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ORIGINAL ARTICLE

Effect of exercise-based cardiac rehabilitation on non-culprit mild coronary plaques in the culprit coronary artery of patients with acute coronary syndrome

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Abstract Approximately, 70 % of acute myocardial infarctions are known to develop from mild atherosclerotic lesions. Therefore, it is important to evaluate mild coronary plaques to prevent acute coronary syndrome (ACS). The aim of the present study was to investigate the effects of exercise-based cardiac rehabilitation (CR) on mild coronary atherosclerosis in non-culprit lesions in patients with ACS. Forty-one men with ACS who underwent emergency percutaneous coronary interventions and completed a 6-month follow-up were divided into CR and non-CR groups. Quantitative coronary angiography (QCA) was performed using the automatic edge detection program. The target lesion was a mild stenotic segment (10–50 % stenosis) at the distal site of the culprit lesion, and the segment to be analyzed was determined at a segment length ranging from 10 to 15 mm. The plaque area was significantly decreased in the CR group after 6 months, but was significantly increased in the non-CR group ($P < 0.05$). The low-density lipoprotein (LDL) cholesterol, LDL/high-density lipoprotein (HDL) ratio and high-sensitivity C-reactive protein (Hs-CRP) levels were significantly reduced in both groups ($P < 0.01$). Peak VO_2 in the CR group was significantly increased ($P < 0.01$). Changes in the plaque area correlated with those in Hs-CRP in both groups, while that association with those in HDL-C was observed in only CR group. Stepwise regression analysis revealed the decrease in Hs-CRP as an independent predictor of plaque area regression in the CR group. CR prevented the progression of mild coronary atherosclerosis in patients with ACS.

Keywords Cardiac rehabilitation · Mild coronary stenosis · Plaque area · Exercise tolerance · High-sensitivity C-reactive protein

Introduction

Percutaneous coronary intervention (PCI) plays a central role in the treatment of acute coronary syndrome (ACS). The restenosis rate following percutaneous coronary intervention was previously reported to be reduced to less than 10 % with a drug-eluting stent (DES) and only 30 % with a bare-metal stent [1–3]. Although DES led to a marked reduction in target lesion revascularization, no significant differences were observed in cardiovascular events or long-term total mortality [4]. In addition, 70 % of acute myocardial infarctions are known to develop from mild atherosclerotic lesions [5]. Therefore, the stabilization of atherosclerotic plaques in patients with mild coronary artery stenosis may contribute to the prevention of ACS.

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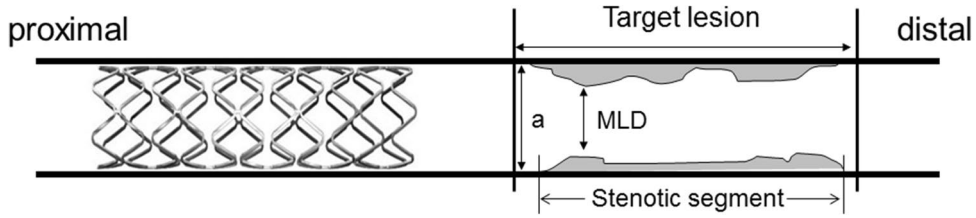

Fig. 1 Target lesion by quantitative coronary analysis. Modified with permission from "Shinzo" [13]. MLD (minimum lumen diameter): the narrowest lumen diameter automatically measured in the average 10–50 % stenotic segment within a length of 10–15 mm. Percentage diameter stenosis (%DS): calculated from (a–MLD)/a. Quantitative coronary analysis parameters were calculated automatically by CAAS2000

Exercise-based cardiac rehabilitation (CR) was recently revealed to play a crucial role in preventing the progression of atherosclerosis and improving the long-term prognoses of patients with ACS [6]. These findings indicated that CR decreased the morbidity and mortality rates by preventing atherosclerosis, and improved physical, psychological, and social functions in patients with cardiovascular disease [7]. Previous studies demonstrated that long-term CR decreased the incidence of cardiovascular events as well as the regression of coronary stenosis [8, 9]. Moreover, short-term (6–12 months) CR has been shown to prevent the progression of stenotic lesions more than conventional treatments [10, 11]. Many of these studies evaluated the mean value of the minimum lumen diameter (MLD) and percentage diameter stenosis (%DS) in all coronary arteries. A previous study reported that coronary endothelial dysfunction distal to the stent was associated with poor neointimal coverage following the implantation of drug-eluting stent [12]; therefore, may progress in the distal segment of the stent atherosclerosis. Few exercise intervention studies have directly examined changes in mild coronary plaques in the distal segment of the stent.

The aim of the present study was to investigate the effects of exercise-based CR on residual mild coronary atherosclerosis in the culprit coronary artery of patients with ACS.

Patients and methods

Subjects and study protocol

Forty-one men with ACS who underwent emergency PCI and completed a 6-month follow-up were divided into CR and non-CR groups. The subjects were divided by the intention of the patients, not by randomization. Exclusion criteria were being older than 80 years old, end-stage renal disease, dementia, inflammatory diseases, known malignant diseases, narrowing of the left main coronary artery (lumen diameter ≤50 %), and a target lesion diameter under 1 mm. Consecutive cases were selected to complete the program of the present study and perform quantitative coronary analysis (QCA) before and after the intervention in both groups. This study was approved by the Ethical Committee of the Kansai Medical University. Written informed consent was obtained from all subjects prior to the start of the study.

Baseline measurements included QCA and biochemical data on admission, and a cardiopulmonary exercise test (CPX) on discharge. Follow-up QCA, biochemical data, and CPX were repeated after 6 months. The repeated CPX was only for the CR group. The CR group performed aerobic exercise (3 times per week for 30 min on a bicycle or treadmill at the anaerobic threshold) and resistance training (modified push-ups, sit-ups, and squats with body weight; 3 sets of 10–15 repetitions at Borg index 11–13, respectively, 3 times per week). The non-CR group received conventional therapy without CR.

Quantitative coronary angiography

Details of QCA used in the present study were described previously [13, 14]. In brief, the automatic edge detection program in the QCA was performed using CAAS2000 (Pie Medical Imaging, Maastricht, The Netherlands). The automatic edge detection program determined the vessel contours by assessing brightness along the scan lines perpendicular to the vessel center. QCA was performed by two technicians who were blinded to other data in this project. The end-diastolic frame, the frame in which the blood vessel was filled with the contrast medium and no branch-overlapping segment were selected for the analysis of both baseline and follow-up coronary angiograms [14–16]. The end-diastolic frames from both angiograms were selected with identical angulations that showed the stenosis most prominently with minimal foreshortening and branch overlapping. The coronary artery segment analyzed included all those with a reference diameter ≥1 mm, and visually 10–50 % stenosis at the distal site of the culprit lesion within the range of 10–15 mm in length (Fig. 1). Selected

target segment was reproduced at baseline and follow-up study using the same angiographic angle. The MLD was defined as the narrowest lumen diameter (mm) in the analyzed segment. Computer software automatically measured the MLD, %DS, plaque area, plaque volume, segment length, and reference diameter.

Evaluation of cardiovascular risk factors

Body weight and body mass index were measured. Blood pressure was taken from the right arm of the seated participant after at least 15 min of rest. Blood samples were collected to determine the serum levels of triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, the LDL/HDL ratio, plasma glucose, HbA1c, estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (Hs-CRP). The eGFR was calculated on the basis of the new Japanese coefficient-modified Modification of Diet in Renal disease study equation: $\text{eGFR}\left(\text{ml/min/1.73m}^2\right) = 194 \times \text{serum Creatinine}^{-1.094} \times \text{Age}^{-0.287}$ [17] Hs-CRP was determined by the latex-enhanced immunonephelometry assay (AU5800, Beckman Coulter Inc., USA). Biochemical indicators, except for Hs-CRP, were measured on admission as the baseline and after 6 months of the intervention. Hs-CRP was also measured before discharge and after 6 months of the intervention.

Cardiopulmonary exercise test

A symptom-limited CPX was performed by all patients using a cycle ergometer (232C-XL; Combi Co., Ltd., Japan). After 5-min rest on the ergometer, exercise started with a 4-min warm-up at 10 watts and 50 rpm, followed by the 10–20 watt ramp method. A 12-lead electrocardiogram, heart rate, and blood pressure were monitored throughout the test using the Stress test system (ECG-9521; NIHON KOHDEN Co., Ltd., Japan). We measured oxygen uptake (VO_2), carbon dioxide output, and minute ventilation on a breath-by-breath basis using an expired gas analyzer (AE-300s; Minato Medical Science Co. Ltd., Japan). The anaerobic threshold was determined by the V-slope method [18]. Peak VO_2 and work rate (WR) were defined as the peak value during incremental exercise.

Statistical analysis

All data were expressed as the mean ± SD. The Chi-square test was used to identify significant differences between categorical variables. The Mann–Whitney test for unpaired data was applied for comparisons between the groups. Differences in continuous variables between two time-points were evaluated by the Wilcoxon test. Correlations between two changes in variables were determined using Spearman's test. Stepwise multiple regression analysis was used to determine the independent predictors of changes in the plaque area. All statistical analyses were performed using SPSS 19.0 J for Windows (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered significant.

Results

Comparison of clinical characteristics at baseline

The clinical characteristics of the study groups are presented in Table 1. The CR group showed significantly higher peak creatine phosphokinase (CPK) levels and significantly lower left ventricular ejection fractions (LVEF) than those of the non-CR group in the baseline. No significant differences were observed in the other variables between the groups. Medications started all on admission in both groups.

Changes in QCA variables for mild stenotic lesions

Changes in QCA parameters are presented in Table 2. No significant differences were observed in MLD (1.9 ± 1.1 vs. 1.7 ± 0.4 mm), %DS (21.9 ± 15.9 vs. 23.6 ± 12.9 %), plaque area (3.6 ± 5.5 vs. 2.1 ± 1.9 mm^2), or plaque volume (10.1 ± 15.4 vs. 5.3 ± 4.5 mm^3) for the baseline QCA parameters between the CR and non-CR groups. Furthermore, no significant differences were noted in the analyzed segment length (13.3 ± 4.6 → 13.7 ± 4.6 mm in the CR group, 12.9 ± 4.4 → 13.2 ± 4.4 mm in the non-CR group) or the reference diameter (2.2 ± 0.6 → 2.3 ± 0.6 mm in the CR group, 2.2 ± 0.4 → 2.4 ± 0.4 mm in the non-CR group) before and after the intervention in both groups. On the other hand, the plaque area was significantly decreased (3.6 ± 5.5 → 2.0 ± 2.9 mm^2, $P < 0.05$) in the CR group, but was significantly increased (2.1 ± 1.9 → 2.9 ± 2.4 mm^2, $P < 0.05$) in the non-CR group. Moreover, changes in the plaque area and volume were significantly different between the two groups. The CR group had an improvement, while the non-CR group had a deterioration (Δplaque area: −1.6 ± 3.4 vs. 0.8 ± 1.2 mm^2, $P < 0.01$; Δplaque volume: −4.3 ± 9.8 vs. 1.1 ± 4.8 mm^3, $P < 0.05$, respectively) (Fig. 2).

Changes in coronary risk factors and exercise tolerance

Changes in coronary risk factors are presented in Table 3. No significant differences in the body weight, blood pressure and blood biomarkers between the two groups were noted in their baseline values. The LDL cholesterol, LDL/HDL ratio and Hs-CRP levels were significantly decreased

Table 1 Clinical characteristics of the study groups in the baseline

	CR group ($n = 21$)	Non-CR group ($n = 20$)	P value
Age (years)	63.1 ± 9.1	61.3 ± 8.4	0.383
Body mass index (kg/m^2)	23.7 ± 2.6	24.0 ± 2.5	0.885
MI/AP	19/2	16/4	0.343
Culprit lesion (RCA/LAD/LCx)	6/13/2	4/12/4	0.724
Stent (BMS/DES)	12/9	11/9	0.890
Peak CPK (IU/L)	3520.9 ± 3275.0	1260.3 ± 2510.1	0.022
LVEF (%)	50.1 ± 15.4	63.1 ± 10.2	0.008
Systolic blood pressure (mmHg)	116.5 ± 15.9	117.9 ± 18.5	0.800
Diastolic blood pressure (mmHg)	72.9 ± 8.9	69.8 ± 10.0	0.291
Hypertension, *n* (%)	13 (61.9)	12 (60.0)	0.901
Dyslipidemia, *n* (%)	12 (57.1)	12 (60.0)	0.228
Diabetes mellitus, *n* (%)	5 (23.8)	5 (25.0)	0.929
Current smoker, *n* (%)	11(52.3)	10 (50.0)	0.939
AT VO_2 (ml/kg/min)	11.0 ± 1.7	11.4 ± 2.4	0.366
Peak VO_2 (ml/kg/min)	18.0 ± 4.2	19.4 ± 4.3	0.147
Medication			
Statin, *n* (%)	14 (66.7)	16 (80.0)	0.335
ARB or ACE, *n* (%)	13 (61.9)	15 (75.0)	0.368
β-blocker, *n* (%)	8 (38.1)	12 (60.0)	0.161
Calcium-channel blocker, *n* (%)	2 (9.5)	4 (20.0)	0.343
Diuretic, *n* (%)	1 (4.8)	2 (10.0)	0.520

Values are expressed as the mean ± SD

ACE angiotensin-converting enzyme inhibitor, *AP* angina pectoris, *ARB* angiotensin II receptor blocker, *AT* anaerobic threshold, *BMS* bare-metal stent, *CPK* creatine, *DES* drug-eluting stent, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *RCA* right coronary artery, *VO_2* oxygen consumption

Table 2 Changes in mild stenotic atherosclerosis lesions

	CR group ($n = 21$)			Non-CR group ($n = 20$)		
	Baseline	6 months	Δ	Baseline	6 months	Δ
Segment length (mm)	13.3 ± 4.6	13.7 ± 4.6	0.4 ± 2.1	12.9 ± 4.4	13.2 ± 4.4	0.4 ± 2.5
Reference diameter (mm)	2.2 ± 0.6	2.3 ± 0.6	0.1 ± 0.5	2.2 ± 0.4	2.4 ± 0.4	0.2 ± 0.3
MLD (mm)	1.9 ± 1.1	1.9 ± 0.6	0.1 ± 1.2	1.7 ± 0.4	1.7 ± 0.4	0.1 ± 0.2
%DS (%)	21.9 ± 15.9	16.1 ± 15.5	−5.8 ± 16.6	23.6 ± 12.9	26.0 ± 13.2	2.4 ± 8.9
Plaque area (mm^2)	3.6 ± 5.5	2.0 ± 2.9*	−1.6 ± 3.4††	2.1 ± 1.9	2.9 ± 2.4*	0.8 ± 1.2
Plaque volume (mm^3)	10.1 ± 4.6	5.7 ± 8.3	−4.3 ± 9.8†	5.3 ± 4.5	6.4 ± 6.0	1.1 ± 4.8
New lesion, *n* (%)	–	1 (5.9)	–	–	2 (12.5)	–

Values are expressed as the mean ± SD

%DS percentage diameter stenosis, *MLD* minimum lumen diameter

P values are indicated as: * $P < 0.05$ vs. baseline, † $P < 0.05$ vs. Non-CR group, †† $P < 0.01$ vs. Non-CR group

in both groups ($P < 0.01$, respectively) (Table 3). No significant differences were observed in the changes in other variables. The Hs-CRP levels after 6 months were slightly lower in the CR group than in the non-CR group ($P = 0.09$). There were no significant differences in body weights and blood pressures. Statin was administrated after admission, and medical treatments showed no essential difference in the groups during the study period.

CPX was performed in the CR group only after 6 months. Peak VO_2 and peak WR after 6 months were significantly increased in the CR group ($P < 0.01$, respectively).

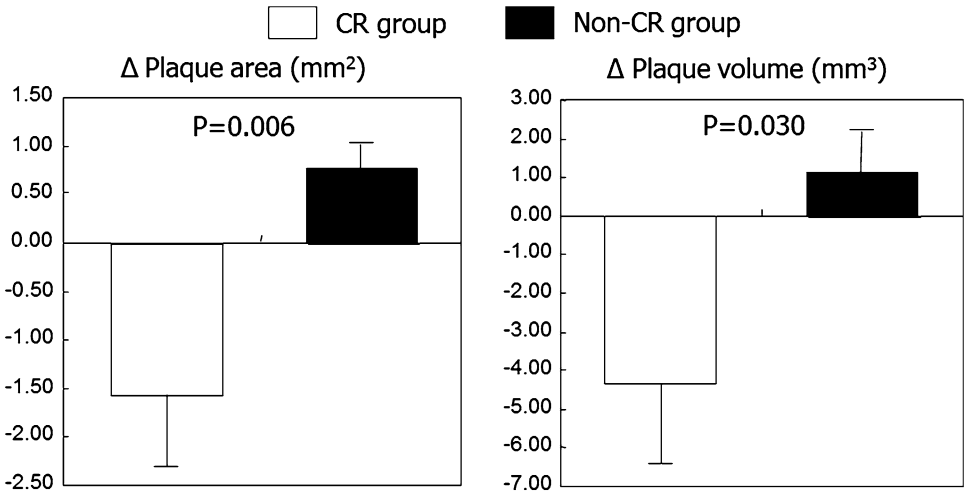

Fig. 2 Comparisons of changes in the plaque area and plaque volume. Changes in the plaque area and volume were significantly different between the two groups. The CR group had an improvement, while the non-CR group had a deterioration

Table 3 Changes in coronary risk factors and exercise tolerance

	CR group ($n = 21$)		Non-CR group ($n = 20$)	
	Baseline	6 months	Baseline	6 months
Body weight (kg)	66.0 ± 9.6	65.3 ± 10.0	66.2 ± 10.2	66.0 ± 10.0
Systolic blood pressure (mmHg)	116.5 ± 15.9	119.5 ± 15.7	117.9 ± 18.5	120.9 ± 19.6
Diastolic blood pressure (mmHg)	72.9 ± 8.9	72.6 ± 8.1	69.8 ± 10.0	72.4 ± 10.1
Triglycerides (mg/dl)	163.1 ± 118.2	141.6 ± 61.5	133.0 ± 54.8	120.4 ± 34.5
HDL cholesterol (mg/dl)	45.9 ± 10.1	45.3 ± 10.2	46.0 ± 16.2	48.5 ± 14.7
LDL cholesterol (mg/dl)	115.0 ± 45.1	81.5 ± 19.0**	122.4 ± 32.8	88.3 ± 17.0**
LDL/HDL ratio	2.7 ± 1.2	1.9 ± 0.6**	3.1 ± 1.2	2.1 ± 0.7**
Plasma glucose (mg/dl)	154.2 ± 44.6	137.5 ± 54.3	144.4 ± 63.3	120.6 ± 32.6
HbA1c (%)	6.7 ± 1.4	6.7 ± 1.2	6.4 ± 1.2	5.9 ± 0.4
eGFR (ml/min/1.73 m^2)	74.8 ± 17.0	70.5 ± 11.6	76.9 ± 17.9	72.1 ± 14.4
Hs-CRP (mg/dl)	0.427 ± 0.519	0.063 ± 0.060**	0.471 ± 0.436	0.140 ± 0.244*
Peak VO_2 (ml/kg/min)	18.0 ± 4.2	20.5 ± 4.2**	19.4 ± 4.3	NA
Peak WR (watt)	95.8 ± 21.2	103.9 ± 23.1**	99.8 ± 23.6	NA

Values are expressed as the mean ± SD

eGFR estimated glomerular filtration rate, *HDL* high-density lipoprotein, *Hs-CRP* high-sensitivity C-reactive protein, *LDL* low-density lipoprotein, VO_2 oxygen consumption, *WR* work rate

P values are indicated as: * $P < 0.05$, ** $P < 0.01$ vs. baseline

Univariate and multiple regression analyses to identify the predictors of coronary plaque regression after CR

The relationship between changes in plaque variables and changes in lipid, inflammation, and exercise tolerance is presented in Table 4. Changes in the plaque area (Δplaque area) correlated with changes in HDL cholesterol levels (ΔHDL) ($r = -0.46$, $P < 0.05$) and Hs-CRP levels (ΔHs-CRP) ($r = 0.62$, $P < 0.01$). Changes in the plaque volume (Δplaque volume) also correlated with ΔHDL ($r = -0.44$, $P < 0.05$) and ΔHs-CRP ($r = 0.56$, $P < 0.01$) in the CR group. Patients in non-CR group were observed only between correlation plaque variables and Hs-CRP ($P < 0.05$). On the other hand, changes in Peak VO_2 (ΔPeak VO_2) correlated with ΔHs-CRP ($r = -0.59$, $P < 0.01$) in the CR group.

We then performed a stepwise multiple regression analysis to identify the independent predictors of plaque area regression in both groups; the independent variables examined were ΔHDL, ΔLDL, ΔHS-CRP, ΔPeak VO_2 (only CR group), adjustment for age, smoking, and the administration of statins. The results revealed that a decrease in Hs-CRP levels was an independent predictor of plaque area regression in the CR group ($r^2 = 0.44$, $P < 0.01$)(Table 5). However, the independent predictor of change in plaque area in the non-CR group could not be detected in these variables.

Table 4 Correlations between changes in plaque variables and changes in lipid, inflammation, and exercise tolerance

CR group	ΔPlaque area	ΔPlaque volume	ΔPeak VO_2
ΔHDL	−0.46*	−0.44*	−0.15
ΔLDL	0.13	0.01	−0.23
ΔLDL/HDL ratio	0.05	0.16	−0.15
ΔHs-CRP	0.62**	0.56**	−0.59**
ΔPeak VO_2	−0.13	−0.20	–
Non-CR group	ΔPlaque area	ΔPlaque volume	ΔPeak VO_2
ΔHDL	−0.06	0.33	NA
ΔLDL	0.26	0.09	NA
ΔLDL/HDL ratio	0.39	0.07	NA
ΔHs-CRP	0.51*	0.57*	NA
ΔPeak VO_2	NA	NA	–

Values are expressed as correlation coefficients

HDL high-density lipoprotein, *Hs-CRP* high-sensitivity C-reactive protein, *LDL* low-density lipoprotein, *VO_2* oxygen consumption

P values are indicated as: * $P < 0.05$, ** $P < 0.01$

Table 5 Stepwise regression analyses to determine the predictors of plaque area regression in the CR group

	β	*P* value
Age	−0.05	0.802
Smoking	0.12	0.535
Statin	0.01	0.957
ΔHDL	−0.34	0.060
ΔLDL	−0.23	0.219
ΔHs–CRP	0.66	0.002
ΔPeak VO_2	0.36	0.118

B standardized partial regression coefficient, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *Hs-CRP* high-sensitivity C-reactive protein, *VO_2* oxygen consumption

Discussion

We evaluated residual mild stenotic lesions in the culprit coronary artery by QCA, and investigated the effects of CR in patients with ACS. The main finding of the present study is that the plaque area and plaque volume significantly decreased in the CR group, whereas both these parameters significantly increased in the non-CR group. The LDL cholesterol, LDL/HDL ratio and Hs-CRP levels were significantly decreased in both groups, while Peak VO_2 significantly increased in the CR group.

Previous studies reported that CR did not allow MLD to progress [10, 11], and physical activity of 2200 kcal/week or more led to a regression in coronary plaques [19]. In addition, lifestyle modifications with a focus on exercise training improved endothelial function, and higher improvement rates have been reported in patients with endothelial dysfunction after exercise training [20]. Based on these findings, we speculated that exercise training, mainly aerobic training, may have beneficial effects by preventing as well as ameliorating arteriosclerosis. The above findings are consistent with the results of the present study. Statins are generally considered to induce the regression of coronary plaques [21–24]. Moreover, an appropriate combination of statin therapy and physical activity may also result in coronary plaque regression [25]. Statin doses in our study were definitely lower than those in the PROVE IT-TIMI22 trial [26] and the SATURN study [27]. In the present study, statins were administered equally to both groups, which led to a significant decrease in LDL cholesterol levels and LDL/HDL ratio. In spite of the advantage of normalizing lipids by the administration with statins in both groups, the plaque area only decreased significantly in the CR group after 6 months. These results indicated that CR may have contributed to regression of atheromatous plaques.

We also demonstrated that changes in both the plaque area and plaque volume in the CR group positively correlated with changes in Hs-CRP levels, and negatively with changes in HDL cholesterol levels. Moreover, changes in peak VO_2 negatively correlated with those in Hs-CRP levels. Stepwise multiple regression analysis identified Hs-CRP as an independent predictor of changes in the plaque area in the CR group. Hs-CRP levels were slightly lower in the CR group than in the non-CR group. Previous studies showed that CR has significant reduction in Hs-CRP [28, 29]. On the other hands, Hs-CRP is an independent predictor of coronary heart disease [30–32], and also that plaque ruptures often occur in patients with higher Hs-CRP [33]. CRP is mainly produced in the liver and also

from atherosclerotic lesions; therefore, it may be related to the progression of atherosclerosis [34, 35]. CRP is considered to act in both a paracrine and autocrine manner on atherosclerotic lesions. CRP inhibits not only nitric oxide (NO) production through endothelial NO synthase, but also promotes the production of interleukin-6 (IL-6), a major inflammatory cytokine, and endothelin-1, a strong endothelium-derived vasoconstrictor [36]. The production of IL-6 in adipose tissue was shown to be inhibited with reductions in body weight and Hs-CRP levels [37]. Since, no significant differences were observed in body weight between both groups, the decrease in Hs-CRP levels in the CR group may have occurred independently of weight loss. Although the inflammatory cytokines that promote the production of CRP are mainly produced in adipose tissue, they are also produced in endothelial cells and skeletal muscles [38, 39]. We speculated that NO production may have increased in the CR group because of an improvement in Peak VO_2, which has been associated with enhanced endothelial function through increases in the number of endothelial progenitor cells [40, 41]. IL-6 levels may simultaneously be decreased due to improvements in skeletal muscle function because peak WR increased in the CR group [38]. It was shown that IL-6 levels were significantly lower in heart failure patients without muscle loss [42]. The results of this study suggest that the prevention of plaque progression through improvements in endothelial function may have occurred via two mechanisms: an increase in Peak VO_2 and a reduction in proinflammatory cytokines. We thought that the substantial plaque regression might be due to the reduction in Hs-CRP by CR. These are the reasons why we presume synergistic effects to induce a strong anti-inflammatory action by more factors other than only medication such as statin may contribute plaque regression through the reduction of HS-CRP in CR group of patients. However, these mechanisms have yet to be examined in detail.

Our study is the first to examine the effects of CR on residual mild plaques in the culprit coronary artery on QCA in patients with ACS. As unstable mild plaques are likely to remain in the culprit artery, in addition to the culprit segment, clinical implications of preventing the progression of mild stenotic lesions are crucial. The distal segment of the culprit lesion was selected as a target lesion because it is less injured by catheter-related insults than the proximal segment.

There were several limitations to the present study. First, intravascular ultrasound (IVUS) is a useful method for analyzing coronary plaque [43], but we did not use IVUS to evaluate plaque lesions. However, changes in the plaque area by QCA have been associated with changes in the plaque volume by IVUS [14]. Thus, QCA is considered to be a useful, reliable, and simple method for detecting changes in coronary atherosclerosis. Because IVUS may also damage the coronary artery intima, additional insults to the normal coronary artery are unacceptable. The reproducibility problem of QCA may still remain. Therefore, meticulous attention was paid to match the analysis frame and imaging angle, as suggested by a previous study [14]. Second, the non-CR group did not perform the CPX after 6 months. However, since the subjects did not perform the exercise-based CR, exercise tolerance cannot be improved. Therefore, exercise tolerance should not be improved in the non-CR group. Third, changes in daily physical activities might be affected for the results in this study. CR group could complete to participation of three times a week in this program, but daily physical activities were not able to be measured. Finally, this study constituted a small sample, nonrandomized, and single center study. CR on an outpatient basis for ACS patients is hardly randomized in clinical practice. It is our intention to emphasize that post-ACS patients with high motivation to improve their lifestyle, despite of higher CPK and lower LVEF in the baseline, resulted in better study outcomes. These data are provocative and should encourage to perform larger multicenter studies.

Conclusions

Exercise-based CR may prevent the progression of residual mild plaques in the culprit coronary artery of patients with ACS. The plaque regression and anti-inflammatory effects of CR on mild stenotic lesions may contribute to prevent the recurrence and development of ACS from a new lesion.

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Conflict of interest The authors declare that they have no conflict of interest.

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