

Introduction

Myocardial perfusion imaging (MPI) by single photon emission computed tomography (SPECT) is widely used in patients with coronary artery disease (CAD). Stress MPI is commonly employed to detect inducible myocardial ischemia and to evaluate the extent and severity of ischemia. MPI has also been employed to evaluate myocardial viability in the infarct zone. MPI data are used when making decisions about treatment, including selection among medical therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). Hachamovitch et al. reported that revascularization showed a greater survival benefit than medical therapy in patients with moderate to severe inducible myocardial ischemia on MPI (1). These days, there is a focus on whether patients with CAD should undergo revascularization in order to improve the prognosis. In the Nuclear Substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial (2), the extent of myocardial ischemia on MPI was significantly reduced in patients treated with a combination of medical therapy and revascularization compared to patients who only received medical therapy, and the risk of adverse events was significantly reduced in patients with greater improvement of myocardial ischemia. In addition, the Japanese

Assessment of Cardiac Events and Survival Study (J-ACCESS) (3) suggested that patients with large myocardial perfusion defects on MPI may have a higher rate of adverse events. Thus, prior clinical research has highlighted the potential relation between MPI findings and the treatment or prognosis of patients with CAD. However, more clinical trials and further evidence are needed to clarify the relationship between MPI findings and the prognosis of CAD.

Therefore, this study was performed to evaluate whether residual ischemia on repeat myocardial perfusion imaging was associated with a worse prognosis in patients receiving optimal medical therapy with or without coronary revascularization.

Methods

Subjects

A total of 188 consecutive patients with stable CAD were retrospectively enrolled between July 2007 and June 2012. They all had ischemic findings in the initial stress/resting MPI and underwent a repeat stress/resting MPI within one year of the initial test. Ischemia was defined on the basis of the summed difference score (SDS) described below. Most of them underwent scheduled repeat MPI for the reevaluation of

CAD without symptoms or cardiac events (n=179), and the others for the evaluation of stable symptoms (n=9). The patients received medical therapy with or without coronary revascularization between the first and second MPI studies. This study was approved by the Ethics Committee of the Gunma Prefectural Cardiovascular Center.

MPI and interpretation of SPECT images

Patients underwent stress and rest MPI according to a one-day protocol using ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin (740 MBq). Stress was induced by ergometer exercise or infusion of adenosine triphosphate (120 µg/kg/min for 6 minutes), as described previously (4).

SPECT images were divided into 17 segments and tracer uptake in the individual segments was scored visually on a scale of 0 to 4 (0: normal, 1: mild hypoperfusion, 2: moderate hypoperfusion, 3: severe hypoperfusion, and 4: defect). The summed stress score (SSS) was calculated as the total score of the 17 segments when patients were under stress and the summed rest score (SRS) was calculated in the same way at rest, after which the SDS was calculated as the difference between the SSS and SRS. We defined %residual ischemia as the percent SDS on repeat MPI relative to that on initial MPI (post SDS×100/pre SDS).

Quantitative gated SPECT (QGS) data were analyzed with QGS software (5), including calculation of the left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (ESV), and left ventricular end-diastolic volume (EDV). These parameters were compared with the findings on initial MPI. Scoring of SPECT images was performed by an expert interpreter.

Follow-up and outcomes

We followed the patients until occurrence of an adverse event or for at least one year after repeat MPI. The study endpoints were the incidence of adverse events, including cardiac death, nonfatal myocardial infarction, hospitalization for heart failure, need for revascularization by PCI or CABG, stroke, and non-cardiac death. Follow up was based on data from the medical records for patients who regularly attended our hospital, while information on the other patients was obtained by telephone interview.

Statistical analysis

Continuous variables were expressed as the median with interquartile range. The unpaired t-test was used to compare continuous variables between groups, while categorical variables were compared with the chi-square test. The relative hazard ratio

for each adverse event (as the dependent variable) was calculated by univariate Cox proportional hazards regression analysis, followed by multivariate regression analysis using the statistically significant variables. Kaplan-Meier cumulative survival curves were drawn for patients with mild %residual ischemia or significant %residual ischemia, and the log-rank test was used to compare survival between these two groups. Receiver operating characteristic (ROC) analysis was employed to evaluate the sensitivity and specificity of each parameter for detecting adverse events.

Results

The median age of the total patient population was 71 (63-76) years, and 138 patients were men. When stress MPI was performed, 103 patients underwent ergometer exercise and 85 patients received adenosine triphosphate. Patients were followed for a median of 36 (15-60) months. During the follow-up period, 54 patients (28.7%) experienced adverse events, including 5 patients (2.7%) with cardiac death, 2 patients (1.1%) with myocardial infarction, 2 patients (1.1%) with hospitalization for heart failure, 34 patients (18.1%) with PCI, 5 patients (2.7%) with CABG, 1 patient (0.5%) with stroke, and 5 patients (2.7%) with non-cardiac death.

Table 1 summarizes the characteristics and SPECT findings of the patients with or

without adverse events. The age, proportion of men, and BMI were similar in both groups. There were no significant differences between the two groups with regard to the prevalence of diabetes, dyslipidemia, hypertension, current smoking, family history of CAD, prior myocardial infarction, and prior revascularization (including PCI and CABG). There were also no significant differences of medications, including beta-blockers, angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors, nitrates, nicorandil, and calcium antagonists.

On initial MPI, both SSS and SDS were significantly higher in the patients with adverse events than in those without adverse events (11 vs. 7; $p=0.019$ and 7 vs.5; $p=0.023$, respectively). In contrast, SRS on initial MPI was similar between the patients with and without adverse events, as were all three scores on repeat MPI. The %residual ischemia was significantly higher in the patients with adverse events than in those without adverse events (20.0% vs. 0.0%, $p=0.044$). There were no significant differences of QGS findings on initial resting MPI (including LVEF, ESV, and EDV) between the patients with and without adverse events.

Table 2 shows the results obtained by univariate Cox proportional hazards regression analysis of factors related to adverse events. A high SSS and high SDS on initial MPI were significantly associated with a higher incidence of adverse events (HR 1.037;

p=0.016 and HR 1.064; p=0.025, respectively), and a higher %residual ischemia was also significantly associated with a higher incidence of adverse events (HR 1.011, p=0.023). Moreover, the presence of diabetes, a high SDS on repeat MPI, and a low LVEF on stress imaging were related to the incidence of adverse events (HR 1.670; p=0.061, HR 1.108; p=0.095, and HR 0.983; p=0.051, respectively). When patients were divided into 2 groups by the median of SSS, which was nine on initial MPI, Kaplan-Meier analysis showed that the frequency of adverse events was significantly lower in patients with a low initial SSS than in patients with a high initial SSS (22.6% vs 36.6%, p=0.025; log-rank test; Fig.1).

When multivariate Cox proportional hazards regression analysis was performed using the above-mentioned variables, %residual ischemia was significantly associated with a higher incidence of adverse events (HR 1.025, p=0.018; Table 3).

Among all patients, the median %residual ischemia was 0.0 (0.0-36.6)%, which means complete resolution of ischemia was achieved in half of the total patient population. ROC analysis indicated that the optimal cut-off value of %residual ischemia for an increased risk of adverse events was 14%, with the sensitivity and specificity being 54.7% and 67.1%, respectively. Therefore, mild %residual ischemia was defined as \leq 14% and significant %residual ischemia was defined as $>$ 14%. Using these definitions,

112 patients (59.6%) had mild %residual ischemia and 76 patients (40.4%) had significant %residual ischemia. Kaplan-Meier analysis demonstrated that the frequency of adverse events was significantly lower in the patients with mild %residual ischemia than in those with significant %residual ischemia (21.4% vs 39.5%, $p=0.001$; log-rank test; Fig. 1). SPECT images of representative patients with mild and significant %residual ischemia are shown in Fig. 2.

As for the individual adverse events, Kaplan-Meier analysis demonstrated that the frequency of revascularization with PCI or CABG and non-cardiac death were significantly lower in the patients with mild %residual ischemia than with significant %residual ischemia (13.6% vs 30.2%; $p=0.002$ and 0.9% vs 5.3%; $p=0.023$; log-rank test; respectively), while cardiac death, myocardial infarction and hospitalization for heart failure were similar between patients with significant and mild %residual ischemia (2.7% vs 2.6%; $p=0.603$, 0.9% vs 1.3%; $p=0.668$, 1.8% vs 0.0%; $p=0.290$ and 0.9% vs 0.0%; $p=0.564$; log-rank test; respectively).

After initial MPI, 113 patients (60.1%) were treated by coronary revascularization, including 97 patients receiving PCI and 16 patients undergoing CABG, and 75 (39.9%) patients were managed by medical therapy. On initial MPI, SDS was significantly higher in the patients with revascularization than in those without revascularization (8

vs. 3, $p < 0.001$), although there were no significant differences of SSS and SRS between patients with and without revascularization (9 vs. 5; $p = 0.096$ and 0 vs. 2; $p = 0.303$, respectively). On repeat MPI, there were no differences of the SSS, SRS, or SDS between the patients with and without revascularization (3 vs. 3, $p = 0.165$; 0 vs. 0, $p = 0.071$; and 1 vs. 0, $p = 0.189$, respectively). According to Kaplan-Meier analysis, the event-free survival rate was similar in patients with and without revascularization ($p = 0.954$; log-rank test).

Discussion

The present study revealed a higher frequency of adverse events in patients with significant %residual ischemia on MPI than in patients with mild %residual ischemia. This finding suggests that detection of more severe %residual ischemia can predict a worse prognosis for CAD patients, and that alleviation of residual ischemia may reduce adverse events.

While the results of the main COURAGE trial indicated that revascularization did not necessarily reduce the risk of hard events in patients with stable CAD (6), some other studies have suggested that revascularization may have an impact on the prognosis (2,

7). Indeed, CAD patients receiving only medical therapy in the main COURAGE trial frequently required subsequent revascularization (6).

In the present study, we defined %residual ischemia as the percent SDS on repeat MPI relative to that on initial MPI. Although %residual ischemia might have simply been evaluated as the SDS on repeat MPI, this would not have assessed the change in the area of ischemic myocardium. In addition, while the absolute difference between SDS on repeat MPI and initial MPI shows the quantitative change of ischemia, it does not indicate the proportional change of residual ischemia. In contrast, the percent SDS on repeat MPI relative to that on initial MPI indicates the proportion of residual ischemia that remains after improvement from baseline and was considered to be the most appropriate prognostic index in patients receiving treatment for CAD. In the COURAGE Trial Nuclear Substudy (2), 5% or more reduction of ischemic myocardium on MPI by optimal medical therapy with or without coronary revascularization was associated with a decrease in the risk of adverse events, including death and nonfatal MI. In Japan, investigation of the prognosis of CAD patients with ischemia on MPI has also suggested that $\geq 5\%$ reduction of ischemia after treatment such as revascularization can decrease the risk of adverse events, including cardiac death, nonfatal MI, and unstable angina pectoris (8). However, the index of $\geq 5\%$ reduction of

ischemia used in these studies was the numerical change of ischemic myocardium and was not the %residual ischemia. Although comparison is difficult, our cut-off value of 14% for %residual ischemia on repeat MPI may represent a larger reduction of ischemic myocardium than the index of $\geq 5\%$ reduction used in those studies, since initial MPI showed 10% ischemic myocardium in our patients versus 8% in the COURAGE Trial Nuclear Substudy (2) and 14% in the Japanese study (8).

Unlike those studies (2, 8), we assessed hospitalization for heart failure and revascularization as adverse events. In our study, the higher frequency of adverse events in patients with significant %residual ischemia than with mild %residual ischemia may be driven by the frequency of revascularization. However, 13 patients (6.9%) in present study experienced adverse events including cardiac death, myocardial infarction, stroke, and non-cardiac death. Kaplan-Meier analysis demonstrated a lower frequency of these composite adverse events in patients with mild %residual ischemia than with significant %residual ischemia, although the difference was not significant, probably due to the small patient population in this study (5.4% vs. 9.2%; $p=0.075$, log-rank test).

In the present study, the frequency of adverse events did not differ between patients with and without revascularization after initial MPI. Although the %residual ischemia

also showed no significant difference between patients with and without revascularization (8.8% vs. 0.0%, $p=0.436$), the difference of SDS on initial and repeat MPI was significantly higher in the patients with revascularization than without revascularization (5 vs. 2, $p<0.001$). These results suggest that revascularization achieves greater reduction of ischemic myocardium on MPI than medical therapy, but is not directly associated with greater reduction of %residual ischemia and a lower frequency of the adverse events.

For patients with significant %residual ischemia like those in the present study, options for improving the prognosis may be additional PCI if coronary stenosis remains apparent or exercise training. Ischemia on MPI associated with angiographic coronary stenosis is reported to be improved by exercise, with consequent reduction of cardiac events (9).

Stress MPI is commonly used to detect inducible myocardial ischemia, but this modality should also be employed to select treatment for CAD patients based on the likely prognosis. Measurement of the coronary artery fractional flow reserve (FFR) has recently become popular for detecting myocardial ischemia, with the ischemic cut-off point being derived by comparison with data from noninvasive modalities, including MPI (10). It has been suggested that coronary lesions requiring PCI should not only be

selected by measuring the FFR ischemic index, but also by considering the prognostic implications. Data from 5-year follow-up of the DEFER study (11) suggested that deferring PCI for intermediate stenosis without ischemia on FFR did not increase the event-free rate for cardiac death or acute myocardial infarction. In addition, the results of the Fractional Flow Reserve vs. Angiography for Multivessel Evaluation (FAME) study (12) indicated that routine measurement of FFR in addition to angiography before PCI decreased the incidence of adverse cardiac events, including death, non-fatal myocardial infarction, and repeat revascularization. Thus, FFR can be utilized to select treatment for CAD patients based on their prognosis, rather than to simply detect myocardial ischemia. While FFR can detect myocardial ischemia, it cannot be used to estimate the quantity of ischemic myocardium to assess %residual ischemia or improvement of the ischemic area. FFR is also not appropriate for assessing myocardial viability, which can be done by MPI. Thus, data obtained by MPI (such as the %residual ischemia index defined in our study) may be more useful for predicting the prognosis of patients with CAD. Accordingly, MPI seems to be potentially useful when selecting treatment for CAD patients, and further investigation of the association between MPI findings and the prognosis are warranted.

Our study had some limitations, since it was retrospective, non-randomized, and

performed in a small patient population. Also, our cut-off value of 14% for dividing patients into groups with mild or significant %residual ischemia may not have been appropriate for patients with an extremely small SDS value on initial MPI. Further investigation with stratification by the SDS value on initial MPI may be required.

Conclusion

In patients receiving medical therapy with or without coronary revascularization, significant %residual ischemia on repeat MPI compared to initial MPI was associated with a higher risk of adverse events than mild %residual ischemia. Thus, more severe residual ischemia on repeat MPI may predict a worse prognosis for CAD patients receiving optimal medical therapy with or without coronary revascularization.

Acknowledgment

The authors acknowledge the staffs in Gunma Prefectural Cardiovascular Center in preparing the manuscript.

Sources of funding

The authors declare that they have no source of funding.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; 107: 2900-6.
2. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008; 117:1283-91.
3. Nishimura T, Nakajima K, Kusuoka H, et al. Prognostic disease using gated myocardial perfusion SPECT: J-ACCESS study. *Eur J Nucl Med Mol Imaging* 2008;

35: 319-28.

4. Matsumoto N, Sato Y, Suzuki Y, et al. Prognostic value of myocardial perfusion single-photon emission computed tomography for the prediction of future cardiac events in a Japanese population: a middle-term follow-up study. *Circ J* 2007; 71: 1580-5.
5. Germano G, Kiat H, Kavanagh P, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; 36: 2138-47.
6. Willam E, Robert A, Koon K, et al. Optimal medical therapy with or without PCI for stable Coronary disease. *N Engl J Med* 2007; 356: 1503-16.
7. De Bruyne B, William F, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014; 371: 1208-17.
8. Hori Y, Yoda S, Nakanishi K, et al. Myocardial ischemic reduction evidenced by myocardial perfusion imaging after treatment results in good prognosis in patients with coronary artery disease. *J Cardiol* 2015; 65: 278-84.
9. Belardinelli R, Paolini I, Cianci G, et al. Exercise training intervention after coronary angioplasty. *J Am Coll Cardiol* 2001; 37: 1891-900.
10. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenosis. *N Engl J Med* 1996; 334:

1703-8.

11. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis. *J Am Coll Cardiol* 2007; 49: 2105-11.
12. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; 360: 213-24.

Figure Legend

Figure.1

Kaplan-Meier curve of event free survival rate for patients with high or low SSS of first MPI, and patients with mild or significant %residual ischemia

Patients with high SSS experimented more adverse events than those with low SSS ($p=0.025$, log rank test), and patients with significant residual ischemia experimented more adverse events than those with mild residual ischemia ($p=0.003$, log rank test).

SSS: summed stress score; MPI: myocardial perfusion imaging

Figure.2

SPECT images of representative cases in patients with mild and significant %residual ischemia

The case with mild residual ischemia which was almost 0% underwent no adverse event during period followed up. The case with significant residual ischemia which was 66.7% underwent the revascularization during period followed up.

SPECT: single photon emission computed tomography; MPI: myocardial perfusion imaging

Tables

Table.1

Characteristics and SPECT findings of patients with or without adverse events

	Adverse event (+) (n=54)	Adverse event (-) (n=134)	p
Age, y	70 (63-76)	71 (61-76)	0.522
Male gender, n (%)	43 (79.6)	95 (70.9)	0.222
BMI, kg/m ²	23.5 (21.7-25.8)	23.1 (20.9-25.5)	0.503
Diabetes mellitus, n (%)	30 (55.6)	58 (43.3)	0.128
Dyslipidemia, n (%)	29(53.7)	86 (64.1)	0.184
Hypertention, n (%)	38 (70.4)	97 (72.4)	0.782
Current smoker, n (%)	20 (37.0)	44(32.8)	0.585
Family history, n (%)	15 (27.8)	30 (22.4)	0.436
OMI, n (%)	27 (50.0)	68 (50.7)	0.927
Prior PCI, n (%)	43 (79.6)	100 (74.6)	0.47
Prior CABG, n (%)	9 (16.7)	16 (11.9)	0.391
Medication			
Beta-blocker, n (%)	24 (44.4)	48 (35.8)	0.274
ACE inhibitor or ARB, n (%)	37 (68.5)	72 (53.7)	0.064
Nitrate, n (%)	21 (38.9)	52 (38.8)	0.992
Nicorandil, n (%)	17 (31.5)	44 (32.8)	0.859
Ca-blocker, n (%)	34(63.0)	70 (52.2)	0.183
SPECT findings			
pre SSS	11 (5-19)	7 (4-13)	0.019
pre SRS	1 (0-8)	1 (0-6)	0.375
pre SDS	7 (3-9)	5 (2-9)	0.023
post SSS	4 (1-9)	3 (0-7)	0.236
post SRS	0 (0-7)	0 (0-4)	0.475
post SDS	1 (0-3)	0 (0-2)	0.092
%residual ischemia	20.0 (0.0-44.4)	0.0 (0.0-22.2)	0.044
stress LVEF (%)	56 (45-64)	60 (47-66)	0.125
rest LVEF (%)	60 (52-69)	63 (51-68)	0.434
stress LVEDV (ml)	103 (83-117)	94 (75-120)	0.235
rest LVEDV (ml)	96 (84-112)	95 (76-118)	0.341
stress LVESV (ml)	44 (33-58)	39 (27-59)	0.177
rest LVESV (ml)	38 (27-50)	37 (25-53)	0.271

SPECT: single photon emission computed tomography; BMI: body mass index; OMI: old myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; ACE: angiotensin converting enzyme; ARB: angiotensin receptor

blocker; 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; %residual ischemia: $\frac{\text{post SDS}}{\text{pre SDS}} \times 100$

Table 2

Univariate Cox proportional hazards regression analysis for adverse event rates

	Hazard ratio	95% CI	p
Age, y	1.006	0.984-1.034	0.618
Male gender	0.979	0.724-1.028	0.592
BMI, kg/m ²	1.035	0.959-1.120	0.380
Diabetes mellitus	1.670	0.976-2.888	0.061
Dyslipidemia	0.661	0.386-1.137	0.133
Hypertention	0.921	0.523-1.698	0.783
Current smoker	1.340	0.757-2.311	0.307
Family history	1.281	0.685-2.275	0.424
OMI	1.014	0.593-1.735	0.958
Prior PCI	1.137	0.608-2.319	0.702
Prior CABG	1.269	0.580-2.474	0.526
Medication			
Beta-blocker	1.330	0.771-2.270	0.301
ACE inhibitor or ARB	1.601	0.916-2.914	0.100
Nitrate	0.990	0.565-1.699	0.972
Nicorandil	0.960	0.527-1.678	0.889
Ca-blocker	1.333	0.775-2.357	0.302
SPECT findings			
pre SSS	1.037	1.007-1.066	0.016
pre SRS	1.019	0.981-1.053	0.313
pre SDS	1.064	1.008-1.117	0.025
post SSS	1.023	0.985-1.057	0.220
post SRS	1.015	0.974-1.050	0.460
post SDS	1.108	0.981-1.231	0.095
% residual ischemia	1.011	1.001-1.020	0.023
stress LVEF	0.983	0.966-1.000	0.051
rest LVEF	0.991	0.974-1.009	0.303
stress LVEDV	1.003	0.998-1.006	0.215
rest LVEDV	1.003	0.998-1.007	0.242
stress LVESV	1.003	0.999-1.007	0.150
rest LVESV	1.003	0.998-1.007	0.204

BMI: body mass index; OMI: old myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; ACE: angiotensin converting

enzyme; ARB: angiotensin receptor blocker; SPECT: single photon emission computed tomography; 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; %residual ischemia: $\text{post SDS} \times 100 / \text{pre SDS}$

Table.3

Multivariate Cox proportional hazards regression analysis for adverse event rates

	Hazard ratio	95%CI	p
Diabetes mellitus	1.649	0.929-2.956	0.088
SPECT findings			
pre SSS	1.016	0.967-1.067	0.514
pre SDS	1.072	0.995-1.151	0.066
post SDS	0.803	0.608-1.047	0.107
%residual ischemia	1.025	1.004-1.043	0.018
stress LVEF	0.999	0.974-1.025	0.940

SSS: summed stress score; SDS: summed difference score; LVEF: left ventricular ejection fraction; %residual ischemia: $\text{post SDS} \times 100 / \text{pre SDS}$