accurately than rest-exercise tetrofosmin scintigraphy and defects on $^{123}$I-BMIPP SPECT images disappear from patients with vasospastic angina (VSA) who respond well to therapy. The intracoronary acetylcholine (ACH) provocation test is the standard procedure for diagnosing VSA despite this test being invasive and complications such as sustained ventricular tachycardia, shock and cardiac tamponade occasionally arise. Takagi, et al have reported ventricular tachycardia/fibrillation developed at a rate of 3.2% during the provocation test in a nationwide multicenter Japanese registry in patients with VSA. Thus, a noninvasive test should be established to identify vasospastic angina. Global myocardial fatty acid metabolism assessed by $^{123}$I-BMIPP using planar imaging is useful, and the severity of myocardial dysfunction is accurately reflected in the delayed heart-to-mediastinum (H/M) ratio in patients with heart disease. However, whether or not planar $^{123}$I-BMIPP imaging can accurately detect disrupted fatty acid metabolism in patients with VSA has not been fully evaluated. The present study attempted to determine whether or not $^{123}$I-BMIPP-planar imaging can detect abnormal fatty acid metabolism after ischemic attack caused by coronary artery spasm.

**Methods**

**Study participants:** We initially enrolled 49 patients with...
VSA who were admitted to the St. Marianna University School of Medicine Hospital between April 2007 and August 2009. We defined VSA as chest pain at rest with or without ST segment changes and ≥ 90% luminal narrowing in the ACH provocation test. Among the study patients, 12 were excluded due to problems with the ACH provocation test \( n = 2 \), abnormal Q waves in electrocardiograms \( n = 2 \), left ventricular ejection fraction (LVEF) < 50% \( n = 2 \), refusal to participate \( n = 5 \), and untreated renal cancer \( n = 1 \). Therefore, 37 patients with VSA including 10 (27%) current smokers were included in the study. The patients were basically treated with sublingual fast- and short-acting nitrates (nitroglycerin) for ischemic attack after the test. Of these, 40.5% who were prescribed calcium antagonists before enrolment could continue them during the study period. Calcium antagonists were withdrawn at least 48 hours before the ACH provocation test to ensure its validity. This study included 13 hypertensive volunteers as controls who underwent exercise stress testing using a treadmill to confirm the absence of ischemic ST-T changes. Hypertension was defined as a systolic blood pressure of 140 mmHg or a diastolic blood pressure DBP of 90 mmHg or receiving antihypertensive therapy. Individuals with structural heart diseases were excluded from the study based on echocardiographic findings. This study was performed in accordance with the ethical principles established in the Declaration of Helsinki. The St. Marianna University School of Medicine Institutional Committee on Human Resources (Kawasaki, Japan) approved the study protocol. The nature and purpose of the study and the risks involved were fully explained to all participants, who then provided written informed consent to participate in all procedures associated with the study.

**Provocation test for coronary vasospasm:** Two experts performed multidirectional coronary angiography in all patients with VSA using a Judkins catheter. A temporary pacing lead was inserted into the right ventricle of each patient and set at a pacing rate of 40 beats/min. An incremental dose of ACH was injected every 30 seconds (up to 50 and 100 μg into the right and left coronary arteries, respectively). Coronary arteriography was performed if the ST segment changed and/or chest pain developed at 3 minutes after each injection. Induced coronary vasospasm that did not spontaneously terminate was released by administering isosorbide dinitrate (1 - 2 mg) via the intracoronary catheter. The provocation test proceeded to the contralateral coronary artery even when right coronary artery spasm was induced. We defined VSA as luminal diameter narrowing of ≥ 90%.

**123I-BMIPP myocardial scintigraphic images:** 123I-BMIPP images were typically acquired two weeks after the ACH provocation test (mean, 10.5 days). Planar images were acquired at 15 minutes (early) and at 4 hours (delayed) after injecting 123I-BMIPP (111 MBq; Nihon Medi-Physics, Tokyo) into the left antecubital vein. Before the SPECT study, we acquired anterior and lateral planar images for 90 seconds using a double-head gamma camera (E.CAM Duet, Toshiba Medical, Tokyo) with a low-energy and general-purpose collimator, as well as a gamma camera with a low-energy, general-purpose collimator and a 256 × 256 matrix. Two detectors (2 × 180°) acquired 60 views for 19 seconds in 6° increments using a 64 × 64 matrix. Energy discrimination was centered at 160 keV with a 20% window. Transaxial images were reconstructed after filtered back projection using a Butterworth filter (order 8; cut-off frequency 0.27 cycles/pixel) combined with a ramp filter. Horizontal long-axis, vertical long-axis, and short-axis slices were generated after reorienting the axes.

**Blood sampling and echocardiography:** Blood samples were collected before breakfast. Brain natriuretic peptide (BNP) was measured using a fluorescent enzyme immunoassay and total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and HbA1c were measured using standard assays. Left ventricular volume and LVEF were calculated by Simpson’s rule using echocardiography (Apio®; Toshiba, Tokyo) with a 3.5 MHz transducer. **Data analysis:** Regions of interest (ROI) were drawn over the entire heart and upper mediastinum in the anterior planar images. The H/M ratio and washout rate (WR) of 123I-BMIPP were calculated based on ROI counts as:

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H/M = \frac{\text{mean pixel count of cardiac ROI}}{\text{mean pixel count of mediastinal ROI}}
\]

\[
WR (\%) = \left[\frac{\text{mean early − mean delayed cardiac pixel count}}{\text{mean early cardiac pixel count}}\right] \times 100
\]

We calculated WR without background and/or time delay correction. \(^{12-14}\) Regional tracer uptake was assessed using a 5-point scoring system (0, normal; 1, slightly reduced; 2, mildly reduced; 3, severely reduced; 4, no uptake) on the early and delayed SPECT images. \(^{15}\) The left ventricular myocardium was divided into 17 segments corresponding to the vascular territories of the 3 major coronary arteries. The total defect score (TDS) was calculated as the sum of all defect scores. Two experienced nuclear cardiologists independently interpreted the images. We concluded that abnormal uptake corresponded to coronary territories after finalizing all measurements from regional uptake and conventional coronary angiograms.

**Statistical analysis:** Data are expressed as the mean ± standard deviation. Continuous values and categorical variables between the two groups were compared using the \( t \) test and the \( \chi^2 \) test, respectively. The overall performance of receiver operating characteristic (ROC) analysis was determined by measuring the area under the curve (AUC). Standardized values were defined by dividing the differences between the observed values and the sample means by the corresponding standard deviation. \(^{16}\) Smoothing curves were computed by LOWESS regression in STATA statistical software (Version 11. College Station, TX, USA). The estimated nonparametric curves were plotted with connect. The level of statistical significance was set at \( P < 0.05 \). All data were analyzed using STATA statistical software Version 11.

**Results**

The baseline clinical characteristics in the control and VSA groups (Table I) were similar except for the rate of hypertension. Blood chemistry, blood pressure, and LVEF did not differ significantly between the two groups (all \( P > 0.1 \)). None of the patients had coronary stents or a > 50% obstructive lesion in any vessel. Among the patients with VSA, 24 and 13 had single (65%) and multivessel (35%) spasm, respectively. The TDS did not differ significantly between the early standard and delayed images (TDS, 8.3 ± 1.0 versus 8.9 ± 1.1, \( P = 0.334 \)). Abnormalities in the early \( (n = 24, 65\%) \) and delayed \( (n = 27, 73\%) \) SPECT images corresponded to the coronary ar-
Early and delayed ratios of H/M and WR assessed by planar imaging: Figure 1 shows the early and delayed H/M ratios and WR in the control and VSA groups. The early and delayed H/M ratios significantly differed between the control and VSA groups (early: 2.7 ± 0.5 versus 2.2 ± 0.3, P = 0.007; delayed: 2.4 ± 0.4 versus 1.8 ± 0.3, P < 0.001). The WR was significantly greater in the VSA group (39.8 ± 11.8%) than in the control group (29.3 ± 11.7%, P = 0.011). Figure 2 shows the relationship between SPECT with H/M ratios and WR in patients with VSA using a local linear smoothing curve. Some patients with lower TDS had lower H/M ratios and greater WR.

Diagnosis of VSA based on planar images: Table II and Figure 3 show the diagnostic performance of 123I-BMIPP planar imaging. The overall AUC defining the accuracy of diagnostic performance was 0.76 (95% confidence interval [CI]: 0.59-0.92) and 0.85 (95% CI, 0.73-0.98) for the early and delayed H/M ratios and 0.74 (95% CI, 0.73-0.90) for washout rates. The AUC for the delayed H/M ratios in the subacute (≤ 14 days) and chronic phases (15 – 30 days) were 0.91 (95% CI, 0.73-0.99) and 0.84 (95% CI, 0.68-0.99), respectively. Figure 4 shows the associations among the findings obtained from planar 123I-BMIPP images with LVEF and log BNP and Figure 5 shows two examples of 123I-BMIPP images.

**Discussion**

We found that patients with VSA had lower H/M ratios and greater WR than hypertensive controls. Planar cardiac 123I-BMIPP imaging accurately identifies global ischemic memory caused by recent coronary artery spasm after the intracoronary acetylcholine provocation test. An area under the ROC curve of 0.85 is consistent with acceptable diagnostic performance and indicates that the delayed H/M ratio has a powerful ability to assess recent ischemia.

123I-BMIPP SPECT imaging abnormalities: Abnormal 123I-BMIPP SPECT uptake corresponded to the coronary territories in about 70% of patients. Watanabe, et al. 17 demonstrated 71% and 95% sensitivity and specificity of 123I-BMIPP imaging for detecting vasospasm at two weeks before catheterization. Our results using SPECT were relatively lower than these values. Among their study population, 38% had reduced wall motion.
with territorial regions that are more likely to correspond with the coronary territories. Our patients with VSA in the absence of wall motion abnormalities might have had relatively mild ischemic attacks. Others have described excellent patient-level agreement (90%) between \(^{123}\)I-BMIPP and thallium SPECT data up to 30 hours after stress-induced ischemic episodes, and regional \(^{123}\)I-BMIPP SPECT abnormalities in 59% of patients two days after the most recent episode of chest pain. One experimental study has found that \(^{123}\)I-BMIPP uptake in ischemic territories recovers during the chronic phase (30 days). Accordingly, time-dependent metabolic changes considerably affect the findings obtained from SPECT images. Compared with atherosclerosis, coronary spasm can assume several forms and unique phenomena such as multiple spasms, repeated chest pain, and silent ischemia. Reduced uptake persists in a specific region, resulting in overlapping or abnormal \(^{123}\)I-BMIPP uptake in other regions due to repeated spasms. Conventional angiography cannot detect microvascular alterations because of system limitations. If \(^{123}\)I-BMIPP can detect microvascular disturbances, then the theory of conventional blood supply to the coronary territories might not be ap-

| Table II. Diagnostic performance of \(^{123}\)I-BMIPP |
|-----------------|--------------|-----------------|-----------------|
|                | AUC (95%CI)  | Cut off value   | Sensitivity (%) | Specificity (%) |
| Overall        |              |                |                 |                 |
| Early H/M ratio| 0.76 (0.59-0.92)* | 2.3            | 59.5            | 76.9            |
| Delayed H/M ratio | 0.85 (0.73-0.98)* | 2.0            | 73.0            | 84.6            |
| Washout rate (%) | 0.74 (0.73-0.90)* | 36.7           | 70.3            | 69.6            |
| Subacute phase (≤ 14 days) |          |                |                 |                 |
| Early H/M ratio | 0.78 (0.61-0.96)* | 2.3            | 64.3            | 77.9            |
| Delayed H/M ratio | 0.91 (0.73-0.99)* | 2.0            | 85.7            | 84.6            |
| Washout rate (%) | 0.81 (0.64-0.99)* | 38.7           | 78.6            | 84.6            |
| Chronic phase (15 - 30 days) |          |                |                 |                 |
| Early H/M ratio | 0.75 (0.56-0.94) | 2.3            | 57.1            | 61.5            |
| Delayed H/M ratio | 0.84 (0.68-0.99)* | 2.0            | 71.4            | 84.6            |
| Washout rate (%) | 0.78 (0.59-0.97)* | 38.0           | 78.6            | 76.9            |

*P < 0.05 for difference between AUC and null hypothesis of true area = 0.5. AUC indicates area under the curve; CI, confidence interval; H/M, heat to mediastinum ratio; and VSA, vasospastic angina.
applicable. These may affect negative correspondence with the coronary territories. Notably, some of our patients with VSA had lower H/M ratios and a greater WR despite a lower TDS, indicating that fatty acid metabolism might recover on SPECT images whereas the H/M ratios and WR values obtained from planar imaging would still indicate disrupted fatty acid metabolism. Thus, global fatty acid metabolism might be considered when assessing ischemic memory in patients with VSA. The discrepancy may be explained by adequate accuracy of SPECT imaging in multivessel disease. We speculated that the prevalence of single/multi spasms might confound the relation of TDS with the H/M ratio and WR. However, we could not find any data to explain the discrepancy from our data with the small sample in the present study. We believe that what appears to be a reduced H/M ratio or increased WR can be more simply explained by the planar 123I-BMIPP imaging in VSA.

**Diagnosis of VSA using 123I-BMIPP planar imaging:** We found significant differences in the early and delayed H/M ratios between the control and VSA groups, and the overall AUC was 0.85 for the delayed H/M ratio. The accumulation rate of 123I-BMIPP in the myocardium at 4 hours after tracer injection is about 5%, which is higher than that of 201Thallium. Kobayashi, et al reported that rapid washout due to back-diffusion (positive washout) in myocytes with impaired fatty acid metabolism results in a mismatch between reduced uptake on 123I-BMIPP images and coronary perfusion on 201Thallium images. Delayed H/M ratios are considered useful for assessing the disordered myocardium in several heart diseases and might accurately reflect impaired fatty acid metabolism. Some investigators have noted that an increased WR of 123I-BMIPP identifies cardiac disease. The severities of the H/M ratios and WR were associated with LVEF but BNP, respectively the present study. Delayed H/M ratios and WR of 123I-BMIPP correlate with LVEF and BNP in patients with chronic heart failure. Accordingly, our findings support the notion that dysfunctional global fatty acid metabolism assessed using planar imaging is closely associated with global left ventricular function. The BNP level in the present study was typically below 50 pg/dL, which is relatively lower than in critical heart failure. We speculate that the traditional risk factors of age, gender, hypertension, and diabetes may confound the relation of BNP level with impaired fatty acid metabolism in VSA.

**Study limitations:** The difference in the rates of hypertension between the controls and patients with VSA was substantial. The uptake of 123I-BMIPP was significantly lower in patients with VSA than in hypertensive controls, although myocardial fatty acid metabolism in the hypertensive heart is considered abnormal. The H/M ratios and washout rate may have been affected by the extension, severity, duration of spasm, and medication. The discrepancy between the SPECT and planar imaging must be considered, however, no data to explain the discrepancy in the present study is also a limitation. Thus, further assessment is needed to evaluate the potential of the discrepancy in the VSA.

**Conclusion:** 123I-BMIPP Planar imaging can also diagnose coronary artery spasm with acceptable diagnostic performance and indicates that the delayed H/M ratio has a powerful ability to assess recent ischemia. This technique might be useful in the face of apparently normal coronary angiographic findings during the subacute and chronic phases after ischemic events.

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**References**


