Original Article

Association between the Clinical Incidence of Cardiac Risk and ^{123}I-Betamethyl-*p*-Iodophenyl-Pentadecanoic Acid Single-Photon Emission Computed Tomography in Patients with Vasospastic Angina

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ABSTRACT

Introduction: ^{123}I-Betamethyl-*p*-iodophenyl-pentadecanoic acid single-photon emission computed tomography (^{123}I-BMIPP-SPECT) is a myocardial fatty acid metabolism imaging technique that has been found to be effective in identifying high-risk patients with known ischemic heart disease. However, its efficacy in assessing vasospastic angina (VA) remains unclear. Hence, in this current study, we aimed to evaluate the association between ^{123}I-BMIPP-SPECT parameters and the clinical incidence of cardiac risk in VA.

Methods: Among the 71 consecutive patients admitted to our hospital for ischemic heart disease who underwent ^{123}I-BMIPP-SPECT, 63 (mean age: 59 ± 12 years) were diagnosed with VA based on invasive coronary angiography and/or clinical examination findings. ^{123}I-BMIPP-SPECT parameters, such as extent and severity scores and washout rate (WR), were calculated using ^{123}I-BMIPP-SPECT data. A multivariate logistic regression model was then used to determine the correlation between ^{123}I-BMIPP-SPECT parameters and major adverse cardiac events (MACEs), including cardiac death, defined as death caused by heart failure (HF), acute myocardial infarction, lethal ventricular arrhythmias, or other definitive cardiac disorders; cardiovascular events (nonfatal acute myocardial infarction, unstable angina pectoris, and arrhythmia requiring hospitalization); and severe HF requiring hospitalization and implantable cardioverter-defibrillator treatment.

Results: Total 16 out of the 63 patients have reportedly experienced MACEs. Moreover, our results showed that a higher ^{123}I-BMIPP WR was associated with an increased incidence of MACEs (odds ratio: 5.105, 95% confidence interval 1.503-17.344, $p = 0.009$).

Conclusions: The findings of this current study show that ^{123}I-BMIPP-SPECT WR may be associated with the clinical incidence of cardiac risk in patients with VA.

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KEYWORDS: vasospastic angina, ^{123}I-betamethyl-*p*-iodophenyl-pentadecanoic acid single-photon emission computed tomography, major adverse cardiac event, incidence

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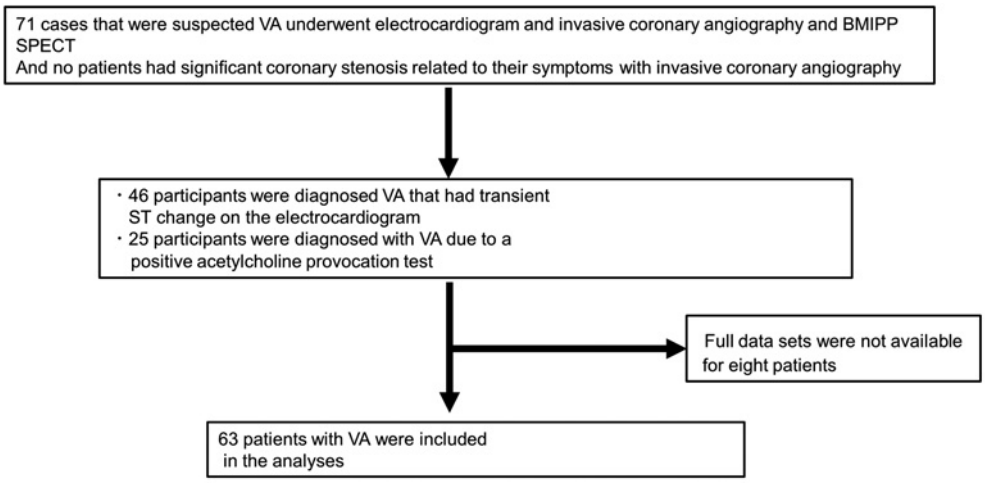

Fig. 1 Flowchart of patient inclusion and exclusion. ^{123}I-BMIPP, ^{123}I-betamethyl-*p*-iodophenylpentadecanoic acid; SPECT, single-photon emission computed tomography; VA, vasospastic angina.

Introduction

Patients with vasospastic angina (VA) have shown good prognosis following calcium antagonist therapy.[1] Although most patients with VA are at low risk, approximately 10% experience nonfatal myocardial infarction or cardiac death.[2] Therefore, identifying patients with VA who are at a high risk for such events is imperative.

Myocardial perfusion imaging has been identified as a key technique for assessing the risk of cardiovascular events in patients with suspected coronary artery disease.[3] In line with this, ^{123}I-betamethyl-*p*-iodophenylpentadecanoic acid (^{123}I-BMIPP) single-photon emission computed tomography (SPECT) has been proven effective for the diagnosis and risk stratification of patients with coronary artery disease, with extensive research regarding its prognostic value in patients with ischemic heart disease.[4] ^{123}I-BMIPP-SPECT is known for its better sensitivity for identifying coronary spasm compared to resting or stress myocardial perfusion imaging. Moreover, some studies have shown that the incidence of chest pain is lower in patients with better ^{123}I-BMIPP activity, which may be useful in diagnosing VA and determining appropriate follow-up treatment.[5, 6] However, to the best of our knowledge, no study has yet examined the impact of ^{123}I-BMIPP-SPECT parameters on the clinical incidence of cardiac risk in VA. Considering that VA can induce myocardial ischemia owing to coronary spasm, it may cause myocardial fatty acid metabolic dysfunction, which can then be associated with the clinical incidence of cardiac risk in VA. Therefore, this current study examined the association between ^{123}I-BMIPP-SPECT washout rate (WR) and the clinical incidence of cardiac risk in VA.

Methods

Patient population

In total, 71 consecutive patients hospitalized due to chest pain, loss of consciousness, or an abnormal electrocardiography (ECG) reading were included in this study. All patients were diagnosed with VA and underwent ^{123}I-BMIPP-SPECT between May 2003 and April 2015. The procedure was performed within 25 days from hospitalization (mean: 7.5 ± 6.5 days). All participants were subjected to invasive coronary angiography, and none had significant stenosis in the coronary arteries.

Among the 71 patients, 46 were diagnosed with VA based on ECG changes (12-lead ECG, n = 40; monitoring ECG, n = 3; and exercise ECG, n = 3) upon the occurrence of angina-like attacks. The condition of 25 patients was determined via invasive coronary angiography with acetylcholine. Ultimately, 63 patients were enrolled in this study after excluding 8 with lacking data (Fig. 1). Takotsubo cardiomyopathy, microvascular angina, pheochromocytoma, and myocarditis were ruled out based on interview responses, physiological examination results, and blood biochemical data. Clinical characteristics, including age, sex, coronary risk factors, blood biochemical data, echocardiography results, and drug treatment, were also assessed.

This retrospective study was approved by the Ethics Committee of Toho University Omori Medical Center. The

study design was approved by the institutional ethics committee after a document with an opt-out policy allowing all patients and/or relatives to refuse participation was uploaded on the web page of Toho University (M20133).

VA diagnosis

The diagnosis of VA was considered definite when the transient ST elevation was ≥ 0.1 mV, the ST depression was ≥ 0.1 mV, or a negative U-wave at two or more relevant leads newly appeared on a 12-lead ECG upon the occurrence of an angina-like attack.

Despite observing no evident ischemic changes on ECG, VA was diagnosed when the patient experienced an angina-like attack that resolved immediately following the administration of nitroglycerine, when the coronary spasm provocation test during cardiac catheterization yielded a positive result, and when the patient satisfied at least one of the following four criteria: angina-like attack that appeared at rest, particularly between night and early morning; exercise tolerance showing significant diurnal variation (particularly reduced exercise capacity in early morning); attacks caused by hyperventilation (hyperpnoea); and attacks suppressed by calcium channel blockers but not β-blockers.[7, 8)]

Invasive coronary angiography

All participants underwent invasive coronary angiography performed by experienced interventionalists based on the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[9)] Using this technique, coronary stenosis was defined as a stenosis diameter of >50%.

Patients without stenosis associated with their symptoms underwent the acetylcholine-induced coronary spasm provocation test, during which acetylcholine was incrementally administered directly into the left and right coronary arteries at doses of 20, 50, and 100 μg. A positive acetylcholine provocation test finding was defined as a transient total or subtotal occlusion (>90% stenosis).[8, 10–12)]

Echocardiographic imaging

Echocardiographic images were obtained from the parasternal window to evaluate left ventricular function (Vivid E9 device, GE Vingmed, Horten, Norway). The left ventricular ejection fraction (LVEF) was calculated using the Teichholz formula.[13)]

^{123}I-BMIPP-SPECT

Patients fasted for at least 3 h prior to ^{123}I-BMIPP-SPECT and during the period between early and late imaging. ^{123}I-BMIPP (111 MBq) was administered while patients were resting. ^{123}I-BMIPP-SPECT data were acquired starting from 20 min (early image) to 240 min (delayed image) after ^{123}I-BMIPP administration using a triple-head gamma camera (Prism IRIX, Shimadzu Corporation, Kyoto, Japan) equipped with low-energy general-purpose collimators. Data were acquired at 360° in 72 steps for 37.5 s each in a 64 × 64 matrix. Images were subsequently processed using a Butterworth filter (order: 8.0, cutoff value: 0.25 cycle/pixel) and reconstructed using a filtered back projection.

^{123}I-BMIPP-SPECT parameters

This study used an automated program for myocardial SPECT (Odyssey, Shimadzu Medical Systems, Osaka, Japan) to calculate the extent and severity scores and WR. For a quantitative analysis of ^{123}I-BMIPP-SPECT images, polar maps of the left ventricle from the apex to the base were created from images in the short axis direction. Thereafter, polar maps were established using data obtained from healthy participants at our hospital to determine the normal range (mean ± 2 SD) of ^{123}I-BMIPP uptake, which was defined as the mean ± 2 SD of ^{123}I-BMIPP uptake in the left ventricular myocardium and extent score in the region with an uptake below −2 SD. Severity score was then calculated based on disease severity. The extent score was calculated as follows: [total number of abnormal cardiac pixel count areas over 17 segments compared to that in the normal database at 20 min after ^{123}I-BMIPP administration]/[total number of areas] × 100. The severity score was calculated as follows: [total difference in cardiac pixel counts of abnormal areas over 17 segments compared to that in the normal database at 20 min after ^{123}I-BMIPP administration]/[total number of areas] × 100. WR (%) was calculated as follows: [mean cardiac pixel counts of ^{123}I-BMIPP at 20 min after ^{123}I-BMIPP injection-mean cardiac pixel counts of ^{123}I-BMIPP at 240 min after ^{123}I-BMIPP injection]/[mean cardiac pixel counts of ^{123}I-BMIPP at 20 min after ^{123}I-BMIPP injection] × 100. The normal WR of ^{123}I-BMIPP-SPECT was based on the report of Miyauchi et al.[14)]

Assessing the clinical incidence of cardiac risk in VA

The end point of this current study was the occurrence of major adverse cardiac events (MACEs), which included cardiac death caused by HF, acute myocardial infarction, fatal ventricular arrhythmia, or other definitive cardiac disorders; cardiovascular events (nonfatal acute myocardial infarction, unstable angina, and arrhythmia requiring hospitalization); severe HF requiring hospitalization; and

Table 1 Characteristics of all the study subjects with or without MACEs

	Total (n = 63)	With MACEs (n = 16)	Without MACEs (n = 47)	*P*-value
Age (years)	59 ± 12	60 ± 11	59 ± 12	0.994
Male (%)	50 (79)	14 (88)	36 (77)	0.352
Obesity (BMI ≥ 25 kg/m^2)	18 (29)	4 (25)	14 (30)	0.714
BMI (kg/m^2)	23.3 ± 3.4	22.9 ± 3.3	23.4 ± 3.5	0.653
Diabetes mellitus	10 (16)	5 (31)	5 (11)	0.051
Hypertension	35 (56)	9 (56)	26 (55)	0.821
Dyslipidemia	30 (48)	7 (44)	23 (50)	0.720
Current smoking	42 (67)	10 (63)	32 (68)	0.682
CKD (eGFR < 60 mL/min/1.73 m^2)	15 (24)	7 (44)	8 (17)	0.030
Max troponin (ng/mL)	8.2 ± 26.4	4.8 ± 7.8	9.4 ± 30.2	0.968
Max CK-MB (U/L)	41.1 ± 73.1	34.8 ± 26.0	43.2 ± 83.4	0.097
BNP (pg/mL)	81.9 ± 127.6	90.0 ± 138.6	75.3 ± 118.6	0.597
Echocardiography				
LVEF (%)	68.1 ± 8.2	68.4 ± 9.1	68.0 ± 8.0	0.658
LVEDV (mL)	110.5 ± 33.6	113.7 ± 29.9	109.4 ± 35.2	0.705
LVESV (mL)	35.3 ± 15.4	36.8 ± 17.5	34.8 ± 14.8	0.962
Medication before Admission				
B-Blocker	5 (8)	1 (6)	4 (9)	0.773
Calcium blocker	21 (33)	7 (44)	14 (30)	0.306
ACEI and ARB	14 (22)	5 (31)	9 (19)	0.315
Statins	9 (14)	1 (6)	8 (17)	0.288
Medication after Discharge				
B-Blocker	3 (5)	0 (0)	3 (6)	0.300
Calcium blocker	63 (100)	16 (100)	47 (100)	–
ACEI and ARB	22 (35)	5 (31)	17 (36)	0.721
Statins	33 (52)	6 (38)	27 (57)	0.168
^{123}I-BMIPP-SPECT				
Extent score (%)	16.9 ± 14.4	13.8 ± 7.4	17.9 ± 16.0	0.912
Severity score (%)	14.7 ± 23.5	11.3 ± 19.7	15.9 ± 24.7	0.886
WR (%)	35.9 ± 7.2	41.4 ± 6.6	34.1 ± 6.5	< 0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; ^{123}I-BMIPP-SPECT, ^{123}I-betamethyl-p-iodphenyl-pentadecanonic acid single-photon emission computed tomography; BNP, brain natriuretic peptide; CKD, chronic kidney disease; CK-MB, creatine kinase-myocardial band; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MACE, major adverse event; WR, washout rate

Continuous variables were analyzed using Mann–Whitney U test, and that of categorical data were examined using chi-square test.

A *p*-value < 0.05 was considered to be statistically significant.

treatment with an implantable cardioverter defibrillator (ICD). Event data were collected retrospectively from the patients' medical records, including in-hospital or out-of-hospital reports. Only the initial event was counted, even when patients experienced several cardiac events during the follow-up period.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation and compared between patients with and without events using Mann-Whitney *U* test. Categorical data were analyzed using chi-square test. Variables, including sex, age, and other factors, determined to be significant ($p < 0.05$) during univariate analysis were included in multivariate logistic regression models to identify factors associated with the incidence of MACEs. The cutoff WR was determined via area under the receiver op-

erating characteristic curve (AUC-ROC) analysis based on the incidence of MACEs. All statistical analyses were performed using the StatMate V software version 5.01 (Advanced Technology for Medicine and Science, Tokyo, Japan), with a *p*-value of <0.05 indicating statistical significance.

Results

Table 1 presents the patients' characteristics, including coronary risk factors; troponin, creatine kinase-myocardial band, and brain natriuretic peptide levels; and LVEF values calculated on echocardiography, medications administered, and ^{123}I-BMIPP-SPECT parameters. The mean age of the patients (n = 63) was 59 ± 12 years, and 50 (79%) patients were men.

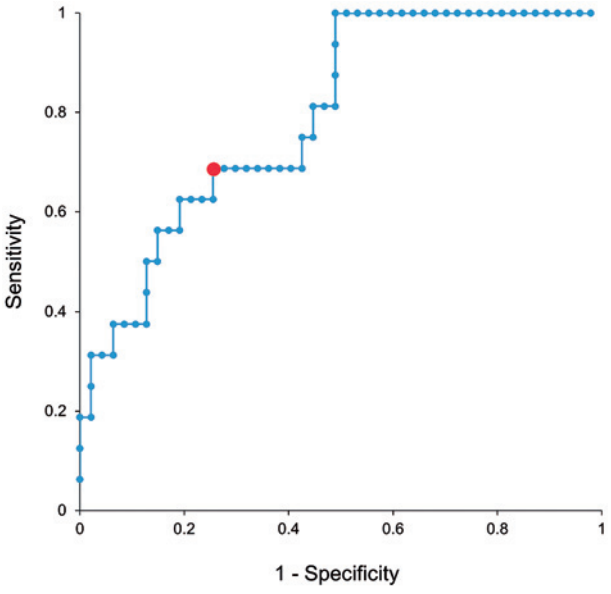

Fig. 2 Receiver operating characteristic curve for the occurrence of major adverse cardiac events based on the cutoff washout rate (WR). The cutoff WR in the high-WR group was 39%, while the area under the receiver operating characteristic curve was 0.79.

In total, 22 patients presented with wall motion abnormalities on echocardiography, whereas 41 did not. Thereafter, 56 patients with a mean ejection fraction of 65.8% underwent left ventriculography, among whom 35 were determined to have wall motion abnormalities.

In total, 16 (25%) patients experienced MACEs at a median follow-up of 4.8 ± 4.7 years. Additionally, five patients died due to cardiac deaths from ischemic heart disease (n = 2) and HF (n = 3), among whom four died out-of-hospital (two died at home after outpatient visit for chest pain and two died of HF while being admitted at another hospital). Furthermore, four patients (one with nonfatal acute myocardial infarction, one with severe HF, and two with unstable angina pectoris) required hospitalization. Moreover, seven patients received ICD treatment. As shown in Table 1, patients who experienced MACEs commonly presented with kidney disease or a high WR. Treatment with calcium antagonist upon admission was not associated with the development of MACEs, and all patients diagnosed with VA received this therapy. The AUC-ROC for predicting MACEs based on the WR was 0.794. The cutoff WR in the high-WR group was 39% (Fig. 2). Multivariate logistic regression analysis found that WR was significantly associated with the incidence of MACEs (Table 2).

Case presentations

Fig. 3 presents the data of a 50-year-old man from the high-WR group who was hospitalized due to loss of consciousness caused by ventricular fibrillation. Echocardiography revealed no wall motion abnormalities, while his LVEF was 82.9%. On the 3rd day of hospitalization, ^{123}I-BMIPP-SPECT showed no abnormal accumulation (Fig. 3 A), although his WR was noted to increase, with a score of 48% (Fig. 3B). Cardiac catheterization revealed no significant stenosis, while left ventriculography results came back normal. On the 8th day of hospitalization, acetylcholine-induced coronary spasm provocation tests showed complete occlusion of the right coronary artery.

Table 2 Multivariable logistic regression analysis for the occurrence of MACEs

	Multivariable analysis	
	Odds ratio (CI)	*P*-value
CKD (eGFR$<$60 mL/min/1.73 m^2)	2.640 (0.701–9.938)	0.151
WR ($\geq$39%)	5.105 (1.503–17.344)	0.009

CI, confidence interval; CKD, chronic kidney disease; MACEs, major adverse cardiac events; WR, washout rate

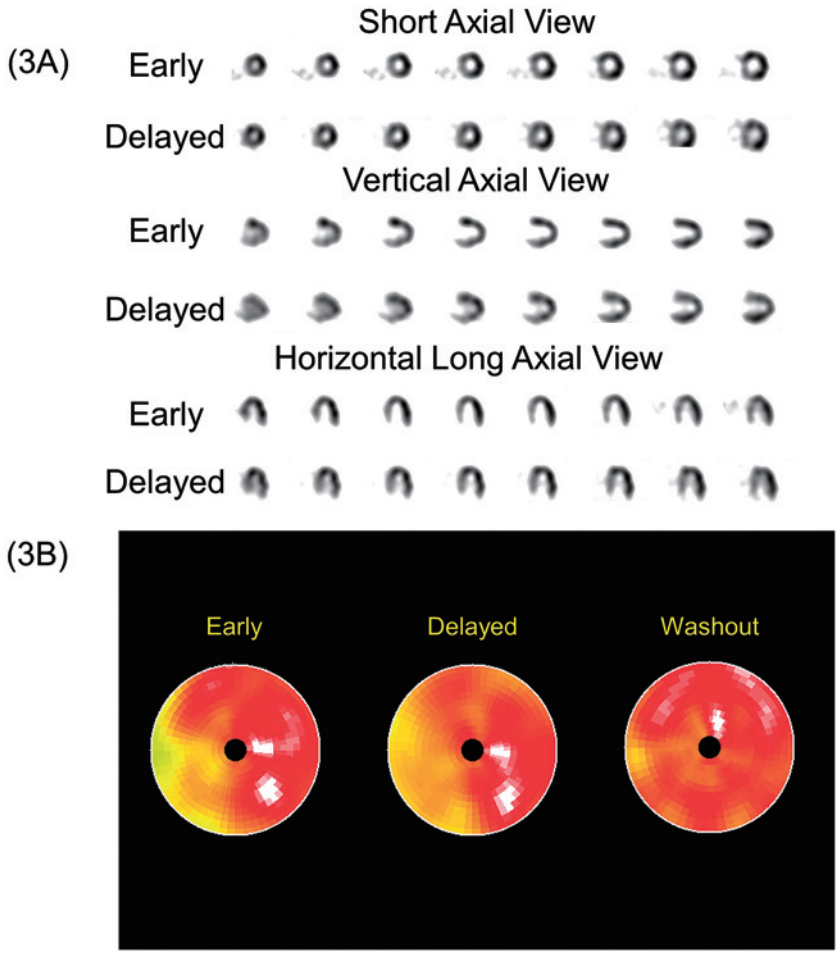

Fig. 3 Polar map display and parameters of ^{123}I-betamethyl-*p*-iodophenyl-pentadecanoic acid single-photon emission computed tomography (^{123}I-BMIPP-SPECT) in a patient from the high-washout rate (WR) group. The patient developed sudden loss of consciousness and was diagnosed with vasospastic angina based on a positive acetylcholine provocation test result. ^{123}I-BMIPP-SPECT images (short axis, vertical, and horizontal long axis images) showed no abnormal accumulation (3A). However, the WR increased to 48% (3B). The patient was admitted to the hospital and underwent implantation of an implantable cardioverter defibrillator.

However, the acetylcholine induction test of the left coronary artery was not performed due to arrhythmia and hypotension. The patient then underwent ICD implantation on the 11th day of hospitalization.

Fig. 4 details the data of an 80-year-old man from the low-WR group who had a history of hypertension and was admitted due to chest and back pains. ECG revealed ST-segment elevations in leads II, III, and aVF and ST-segment depression in leads I, aVL, and V1-6. Echocardiography showed hypokinesis of the inferior wall motion in the left ventricle, with a LVEF of 69.2%. The patient experience reduced chest and back pain immediately after sublingual nitroglycerin administration and improvement in ST elevation on ECG. On the day of hospitalization, coronary artery angiography without acetylcholine-induced coronary spasm provocation tests revealed no significant stenosis. Moreover, left ventriculography showed hypokinesis in the inferior wall. ^{123}I-BMIPP-SPECT on the 4th day of hospitalization revealed decreased accumulation in the posterior wall (Fig. 4A). However, the patient's WR was decreased, with a score of 24% (Fig. 4B). The patient remained event-free for 6 years and 9 months with medication.

Discussion

The findings of this present study demonstrated that

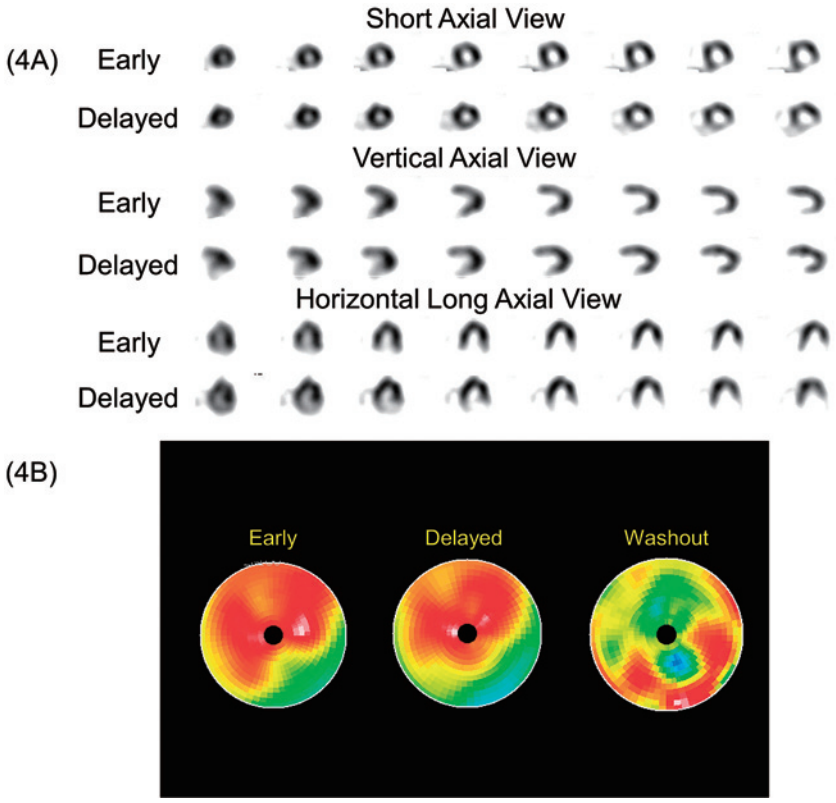

Fig. 4 Polar map display and parameters of ^{123}I-betamethyl-*p*-iodophenyl-pentadecanoic acid single-photon emission computed tomography (^{123}I-BMIPP-SPECT) in a patient from the low-washout rate (WR) group. This patient suffered from chest and back pains. Although electrocardiography revealed ST changes, coronary artery stenosis was not observed on coronary artery angiography. ^{123}I-BMIPP-SPECT images (short axis, vertical, and horizontal long axis images) showed decreased accumulation in the posterior wall (4A). The WR reduced to 28% (4B), and the patient remained event-free for 6 years and 9 months.

the WR of ^{123}I-BMIPP was associated with the incidence of MACEs, suggesting that it might be significantly associated with the clinical incidence of MACEs. In other words, increased ^{123}I-BMIPP-SPECT WR was associated with increased incidence of MACEs.

Mechanisms correlated with a high WR

Several underlying mechanisms correlated with our findings may be considered. First, the ^{123}I-BMIPP-SPECT WR reflects the degree of cardiac damage.[15] Indeed, several investigators in a previous research study had identified altered myocardial fatty acid metabolism in patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, and ischemic HF. Moreover, impaired myocardial fatty acid metabolism had been associated with disease severity.[16–18] Yoneyama et al., who examined the diagnostic accuracy of ^{123}I-BMIPP among patients with VA, demonstrated that heart-to-mediastinum rate and WR during ^{123}I-BMIPP-SPECT were correlated with LVEF and BNP.[19] Therefore, fatty acid metabolism disorders might be associated with the severity of VA. Second, patients with myocardial ischemia exhibited increased ^{123}I-BMIPP-SPECT WR at the later images. Given that catecholamines were no longer secreted and the free fatty acid concentration did not increase after the ischemic state, excess fatty acids must have been washed out of the lipid pool.[20] Moreover, the accelerated washout from the lipid pool into the bloodstream can increase the WR of ^{123}I-BMIPP.

Association between WR and the incidence of cardiac risk in VA

Damage to coronary artery endothelial cells in VA prevents the release of vasodilator nitric oxide (NO), which then induces coronary artery spasm, resulting in myocardial ischemia.[21] Given that myocardial ischemia increases sympathetic nerve activity, Inobe et al. utilized ^{123}I-

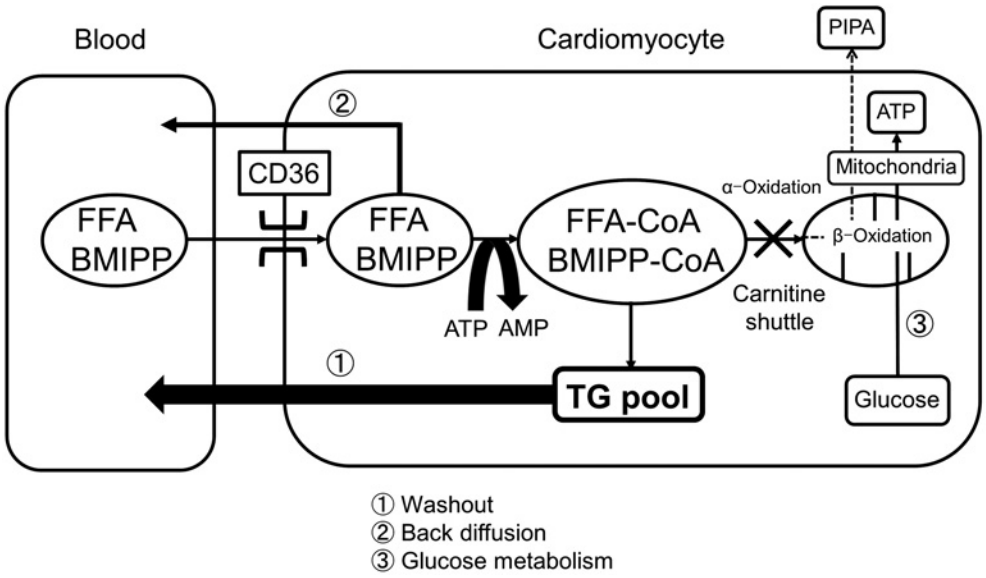

Fig. 5 Intracellular kinetics of ^{123}I-BMIPP in cardiomyocytes. FFA/BMIPP is taken up by cardiomyocytes via CD36-positive fatty acid binding where it is then converted to FFA-CoA/BMIPP-CoA by ATP and incorporated into the TG pool. However, given that myocardial fatty acid metabolism is suppressed, ATP is decreased, and carnitine shuttle in mitochondria is impaired, and FFA/BMIPP is washed out of the TG pool. ^{123}I-BMIPP, ^{123}I-betamethyl-*p*-iodophenyl-pentadecanoic acid; FFA-CoA, free fatty acid-CoA; ATP, adenosine triphosphate; TG, triglyceride; PIPA, ^{123}I-*p*-iodophenil acetic acid.

metaiodobenzylguanidine (^{123}I-MIBG) to assess myocardial sympathetic nerve function in patients with VA and subsequently reported a significant increase in WR of ^{123}I-MIBG.[22] They also reported that the groups with ventricular tachycardia and increased coronary artery spasm activity exhibited a significant increase in the WR of ^{123}I-MIBG. In other words, VA increased cardiac sympathetic nerve activity, which may also be associated with VA activity.[22] In contrast, ^{123}I-BMIPP myocardial scintigraphy showed that cardiomyocytes retain ^{123}I-BMIPP in the triglyceride pool under aerobic conditions.[23] A certain fraction of ^{123}I-BMIPP is washed out via the catabolic system involving alpha-oxidation, followed by beta-oxidation and/or back diffusion of the ^{123}I-BMIPP itself.[24] In the initial state of myocardial ischemia, the sympathetic nervous system is activated, increasing blood catecholamine concentrations and accelerating the degeneration of fat tissues in the body. The excess free fatty acids produced via this mechanism may cause adverse effects on the cardiac muscle cells, such as the induction of fatal arrhythmias, decreased cardiac contractility, and membranous dysfunction.[25, 26] To prevent the aforementioned events, the lipid pool in the cardiac muscle cells expands and incorporates excess free fatty acids.[27, 28] However, even after the improvement of ischemia over time, myocardial fatty acid metabolism and carnitine shuttle in the mitochondria can remain impaired, while adenosine triphosphate remains depleted, causing free fatty acids in the lipid pool to be washout into the bloodstream (Fig. 5).[29] Considering that myocardial ischemia due to coronary artery spasm causes sympathetic activation and is involved in VA activity, increased WR of ^{123}I-BMIPP may be associated with not only impaired carnitine shuttle in mitochondria but also increased sympathetic activation due to myocardial ischemia. Therefore, increased WR of ^{123}I-BMIPP may be associated with the incidence of cardiac risk in VA. Factors that may increase the WR of ^{123}I-BMIPP include the intensity, extent, duration, and frequency of myocardial ischemia due to coronary spasm. However, this subject calls for further research in the future for assessment.

Overall, the findings of this current study suggest that ^{123}I-BMIPP WR assessed via SPECT can be used for early risk stratification in the care and management of patients with VA.

Limitations of the study

This present study has certain limitations worth noting. First, the relatively small sample size precluded the statical reliability of the study. However, our findings showed

that a high WR was significantly associated with the incidence of MACEs. Moreover, considering that the timings at which each patient underwent ^{123}I-BMIPP-SPECT varied, the WRs might have been underestimated. Finally, this current study retrospectively analyzed myocardial SPECT data of patients with VA. However, future prospective studies with larger populations should be conducted to validate the prognostic value of ^{123}I-BMIPP-SPECT WR in patients with VA.

Conclusions

The present study demonstrated that the quantitative assessment of ^{123}I-BMIPP-SPECT WR may be associated with the clinical incidence of cardiac risk in patients with VA.

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Authors' contributions: All authors substantially contributed to the conception and design of the work, as well as to data analysis and interpretation. S.I., H.H., and R.N. interpreted the data. S.I. performed statistical analyses and drafted the manuscript. H.H., R.N., S.M., J.Y., and T.I. reviewed and revised the manuscript. All authors approved the version submitted for publication.

Ethics statement: This retrospective study was approved by the Ethics Committee of Toho University Omori Medical Center (M 20133).

Conflicts of interest: None declared.

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