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LEFT VENTRICULAR DYSSYNCHRONY IN PATIENTS WITH MODERATE CORONARY STENOSIS AND BORDER LINE FRACTIONAL FLOW RESERVE

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ABSTRACT

The cutoff values of fractional flow reserve (FFR) to detect physiological myocardial ischemia are still controversial. Some studies have reported that left ventricular (LV) dyssynchrony occurs in patients with coronary artery disease (CAD). The purpose of this study was to investigate LV dyssynchrony in patients with moderate coronary stenosis and borderline FFR, using stress electrocardiographically-gated myocardial perfusion single-photon emission computed tomography (SPECT). The study population comprised 10 patients with moderate (50–75% diameter) stenosis and an FFR in the range 0.75–0.90, who were compared to 10 control subjects. All underwent stress myocardial ^{99m}Tc-sestamibi (MIBI) or tetrofosmin SPECT imaging. The regional time to end systole (TES), time to peak ejection (TPE), and time to peak filling (TPF) were obtained as indexes of perfusion and function, using gated SPECT (pFAST) in combination with Cardio Gated SPECT Regional Assessment for LV Function (cardioGRAF). The dyssynchrony index (DI) was also calculated. The DI of post-stress TES was significantly greater than that of rest in patients with moderate CAD (4.8 ± 2.8 vs. 2.7 ± 1.5, P = 0.01), but there were no significant differences in the control subjects (3.0 ± 1.7 vs. 2.9 ± 1.9, P = 0.99). There were no significant differences in TPE and TPF between the groups. In conclusion, LV dyssynchrony may occur after stress in patients with coronary stenosis and borderline FFR, even without a significant reduction in perfusion.

Key Words: left ventricular dyssynchrony, fractional flow reserve, stress electrocardiographically-gated myocardial perfusion single-photon emission computed tomography

INTRODUCTION

Using fractional flow reserve (FFR) for guidance during percutaneous coronary intervention (PCI) improves the outcome compared with angiographically guided PCI alone.[1)] An FFR <0.75 is associated with inducible ischemia (specificity 100%), whereas a value >0.80 indicates the absence of inducible ischemia (sensitivity 90%). The FFR range 0.75–0.80 is considered as a gray zone, in which clinical judgment must complement quantitative assessments in forming the final treatment decision.[2, 3)]

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Electrocardiographically (ECG)-gated myocardial perfusion single-photon emission computed tomography (SPECT), incorporating the assessment of perfusion and function using gated SPECT (pFAST) or Cedars Quantitative-Gated SPECT (QGS) software has enabled the analysis of regional left ventricular (LV) wall motion and wall thickness.[4, 5] It has been documented that LV wall motion abnormality after stress is a sensitive marker of myocardial ischemia.[6, 7, 8] A decrease of only 10–20% in subendocardial flow is a sufficient to provoke regional wall motion abnormality, but it is insufficient to produce an obvious myocardial perfusion defect on myocardial perfusion SPECT.[9, 10]

Using ECG-gated myocardial perfusion SPECT with QGS, Horigome *et al.* found that LV dyssynchrony occurs after adenosine stress in patients with coronary artery disease (CAD).[11] Therefore, it is of interest to determine the relationship between borderline FFR and stress-induced LV dyssynchrony in CAD patients because it may be useful for treatment decision.

The purpose of the present study was to investigate LV dyssynchrony in patients with moderate coronary stenosis but with borderline FFR, using exercise or adenosine-stress ECG-gated SPECT.

MATERIAL AND METHODS

Patients

Fourteen consecutive patients with known or suspected myocardial ischemia, based on stress 99mTc-sestamibi (MIBI) or 99mTc-tetrofosmin gated-SPECT, underwent coronary angiography and FFR between June 2000 and August 2012 at Ogaki municipal hospital. Three patients with FFR <0.75 or >0.90 and one patient with significant (90%) stenosis were excluded. Finally we enrolled 10 patients who had only moderate stenosis and FFR in the range 0.75–0.89 (CAD group).

Ten control subjects with normal coronary arteries on a previous conventional coronary angiogram (CAG) or coronary CT angiography also underwent stress using 99mTc-sestamibi (MIBI) gated-SPECT because of suspected angina, but were found to have normal rest and stress myocardial perfusion imaging. Approval from the ethical committee was obtained for anonymous review of the data.

Stress myocardial perfusion imaging

Nine CAD patients and 7 control subjects underwent exercise-stress perfusion scintigraphy, while 1 CAD patient and 3 control subjects underwent adenosine-stress myocardial perfusion scintigraphy. Stress myocardial perfusion imaging with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin was performed using a 1-day protocol. Anti-ischemic agents or beta-blocking agents were withdrawn 48 h before the scintigraphic test. Beverages containing caffeine were also prohibited for at least 12 h before the test.

A symptom-limited treadmill exercise test was performed, during which 370 MBq of ^{99m}Tc-sestamibi or 370 MBq of ^{99m}Tc-tetrofosmin was injected at peak stress, and exercise at the same level was continued for an additional 1 min. Image acquisition was initiated 30 min after the tracer injection. 740 MBq of ^{99m}Tc-sestamibi or 740 MBq of ^{99m}Tc-tetrofosmin was re-injected 3hrs after the initial imaging at rest, and ECG-gated myocardial SPECT images were acquired 30 min after the tracer injection.

For the adenosine stress group, adenosine (Adenoscan, Daiichi-Sankyo Co. Ltd., Tokyo, Japan, 120 μg/kg/min) was administered intravenously for 6 min. Three minutes later, 370 MBq of ^{99m}Tc-sestamibi or 370 MBq of ^{99m}Tc-tetrofosmin was given intravenously. Image acquisition was initiated 30 min after stress. The rest image was acquired in the same way as during the

exercise-stress protocol.

Date acquisition was performed using a parallel dual-head angular rotating γ-camera system (Vertex; ADAC Laboratories, Milpitas, CA) equipped with low energy, high-resolution collimators. Images were obtained over a 180° arc with an acquisition time of 20 s per stop. A 20% symmetric energy window was centered over a 140 KeV photopeak of ^{99m}Tc. The maximum matrix size was 128 × 128. The ECG-gated image was acquired at 16 frames per cardiac cycle, with a beat acceptance window of 30% of the average R-R interval. SPECT images were reconstructed relative to the anatomical axis of the LV. The conventional short-axis, vertical long-axis, and horizontal long-axis slices were generated with dedicated software, combined with filtered back-projection using a Butterworth filter (order of 10 cutoff frequency of 0.32 cycles/pixel) and a ramp filter. No scatter or attenuation correction was applied.

Quantitative-gated SPECT analysis

Each reconstructed image was processed with pFAST version 2.4[4] to determine the inner LV edge. The pFAST data files were further processed with Cardio Gated SPECT Regional Assessment for LV Function (cardioGRAF) to generate the global and regional time-volume curves representing the 17 LV segments on the basis of the recommendation of the American Heart Association Scientific Statements,[12] using a Fourier curve-fitting analysis with three harmonics (1(A)).[5, 13] The selected functional and temporal parameters were as follows. The LV ejection fraction (EF) and peak ejection rate (PER), which correspond to global LV systolic function, and peak filling rate (PFR) and first-third filling rate (1/3FR), which correspond to global LV diastolic function,[14] were derived. The PFR was defined as the maximum FR during the whole diastolic period. The regional time to end systole (TES) and time to peak ejection (TPE), which correspond to systolic temporal parameters, and the time from 0 to peak filling during the whole diastolic period (TPF), which corresponds to the diastolic temporal parameter in each LV segment, were obtained using the cardioGRAF.[14] The dyssynchrony index (DI) was calculated as (the standard deviation [SD] of each temporal parameter among 17 LV segments) × 100/R-R interval. The DI of TES (TES-DI) and of TPE (TPE-DI), which correspond to regional LV systolic dyssynchrony, and the DI of TPF (TPF-DI), which corresponds to regional LV diastolic dyssynchrony, were also calculated (Figure 1(B)).

Coronary angiography and functional flow reserve

According to the American Heart Association criteria,[15] the degree of coronary artery stenosis was rated visually using a caliper by two experienced interventional cardiologists. Fractional flow reserve was evaluated for patients with moderate coronary stenosis of 50–75%. Intracoronary pressure was measured using a 0.014-inch pressure-monitoring guidewire (Pressure wire Certus or Aeris, St Jude Medical, Uppsala, Sweden). Fractional flow reserve was assessed after the administration of adenosine (150 μg/kg/min) through a vein. FFR was calculated as the ratio of the mean distal (trans-stenotic) coronary pressure measured by the pressure wire to the mean aortic pressured measured by guiding catheter at maximal hyperemia.[16]

Statistical analysis

Data are generally presented as mean ± SD or as a percentage. Comparisons were made using Student's t-test for normally distributed variables and Mann–Whitney's U test for non-normally distributed variables. Categorical data were assessed using Fisher's exact probability test. A probability of less than 5% was considered to represent a statistically significant difference. Analysis was performed using the SPSS computer software (version 11.0, SPSS Inc., Chicago, Illinois, USA).

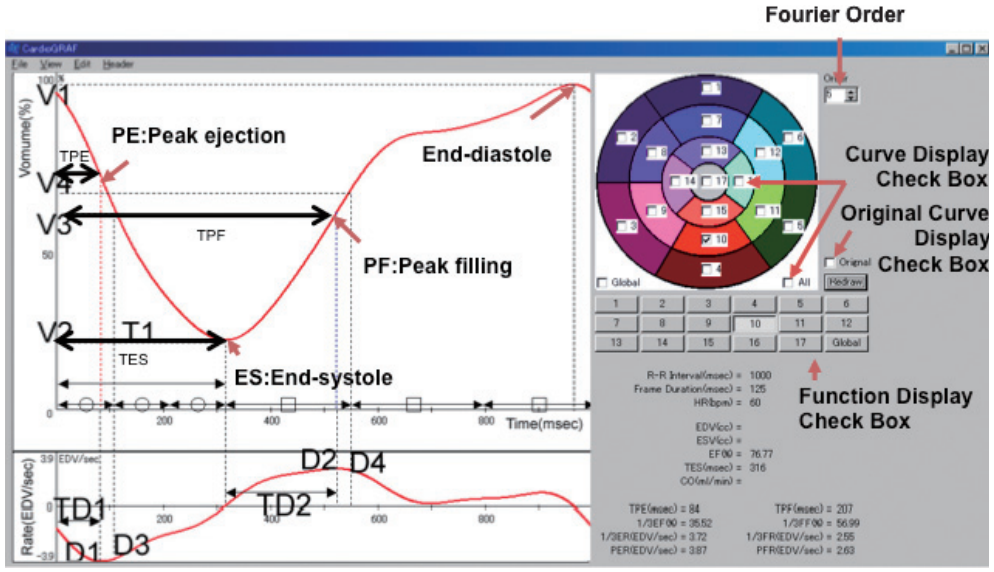

Fig. 1(A)

$$\text{TES-DI} = \frac{\text{SD of TES among 17segments} \times 100}{\text{R-R interval}}$$

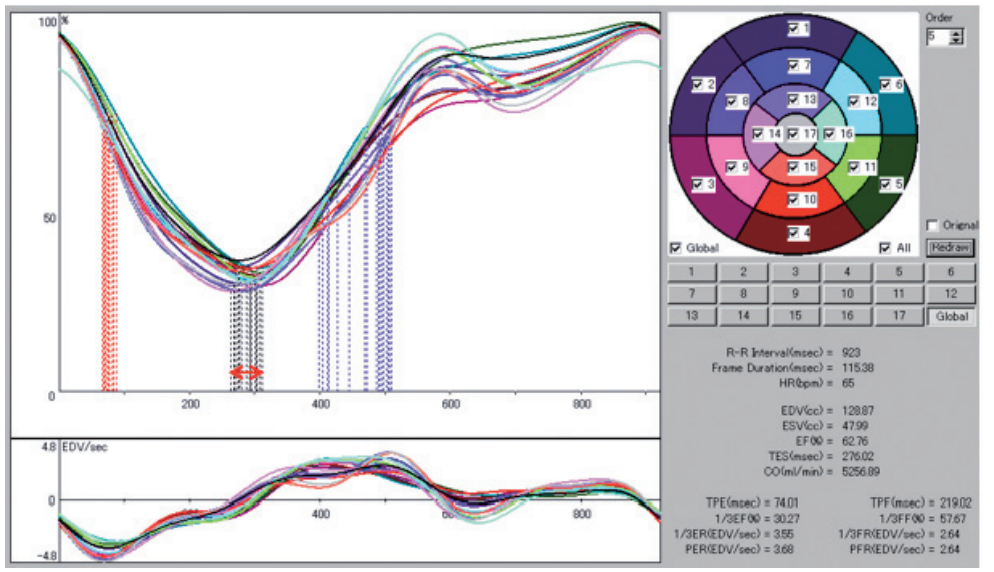

Fig. 1(B)

Fig. 1 Regional left ventricular wall motion obtained by cardioGRAF.
(A) TES, time to end systole(ms); TPE, time to peak ejection (ms); TPF, time from 0 to peak filling (ms).
(B) The dashed lines demonstrate the TES (black), TPE (red), TPF (blue) for each of the 17 segments. The dyssynchrony index (DI) was calculated as (the standard deviation (SD) of each temporal parameter among 17 LV segments) ×100/R-R interval.

RESULTS

Clinical characteristics of the patients

No significant differences were observed in age or heart rate between the 2 groups (Table 1). The prevalence of dyslipidemia was significantly higher in the CAD group than in the control group (8 [80%] vs. 3 [30%], P = 0.035). There were no differences in other coronary risk factors. Three patients in the CAD group but none of the control subjects had previously undergone PCI.

Table 1 Clinical characterisitic

	Control (n=10)	CAD patients (n=10)	P
Age (years)	71.1±9.7	65.2±8.3	0.16
Male	5 (50%)	7 (70%)	0.33
Hypertension	5 (50%)	4 (40%)	0.50
Hypercholesteremia	3 (30%)	8 (80%)	0.035
Diabetes mellitus	2 (20%)	5 (50%)	0.18
History of MI	0 (0%)	2 (20%)	0.24
History of PCI	0 (0%)	3 (30%)	0.11
Resting HR (/min)	67.4±11.6	71.0±12.9	0.52

Data are expressed as mean ± SD or number (%).

CAD, coronary artery disease; HR, heart rate; MI, myocardial infarction; PCI, parcutaneus coronary intervention.

Global left ventricular functional analysis

The data concerning the global LV functional assessments are presented in Table 2. There were no significant differences in end-diastolic volume, end-systolic volume, EF, PER, PFR, and 1/3FR at either rest or post-stress between the 2 groups. There were no significant differences in TES, TPF at either rest or post-stress between the 2 groups. Although there was no difference in TPE at rest, post-stress TPE significantly greater in the CAD group than in the control group (132.6 ± 14.7 vs. 107.9 ± 16.0, P = 0.002).

Regional left ventricular temporal analysis

In the CAD group, post-stress TES-DI was significantly higher than that at rest (4.8 ± 2.8 vs. 2.7 ± 1.5, P = 0.01), whereas no significant change was seen in the control group (2.9 ± 1.9 vs. 3.0 ± 1.7, P = 0.99) (Figures 2 and 3 and 4). No significant changes were observed in TPE-DI (3.6[2.7–4.1] vs. 3.7[2.5–4.8], P = 0.80 in the CAD group; 3.3[1.5–6] vs. 3.5[1.4–4.9], P = 0.24 in the control group, respectively) and TPF-DI (8.8±3.5 vs. 9.3±5.4, P = 0.7 in the CAD group ; 8.4±6.7 vs. 8.8±7.4 , P = 0.63 in the control group, respectively) between rest and post-stress in either group.

Table 2 Global left ventricular functional analysis

	LV function at rest		
	Control	CAD	P
EDV (ml)	135.7±41.4	208.5±180.1	0.55
ESV (ml)	45.6±17.6	89.0±111.7	0.50
EF (%)	67.0±4.2	62.9±9.2	0.21
PER (EDV/s)	3.4±0.5	3.2±0.5	0.47
PFR (EDV/s)	2.4±0.5	2.3±0.6	0.89
1/3FR (EDV/s)	1.7±0.9	1.6±0.8	0.84
TES (ms)	302.3±30.1	304.0±26.2	0.89
TPE (ms)	108.0±13.8	108.9±25.5	0.92
TPF (ms)	254.4±162.3	254.0±129.8	0.99
HR	67.4±11.6	71.0±12.9	0.52
	LV function at stress		
EDV (ml)	131.7±31.9	213.9±207.5	0.88
ESV (ml)	47.0±14.4	94.0±112.4	0.29
E F(%)	64.6±4.6	59.5±7.8	0.09
PER (EDV/s)	3.2±0.5	2.8±0.8	0.16
PFR (EDV/s)	2.4±0.4	2.3±0.9	0.80
1/3FR (EDV/s)	1.94±0.6	1.6±1.1	0.41
TES (ms)	307.5±25.1	309.8±50.7	0.90
TPE (ms)	107.9±16.0	132.6±14.7	0.002
TPF (ms)	202.7±69.0	182.6±52.8	0.48
HR	68.3±11.9	72.6±14.6	0.48

Data are expressed as mean ±SD.

1/3FR, first-third filling rate; CAD, coronary artery disease; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; LV, left

ventricular; PER, peak ejection rate; PFR, peak filling rate; TES,

time to end systole; TPE, time to peak ejection; TPF, the time to peak Filling.

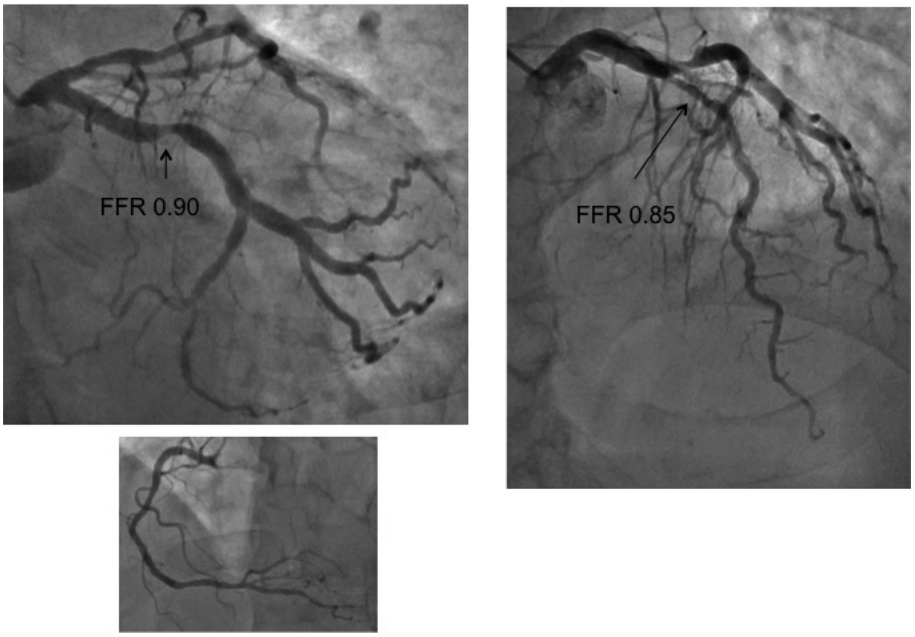

Fig. 2(A)

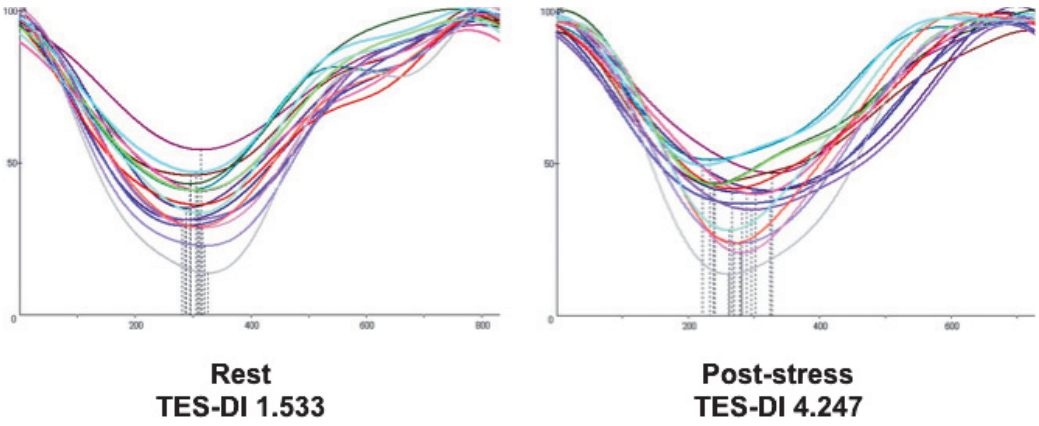

Fig. 2(B)

Fig. 2 An example of CAD patients.
(A) 68-y-old man who had moderate stenosis with FFR 0f 0.85 in left anterior descending coronary artery.
(B) Comparison of TES-DI of a CAD patient between rest and stress. TES, time to end systole(ms); DI, dyssynchrony index.

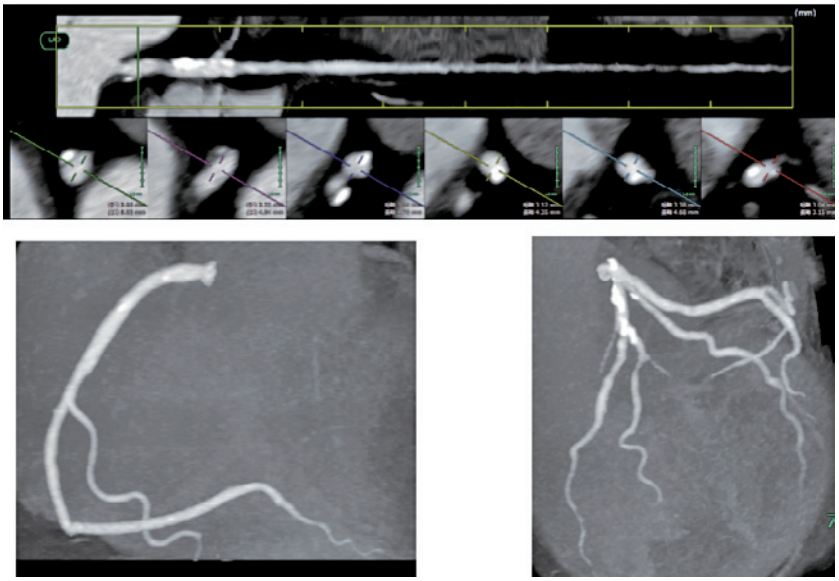

Fig. 3(A)

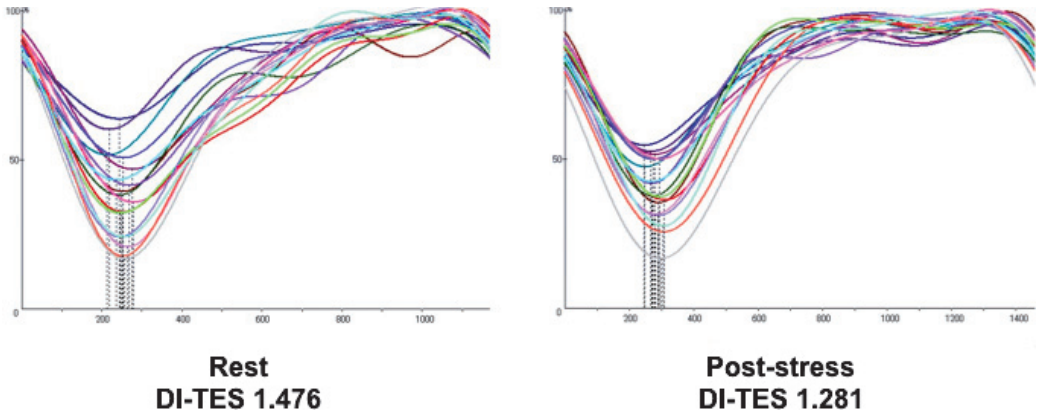

Fig. 3(B)

Fig. 3 An example of control subjects.
(A) 74-y-old man. There seems to be a stenosis in left anterior descending coronary artery because of calcified lesion.But there are not stenosis by cross-sectional image.
(B) Comparison of TES-DI of a control subject between rest and stress. TES, time to end systole(ms); DI, dyssynchrony index.

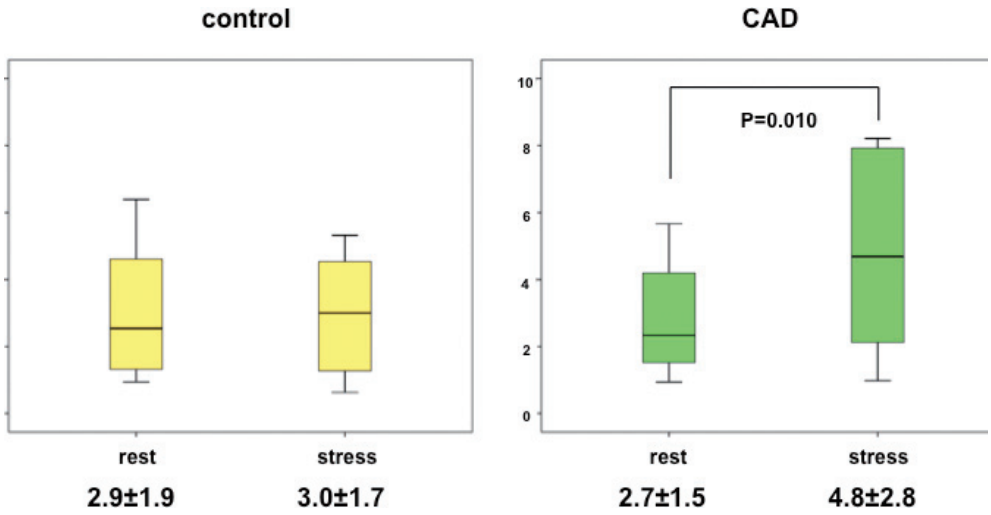

Fig. 4 Comparison of TES-DI between rest and stress.
TES, time to end systole(ms); TPE, time to peak ejection(ms); TPF, timeto peak filling(ms); DI, dyssynchrony index.

DISCUSSION

Several randomized trials have reported that FFR-guided PCI improves prognosis.[1, 17, 18] Generally, PCI was performed in patients with FFR <0.75 and deferred in those with FFR >0.80. For patients with an FFR in the range 0.75–0.80, the decision was left to the operator's discretion. The cutoff value (0.75 or 0.80) was defined according to the ischemic evidence on stress-rest myocardial perfusion scintigraphy.[2] Therefore, we hypothesize that moderate stenosis with an FFR of 0.75–0.89 induces post-stress LV dyssynchrony without an obvious perfusion defect.

Some studies using ECG-gated SPECT have shown that post-stress functional parameters might differ from the true resting parameters because of extensive post-ischemic myocardial stunning.[19, 20] In addition, many studies using gated-SPECT have reported that systolic and diastolic LV wall motion abnormalities are induced by exercise or adenosine stress in CAD patients.[7, 21]

Some studies have reported that the assessment of wall motion abnormality immediately after stress gives an incremental diagnostic value to myocardial perfusion SPECT alone for identifying mild single-vessel and multi-vessel CAD.[6, 8, 22] Yoda *et al.* demonstrated that wall motion analysis added an incremental value to myocardial perfusion SPECT alone for detecting myocardial ischemia in patients with mild (50–75% stenosis), single-vessel CAD.[8] On the other hand, some studies have shown that wall motion analysis by ECG-gated SPECT appears to be of little value in the detection of mild CAD. Perhaps it may depend on the duration of post-stress myocardial stunning. Usually, image acquisition is begun 15–45 min after stress and completed 30–60 min after stress in order to avoid the noise from high isotope accumulation in the liver, gallbladder, spleen and intestines. In an experimental model of single-vessel CAD, Hormans *et al.* showed that post-ischemic myocardial stunning only persists 15–30 min after exercise.[23] In humans, Ambrosio *et al.* showed that post-exercise myocardial stunning might persist for 120 min, but the time span between exercise cessation and regional functional recovery depends on the angiographic severity; that is, less severe angiographic lesions were associated with more prompt functional recovery.[24] Yoda *et al.* demonstrated an improved sensitivity for detecting single-vessel

mild CAD by analyzing wall motion immediately after exercise. They indicated that post-exercise data acquisition was completed within 17 min after exercise cessation in all patients.[8] On the other hand, in this study, image acquisition was begun within 30 min after stress cessation.

Recently, myocardial perfusion SPECT has enabled the analysis of regional LV wall motion and wall thickness in combination with QGS or pFAST software.[4, 5, 13, 14] A previous study reported that LV mechanical dyssynchrony occurs in CAD patients with narrow QRS complexes and without previous myocardial infarction.[25] Few studies have investigated whether LV dyssynchrony is induced by myocardial stunning after stress. Horigome *et al.* indicated that LV dyssynchrony detected by QGS occurs after adenosine stress in CAD patients.[11] In this study, post-stress LV systolic dyssynchrony occurred in the CAD patients with only moderate stenosis and FFR in the range 0.75–0.89. Most enrolled patients had only left anterior descending lesion. In such patients, the time to end systole of apical or anteroseptal wall tended to be prolonged. However, this study included patients having multiple moderate stenosis. In addition, it may be difficult to identify the vessel feeding abnormal area. Therefore, further examination should be evaluated from this point. In excluded patients with FFR<0.75, post stress LV systolic dyssynchrony occurred. However FFR didn't reflect the range of ischemia. Thus, there was no correlation between values of FFR and DI.

TES/RR was prolonged after stress in CAD patients. On the contrast, there were not significant change in TPE-DI between rest and post-stress. In the previous report, maximal difference of TES was prolonged after stress in CAD patients, although maximal difference of TPE was not significantly prolonged.[11] Therefore the variation of segmental TPE may be hard to detect.

The global LV functional parameters and diastolic dyssynchrony indexes did not change with stress. However, the small sample size and the difficulty of detecting the timing of peak filling on the time-velocity curve might have affected our results.

This study has some limitations. First, the sample size was very small. Second, the CAD group included patients who had undergone PCI or myocardial infarction but did not have a perfusion defect. These patients were enrolled in order to increase the very small sample size, because we thought it would be of value to assess the wall motion in the absence of a perfusion defect. However, it is possible that the dyssynchrony we observed might not have been the result of the lesion calculated by FFR, but could have been due to another lesion or to myocardial remodeling. Ten control subjects without CAD were enrolled for purposes of comparison with the scintigraphic data of the CAD patients. Since they had some risk of developing atherosclerosis, they underwent conventional coronary angiography or coronary CT angiography. Accordingly, it remains unknown whether they were really healthy subjects. Moreover, they might have had a mild stenosis with FFR <0.90. However, ethical reasons precluded performing invasive coronary angiography and FFR evaluation in known healthy control subjects.

If the post-stress LV dyssynchrony affect the prognosis of patients, revascularization therapy is required for patients with moderate CAD in whom post-stress LV dyssynchrony occur regardless of value of FFR.

CONCLUSION

Post-stress LV dyssynchrony was observed in patients with moderate stenosis and FFR in the range 0.75–0.89. Our results might be of incremental diagnostic value and could aid appropriate decision making strategies in CAD patients with moderate coronary stenosis.

DISCLOSURES

Dr. Hideki Ishii received lecture fees from Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., and Otsuka Pharma Inc. Dr. Toyoaki Murohara received lecture fees from Bayel Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Sanofi-aventis K.K., and Takeda Pharmaceutical Co., Ltd. Dr. Toyoaki Murohara received unrestricted research grant for Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc, Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-aventis K.K., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd.

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