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Original article

Myocardial ischemic reduction evidenced by gated myocardial perfusion imaging after treatment results in good prognosis in patients with coronary artery disease

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ABSTRACT

Background: There are no nuclear cardiology reports indicating the prediction of prognosis based on ischemic reduction after revascularization in Japanese patients with coronary artery disease (CAD). We aimed to evaluate quantitatively ischemia using myocardial perfusion single photon emission computed tomography (SPECT) before and after treatment such as revascularization and to determine a relationship between the ischemic reduction and the incidence of major cardiac events (MCEs) after the treatment in patients with CAD.

Methods: We retrospectively investigated 513 patients who underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion SPECT between October 2004 and March 2011 and who had a significant stenosis with 75% or greater narrowing of the coronary arterial diameter detected by coronary angiography performed after confirmation of ≥5% ischemia with SPECT. The patients underwent the treatment including revascularization and medication and thereafter were re-evaluated with SPECT during a chronic phase and followed up to confirm prognosis for ≥1 year. The follow-up period was 33.4 ± 16.4 months. The endpoint was the incidence of the MCEs consisting of cardiac death, non-fatal myocardial infarction, and unstable angina pectoris.

Results: During the follow-up, 45 patients experienced MCEs comprising cardiac death (n = 13), non-fatal myocardial infarction (n = 3), and unstable angina pectoris (n = 29). The multivariate Cox proportional hazards regression model analysis for the risk of the MCEs showed the changes in the summed difference score % (p = 0.0102) and the stress left ventricular ejection fraction after the treatment (p = 0.0146) as significant independent variables. The incidence of the MCEs significantly decreased in the patients with ≥5% ischemic reduction than in the patients without ≥5% ischemic reduction and in the patients without residual ischemia than in the patients with the residual ischemia.

Conclusion: Myocardial ischemic reduction detected by nuclear cardiology leads to a decrease in MCE rates after treatment in Japanese patients with CAD.

Introduction

Myocardial perfusion single photon emission computed tomography (SPECT) has been well recognized as a useful imaging method for the prediction of future cardiac events in patients with known or suspected coronary artery disease (CAD) since the reports of Hachamovitch et al. [1,2].

In Japan, myocardial perfusion SPECT has also commonly been used to predict cardiac events in patients with CAD. Risk stratification of cardiac events by nuclear cardiology has been demonstrated in some large-scale prognostic studies including the multicenter prospective Japanese Assessment of Cardiac Events and Survival Study in patients with ischemic heart disease (J-ACCESS) [3], in asymptomatic patients with type 2 diabetes (J-ACCESS 2) [4], and patients with chronic kidney disease (J-ACCESS 3) [5], and another single-center large-scale prospective study [6]. In those studies, patients who underwent revascularization within 60 days after baseline SPECT were excluded from assessment and the prognosis of patients with CAD was predicted based on the baseline SPECT. However, it is also

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clinically important to evaluate cardiac event rates after revascularization.

The COURAGE (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial [7] was conducted to compare cardiac event rates between patients with stable angina pectoris undergoing percutaneous coronary intervention (PCI) with optimal medical treatment and those receiving optimal medical treatment alone in the USA. The incidence of cardiac death and non-fatal myocardial infarction (MI) was 19.0% in the patients with PCI and 18.5% in those without PCI, and long-term prognosis was similar between the two patient populations. However, a nuclear sub-study [8] of the COURAGE trial in 314 patients who underwent SPECT before and after PCI provided interesting data, namely, significant ischemic reduction was observed in patients treated with optimal medication adding PCI. Prognosis was more favorable in the patients with at least 5% ischemic reduction after PCI than without at least 5% ischemic reduction after PCI and also with residual ischemia approaching zero.

Assessment of myocardial ischemia with SPECT before and after PCI is considered to be useful for the prediction of prognosis after PCI on the basis of the results from the nuclear sub-study of the COURAGE trial. However, the evaluation of ischemic reduction after PCI was not the primary objective in the study and was based on sub-analysis; the number of patients evaluated was small and the patients had relatively mild ischemia with a pre-treatment ischemic total perfusion deficit being approximately 8%. In addition, because the study subjects were patients with stable effort angina, the data obtained from the nuclear sub-study cannot be applied to patients with history of MI and more severe cases, who should be cared for in usual clinical practice. Furthermore, there are no reports indicating such data in Japanese patients. We, therefore, have conducted this retrospective prognostic study in Japanese patients with CAD to evaluate quantitatively myocardial ischemia using SPECT before and after revascularization and to determine a relationship between the ischemic reduction and the incidence of cardiovascular events after the revascularization.

Materials and methods

The institutional review board of Nihon University Itabashi Hospital approved this study, which proceeded in accordance with the ethical standards established in the 1964 Declaration of Helsinki. All study participants provided written informed consent prior to inclusion in this study.

Patient population

We retrospectively investigated 513 patients with CAD who underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion SPECT [6,9–13] at Nihon University Itabashi Hospital between October 2004 and March 2011 and who had a significant stenosis with 75% or greater narrowing of the coronary arterial diameter detected by coronary angiography (CAG) performed after confirmation of at least 5% ischemia by the SPECT. The patients underwent treatment including revascularization and medication, and thereafter were re-evaluated with the SPECT during a chronic phase and followed up to confirm prognosis for at least 1 year. The interval between the first SPECT and the CAG was 1.7 ± 3.4 months, that between the CAG and revascularization was 1.1 ± 4.5 months and that between the revascularization and the second SPECT was 10.3 ± 8.5 months. The second SPECT was performed at 14.1 ± 11.3 months after the first SPECT (Fig. 1). We excluded patients aged ≤20 years, those with hypertrophic or dilated cardiomyopathy, those with serious valvular heart disease, those with heart failure with class III or higher New York Heart Association (NYHA) functional classification, and those with less than 5% ischemia detected by the first SPECT.

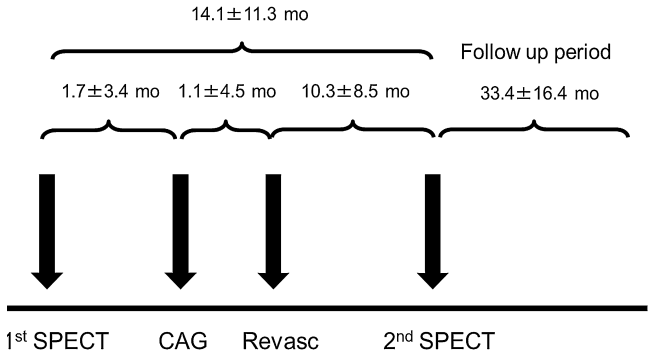

Fig. 1. Timing of nuclear cardiology, coronary angiography and revascularization. SPECT, single photon emission computed tomography; CAG, coronary angiography; Revasc, revascularization; mo, month.

Follow-up examinations were based on medical records for patients who periodically attended the hospital and responses to a posted questionnaire for patients who did not. The follow-up was successful for 483 patients (94%), but failed for the remaining 30 patients. Data from all 483 patients were finally included in the analysis.

Electrocardiogram-gated dual-isotope myocardial perfusion SPECT

The procedure of rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin electrocardiogram (ECG)-gated myocardial perfusion SPECT was performed according to a protocol previously reported [6,9–13]. All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq) and a 16-frame gated SPECT imaging was initiated 10 min after injection during rest. Then an i.v. injection of ^{99m}Tc-tetrofosmin (740 MBq) was performed under stress induced by ergometer exercise in 23% of the patients or by adenosine triphosphate in 77%. Sixteen-frame gated SPECT image acquisition was initiated 30 min after the exercise or 30–60 min after the adenosine triphosphate stress. The acquisition was performed in a supine position and subsequently in a prone position. No attenuation or scatter correction was used. Twelve-lead ECG was monitored continuously during stress tests. Heart rate and blood pressure were recorded at baseline and every minute for at least 3 min after the stress.

The projection data over 360° were obtained with 64 × 64 matrices and a circular orbit. A triple-detector SPECT system equipped with low-energy high-resolution collimators was used (Toshiba, GCA9300A, Tokyo, Japan).

SPECT images were reconstructed from the data with a data processor (Philips North America, JETStream Workspace 3.0, Andover, MA, USA) combined with a Butterworth filter of ^{201}Tl (order 5; cut-off frequency 0.42 cycles/cm), that of ^{99m}Tc (order 5; cut-off frequency 0.44 cycles/cm) and a ramp filter.

SPECT image interpretation

The SPECT images were divided into 20 segments [14] on three short-axes (distal, mid, basal) and one on vertical long-axis (mid) slices, and the tracer uptake of each segment was visually scored using a 5-point scale (0: normal; 1: slight reduction of uptake; 2: moderate reduction of uptake; 3: severe reduction of uptake; and 4: absence of uptake). The sum total of the scores of 20 segments in the stress and rest images provided the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. The respective summed scores were converted into percent of the total myocardium (visual % myocardium). Visual % myocardium was derived from a summed score divided by the maximum potential score (4 × 20) and multiplied by 100.

When the SSS score was 4, the visual % myocardium was 5%. When SDS% was 0% after treatment was defined as 'no residual ischemia' and when SDS% was ≥1% after treatment was defined as 'residual ischemia'. A change in SDS% (ΔSDS%) was a difference between SDS% by the first and second SPECT. The visual semi-quantitative scoring was performed by two independent expert interpreters who were not provided with patient's clinical information. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the summed defect score, was 0.92, indicating very good reproducibility.

Patient follow-up

All the 483 patients were followed up for at least 1 year (33.4 ± 16.4 months) after the second SPECT. The study endpoint was the incidence of major cardiac events (MCEs) during the follow-up, consisting of cardiac death, non-fatal MI, and unstable angina pectoris (UAP) identified from medical records or from responses to a posted questionnaire. When a patient had several cardiac events, only the first event was taken as the follow-up endpoint.

Statistical analysis

Continuous variables were calculated as means and standard deviations. Intergroup comparisons of continuous and categorical variables were achieved using an unpaired t test and the χ^2 test, respectively. A paired *t*-test was used to analyze the significance of difference of the summed defect scores and of left ventricular function on the quantitative gated SPECT before and after the treatment. Univariate analyses proceeded using a Cox proportional hazards model. Multivariate analyses proceeded using a stepwise Cox proportional hazards model. Kaplan–Meier survival analyses were estimated for patients with and without ≥5% ischemic reduction and for patients with and without residual ischemia after the treatment. Receiver operating characteristic (ROC) analysis was employed to evaluate sensitivity and specificity for the detection of ischemic reduction. All data were analyzed using MedCalc Software Version 12.6.1.0 (Mariakerke, Belgium). A p value of <0.05 was considered statistically significant.

Results

Cardiac event rates and patient characteristics

During the follow-up, 45 (9.3%) of 483 patients experienced MCEs including cardiac death ($n = 13$), non-fatal MI ($n = 3$), and UAP ($n = 29$). Table 1 summarizes the characteristics of the patients with and without MCEs. The proportions of patients treated with medications including aspirin, statins, β-blockers, calcium antagonists, nitrates, angiotensin II receptor blockers, or angiotensin-converting enzyme inhibitors were similar between two groups with and without MCEs. The proportions of patients with a typical chest pain, those with a history of MI or revascularization, and those with hypertension, diabetes mellitus, hyperlipidemia, or smoking habit were similar between the two groups. Also, estimated glomerular filtration rates and the severity of CAD detected by CAG were similar between the two groups. The proportions of patients undergoing PCI were 76% (34/45) in the group with MCEs and 75% (328/438) in the group without MCEs. One of the patients with MCEs and 40 of the patients without MCEs underwent coronary artery bypass grafting. Remaining patients (10 and 70 in the groups with and without MCEs, respectively) received medication alone, mainly by reason of an inappropriate lesion for revascularization or operator's decision.

Table 1
Characteristics of patients with and without major cardiac events.

	Major cardiac event (+) $N = 45$		Major cardiac event (−) $N = 438$		p value
Male patients	38	84%	352	80%	0.6438
Age	67 ± 11		67 ± 9		0.4354
Typical chest pain	16	36%	165	38%	0.9065
History of MI	24	53%	171	39%	0.0889
History of revascularization	28	62%	208	47%	0.0843
Hypertension	34	76%	345	79%	0.7576
Diabetics	25	56%	208	47%	0.3818
Hyperlipidemia	19	42%	256	58%	0.0530
Smoking	18	40%	161	37%	0.7897
Aspirin	43	96%	423	97%	0.9432
Statins	22	49%	263	60%	0.1971
β-blockers	14	31%	162	37%	0.5371
Ca-antagonists	25	56%	208	47%	0.3818
Nitrates	17	38%	182	42%	0.7407
ARB	22	49%	217	50%	0.9419
ACE inhibitor	7	16%	37	8%	0.1916
eGFR	52.9 ± 27.3		59.0 ± 23.3		0.0987
Angiographic CAD					
1 Vessel	10	22%	150	34%	0.1427
2 Vessels	19	42%	136	31%	0.1735
3 Vessels	16	36%	152	35%	0.9611
Treatment					
PCI	34	76%	328	75%	0.9347
CABG	1	2%	40	9%	0.1926
Medication	10	22%	70	16%	0.3888

MI, myocardial infarction; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Visual % myocardium and left ventricular function

Table 2 summarizes the changes in visual % myocardium (SSS%, SRS%, and SDS%) for myocardial defects detected by the SPECT and in left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) estimated with the quantitative gated SPECT before and after the treatment in the patients with and without MCEs. The SSS% and SDS% significantly improved after the treatment in the two groups. The magnitude of the ΔSDS% was significantly larger in the patients without MCEs than with MCEs (8.3 ± 8.9 vs. 4.4 ± 7.1; $p = 0.0037$, Fig. 2). No significant improvement was observed in the SRS% in either group. No changes in the left ventricular function parameters were observed after the treatment in the patients with MCEs. In contrast, the patients without MCEs had significant improvement of the left ventricular function after the treatment ($p < 0.0001$ for LVEF, $p \leq 0.0469$ for LVEDV, $p \leq 0.0062$ for LVESV).

ROC analysis for detection of MCEs by changes in SDS%

ROC analysis indicated that an optimal cut-off value of changes in the SDS% (ΔSDS) was 5%. The sensitivity and specificity for detection of MCEs were 65% and 56%, respectively (Fig. 3). On the basis of this result, the frequency of ≥5% ischemic reduction was significantly different between the patients with and without MCEs, being 44% (20/45) and 67% (292/438), respectively ($p = 0.0050$).

Prediction of MCEs

Table 3 summarizes the results of univariate Cox proportional hazards regression model analysis with MCE rates as the dependent variable. Significant variables associated with increased

Table 2
Visual segmental scores for myocardial defects and left ventricular functions before and after the treatment[a] in the patients with and without major cardiac events.

	Major cardiac event (+) N = 45		p value	Major cardiac event (−) N = 438		p value
	Before	After		Before	After	
SSS%	18.2 ± 11.4	14.0 ± 11.1	0.0025	19.5 ± 11.0	11.5 ± 11.8	<0.0001
SRS%	6.0 ± 7.4	6.1 ± 8.6	0.8580	5.3 ± 8.1	5.7 ± 9.1	0.1458
SDS%	12.3 ± 6.2	7.9 ± 7.3	0.0002	14.2 ± 7.5	5.9 ± 6.4	<0.0001
0%	0 0%	6 13%		0 0%	148 34%	
1–4.9%	0 0%	9 20%		0 0%	55 13%	
≥5%	45 100%	30 67%		438 100%	235 54%	
LVEF						
Rest	53.7 ± 13.7	53.7 ± 14.1	0.9842	56.9 ± 13.9	58.8 ± 14.0	<0.0001
Post stress	50.7 ± 13.4	51.5 ± 13.4	0.5796	54.1 ± 13.5	57.2 ± 13.6	<0.0001
LVEDV						
Rest	97.2 ± 51.4	96.1 ± 44.4	0.7924	93.0 ± 42.9	91.0 ± 42.7	0.0469
Post stress	117.2 ± 54.0	112.8 ± 50.6	0.3732	110.4 ± 47.3	105.3 ± 47.4	<0.0001
LVESV						
Rest	50.9 ± 44.7	49.8 ± 41.1	0.7594	44.9 ± 36.4	42.4 ± 36.7	0.0062
Post stress	64.3 ± 48.2	61.1 ± 46.9	0.4245	55.9 ± 40.8	50.2 ± 40.1	<0.0001

SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.
[a] The treatment consists of percutaneous coronary intervention, coronary artery bypass grafting, and medication.

MCE rates were history of revascularization ($p = 0.0480$), the SDS% after the treatment ($p = 0.0429$), the ΔSDS% ($p = 0.0039$), ≥5% ischemic reduction ($p = 0.0108$), rest and stress LVEF after the treatment ($p = 0.0117$ and $p = 0.0046$) and stress LVESV after the treatment ($p = 0.0428$).

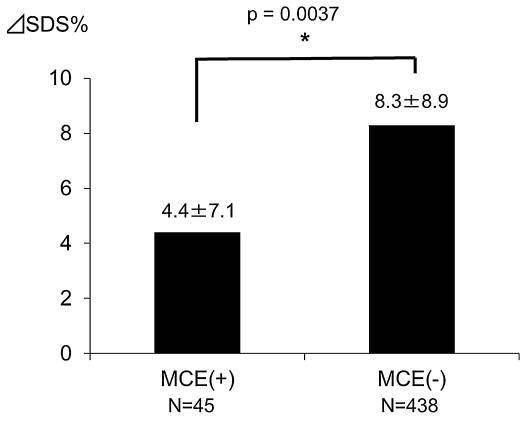

Fig. 2. Comparison of ischemic reduction (ΔSDS%) between patients with and without major cardiac events (cardiac death, non-fatal myocardial infarction, and unstable angina pectoris). SDS, summed difference score; MCE, major cardiac event.

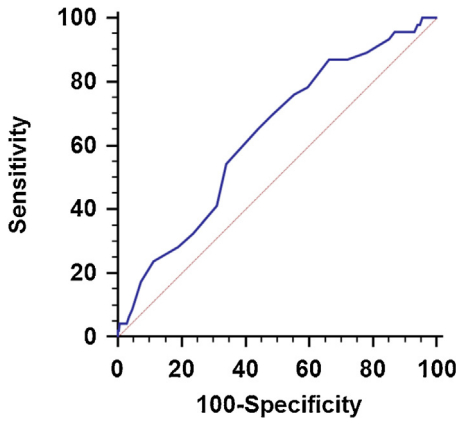

Fig. 3. Receiver operating characteristic curves for detection of major cardiac events by changes in summed difference score%. Major cardiac event, cardiac death, non-fatal myocardial infarction, and unstable angina pectoris.

The multivariate Cox proportional hazards regression model analysis for risk of the MCE showed the ΔSDS% ($p = 0.0102$) and the stress LVEF after the treatment ($p = 0.0146$) as significant independent variables (Table 4).

Incidence of MCEs based on ischemic reduction or residual ischemia after treatment

Fig. 4 illustrates Kaplan–Meier curves of the MCE-free survival for the patients with ($n = 312$) and without ($n = 171$) ≥5% ischemic reduction after the treatment. The incidence of the MCEs

Table 3
Univariate Cox proportional hazards regression analysis.

	Chi-square	Hazard ratio	95% Confidence interval	p value
Age	0.386	1.0106	0.9775–1.0447	0.5377
Male patients	0.413	1.2944	0.5783–2.8974	0.5323
History of MI	2.028	1.5509	0.8519–2.8236	0.1532
History of revascularization	4.041	1.8551	1.0087–3.4117	0.0480
Hypertension	0.006	1.0225	0.5822–1.7958	0.9386
Diabetes mellitus	1.805	1.5064	0.8280–2.7407	0.1818
Hyperlipidemia	3.901	0.5479	0.3007–0.9985	0.0506
Smoking	0.001	0.9989	0.5428–1.8385	0.9973
Statin use	2.700	0.5822	0.2995–1.1317	0.1125
SSS% before treatment	0.501	0.9901	0.9627–1.0182	0.4866
SRS% before treatment	0.284	1.0096	0.9755–1.0450	0.5862
SDS% before treatment	3.075	0.9599	0.9146–1.0074	0.0982
SSS% after treatment	1.976	1.0171	0.9945–1.0401	0.1417
SRS% after treatment	0.234	1.0078	0.9776–1.0389	0.6198
SDS% after treatment	3.655	1.0430	1.0015–1.0861	0.0429
ΔSDS%	9.212	0.9413	0.9035–0.9806	0.0039
≥5% Ischemic reduction	6.497	0.4616	0.2556–0.8336	0.0108
Rest LVEF after treatment	5.879	0.9760	0.9579–0.9945	0.0117
Rest LVEDV after treatment	1.189	1.0036	0.9975–1.0097	0.2513
Rest LVESV after treatment	2.176	1.0052	0.9989–1.0116	0.1086
Stress LVEF after treatment	7.598	0.9716	0.9525–0.9910	0.0046
Stress LVEDV after treatment	1.767	1.0038	0.9985–1.0091	0.1584
Stress LVESV after treatment	3.403	1.0058	1.0002–1.0113	0.0428
eGFR	1.617	0.9919	0.9799–1.0041	0.1955

The treatment mentioned in this table consists of percutaneous coronary intervention, coronary artery bypass grafting, and medication. MI, myocardial infarction; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; ΔSDS%, a difference between SDS% by the first and second single photon emission computed tomography; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; eGFR, estimated glomerular filtration rate.

Table 4
Multivariate Cox proportional hazards regression analysis.

	Hazard ratio	95% Confidence interval	*p* value
ΔSDS%	0.9480	0.9104–0.9872	0.0102
Stress LVEF after treatment	0.9744	0.9544–0.9948	0.0146

The treatment mentioned in this table consists of percutaneous coronary intervention, coronary artery bypass grafting, and medication SDS, summed difference score; ΔSDS%, a difference between SDS% by the first and second single photon emission computed tomography; LVEF, left ventricular ejection fraction.

significantly decreased in the patients with ≥5% ischemic reduction than in the patients without ≥5% ischemic reduction ($p = 0.0090$).

Fig. 5 illustrates Kaplan–Meier curves of the MCE free survival for the patients with ($n = 329$) and without ($n = 154$) residual ischemia after the treatment. The incidence of the MCEs significantly decreased in the patients without residual ischemia than in the patients with residual ischemia ($p = 0.0088$).

Typical SPECT images

Fig. 6 shows typical polar maps obtained in a patient with ischemic reduction who had a good prognosis (a) and a patient without ischemic reduction who had a poor prognosis (b).

The patient (a) was a 62-year-old male with stable effort angina. The first SPECT showed extensive ischemia in the region of the left anterior descending artery (LAD). He underwent CAG, which evidenced 99% stenosis in the proximal region of the LAD and 75% stenosis in the middle region of the left circumflex artery (LCX), and underwent PCI for the stenosis in the LAD. No ischemia was detected in the LAD region by the second SPECT. The ischemic reduction (ΔSDS%) was 38.8% and no residual ischemia was observed. Thereafter, he experienced no cardiac events and had a good prognosis.

The patient (b) was a 76-year-old male with old MI. The first SPECT showed infarction and peri-infarction ischemia in the LCX region. CAG evidenced 100% stenosis in the middle region of the LCX and 90% stenosis in the distal region of the right coronary artery. Therefore, he underwent PCI for the stenosis in the LCX, but the results of the PCI for the LCX lesion were unsuccessful. The second SPECT showed the same finding consisting of infarction and ischemia as detected by the first SPECT. The ΔSDS% was 1.2% and the residual ischemia was 13.8%. Subsequently he was followed up with medication but had cardiac death.

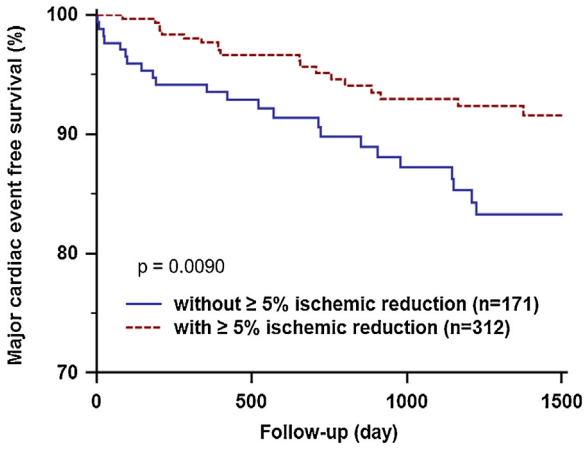

Fig. 4. Kaplan–Meier curves of major cardiac event-free survival for the patients with and without ≥5% ischemic reduction after the treatment. Major cardiac event, cardiac death, non-fatal myocardial infarction, and unstable angina pectoris.

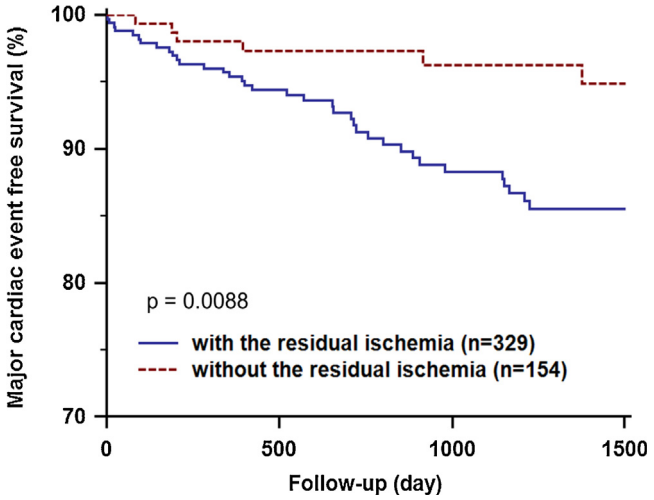

Fig. 5. Kaplan–Meier curves of major cardiac event-free survival for the patients with and without residual ischemia after treatment. Major cardiac event, cardiac death, non-fatal myocardial infarction, and unstable angina pectoris.

Discussion

This is the first report in Japan, demonstrating that prediction of future cardiac events based on ischemic reduction after revascularization and nuclear cardiology in patients with CAD. The patients experienced ≥5% ischemic reduction after treatment including revascularization and medication had significantly lower incidence of MCEs in comparison with the patients without ischemic reduction. The left ventricular function evaluated with the quantitative gated SPECT significantly improved after the treatment in the patients without MCEs than with MCEs. Also, the ischemic reduction and stress LVEF after the treatment were significant independent variables for prediction of future MCEs.

In an exploratory analysis, an optimal cut-off value of the post-treatment SDS% was 0% on the basis of the ROC curve indicating relationship between the SDS% and cardiac events after the treatment. As a natural result, a survival rate estimated by Kaplan–Meier analysis was significantly higher in patients without (0%) residual ischemia than with (>1%) residual ischemia after the treatment. Ideal revascularization is to result in complete elimination of residual ischemia. However, it is hard to completely remove ischemia in multivessel disease because re-evaluation with SPECT indicates a high probability of residual ischemia after treatment of the primary lesion. In the present results, as shown in Table 2, the proportion of patients with the post-treatment SDS% = 0% was only 34% in the group without MCEs and that of those with the post-treatment SDS% ≥ 5% was not statistically different between the groups with and without MCEs (67% and 54%, $p = 0.1302$). Consequently, a significant variable predicting MCEs in patients with >1% residual ischemia should be further investigated in a future study.

In the present study, ≥5% ischemic reduction resulted in the improvement of prognosis in a larger number of patients than that in COURAGE Nuclear Sub-study [6]. The "5%" was also a cut-off value demonstrated in the COURAGE Nuclear Sub-study. Therefore, it may be a consistent target value for the reduction of ischemia where revascularization is performed to improve prognosis in any racial patient with CAD. In addition, the pre-treatment mean ischemic % myocardium in our study patients was 14% as the SDS% and larger than that in the COURAGE Nuclear

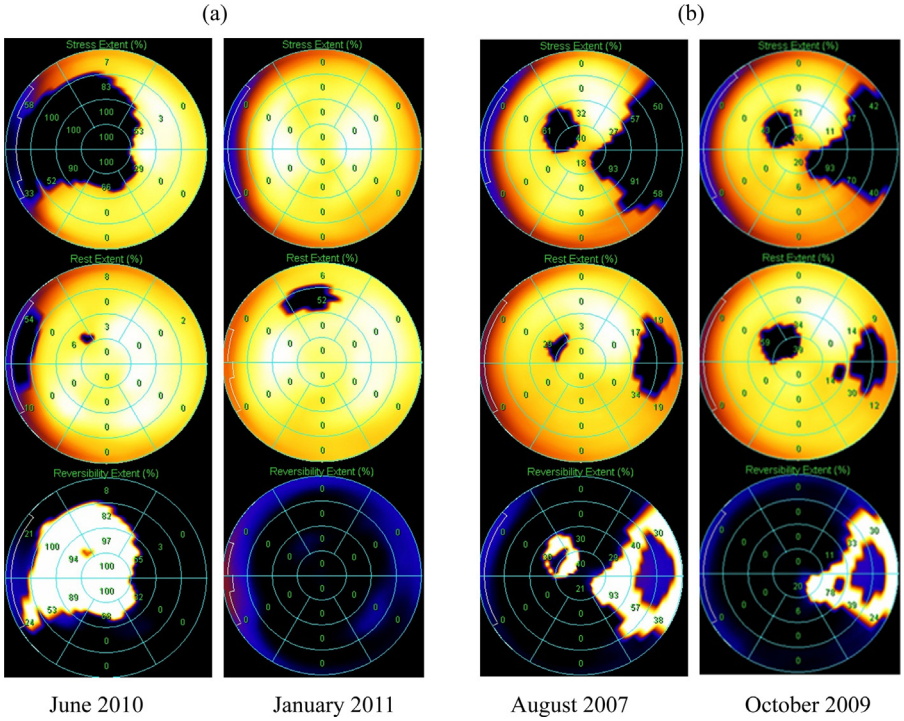

Fig. 6. Typical polar maps in a patient with ischemic reduction who had a good prognosis (a) and a patient without ischemic reduction who had a poor prognosis (b).

Sub-study (8%). Therefore, our results demonstrate that the achievement of ≥5% ischemic reduction by treatment such as revascularization and elimination of residual ischemia led to avoidance of cardiovascular events even in patients with severe ischemia.

Fractional flow reserve (FFR), which is a physiological ischemic variable, is used for the determination of therapeutic strategy and the prediction of prognosis like SPECT. The FAME (Fractional Flow Reserve vs. Angiography for Multivessel Evaluation) study [15] was conducted to compare the rate of death, non-fatal MI, or repeat revascularization at 1 year in patients with multivessel CAD who underwent PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography, to obtain results such that routine measurement of FFR significantly decreased the incidence of the adverse cardiac events. In the FAME 2 study [16], the risk of adverse cardiac events, especially urgent repeat revascularization, significantly more reduced in patients with stable multivessel CAD who underwent PCI with implantation of drug-eluting stents guided by FFR measurements and optimal medical treatment than those who underwent optimal medical treatment alone. The other randomized trial (DEFER study) [17] was conducted to evaluate whether FFR could determine the appropriateness of PCI in patients for whom PCI was planned and who had no evidence of ischemia. The PCI was an appropriate treatment and markedly improved functional class in patients with FFR ≤ 0.75 before the planned intervention but did not benefit those with FFR > 0.75.

In all the three studies mentioned above, adoption of revascularization and prediction of prognosis were based on physiological evaluation of stenosis with FFR. The procedure of the FFR estimation was hard to be conducted in all patients intended to undergo PCI because that was invasive. Actually, the FFR was not estimated in patients with stenosis being anatomically difficult for a pressure wire to be inserted and the FFR was incorrect if one vessel had multiple stenoses. In addition, the procedure for the FFR determination has a risk of life-threatening events such as perforation of coronary arteries because of the invasive procedure. In contrast, SPECT allows non-invasive assessment of ischemic reduction and residual ischemia before and after PCI and there is evidence of its use for the prediction of prognosis of patients with CAD [1–6]. Therefore, the results from the present nuclear cardiology study would lead to high quality management for patients with CAD in clinical practice.

This study has limitations. It was a retrospective, single center, relatively small size investigation. However, the number of patients in our study was 483, although it was a single center study, and was larger than that (n = 314) in the COURAGE Nuclear Sub-study [8], which provided evidence in nuclear cardiology, and also was comparable to the target number of patients (n = 500) in another multicenter prospective study (J-ACCESS 4) [18].

In conclusion, myocardial ischemic reduction leads to decrease MCE rates after treatment such as revascularization. Quantitative assessment of myocardial ischemic reduction by serial nuclear cardiology studies is useful for prediction of prognosis in Japanese patients with CAD.

Conflict of interest

All authors declare that they have no conflict of interest.

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