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ORIGINAL ARTICLE

Clinical Effects of Supervised Cardiac Rehabilitation in Patients With Angina and Non-Obstructive Coronary Artery Disease and Impaired Myocardial Flow Reserve Assessed Using ^{13}N-Ammonia Positron Emission Tomography

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Background: The efficacy of exercise-based cardiac rehabilitation (CR) in patients with angina and non-obstructive coronary artery disease (ANOCA) remains unclear. This study investigated whether a multidisciplinary CR program improves myocardial flow reserve (MFR), symptom status, and exercise capacity in patients with ANOCA.

Methods and Results: Myocardial blood flow at rest and during ATP-induced hyperemia was quantified using ^{13}N-ammonia positron emission tomography (PET) in 29 patients diagnosed with ANOCA and impaired MFR (<2.5). Overall, 16 patients completed the 5-month CR program (complete CR group) and 13 did not (non-complete CR group). At baseline and the 5-month follow-up PET, symptom status and exercise capacity were assessed using the Seattle Angina Questionnaire (SAQ)-7 and cardiopulmonary exercise testing, respectively. The MFR in the complete CR group increased significantly (P=0.001) from a median of 1.60 (interquartile range [IQR] 1.43–1.98) to 2.09 (IQR 1.83–2.48). Significant improvements were also seen in the median SAQ-7 total score (from 16 [IQR 11–20] to 11 [IQR 8–14]; P=0.008) and peak oxygen consumption ($\dot{V}O_2$; from 14.2 [IQR 12.4–15.8] to 15.3 [13.0–17.9] mL/kg/min; P=0.02). In contrast, there were no improvements in MFR (P=0.83) or peak $\dot{V}O_2$ (P=0.27) in the non-complete CR group.

Conclusions: The 5-month exercise-based CR significantly improved MFR, symptom status, and exercise capacity in patients with ANOCA and impaired MFR.

Key Words: Cardiac rehabilitation; Coronary microvascular dysfunction; Exercise capacity; Positron emission tomography; Quality of life

The diagnosis of angina and non-obstructive coronary artery disease (ANOCA) is a therapeutic challenge with ANOCA contributing to significant economic, social, and healthcare costs.[1] ANOCA comprises different pathophysiological disease entities, including coronary microvascular dysfunction (CMD), coronary endothelial dysfunction, and epicardial coronary vasospasm.[2] In particular, >50% of patients with ANOCA are believed to have CMD.[1,3] CMD is typically defined as impaired vasodilation of the arterioles, leading to an inadequate increase in myocardial blood flow (MBF) from rest to stress; however, significant variation has been reported in the diagnostic criteria used to define CMD.[1] Positron emission tomography (PET) is one of the most accurate imaging modalities for non-invasively identifying CMD by assessing MBF and myocardial flow reserve (MFR).[1,4]

The optimal management of patients with ANOCA remains a major unmet need due to the lack of large randomized studies with homogeneous patient groups, making it difficult to generate evidence-based recommendations. Currently, no established treatments are available for ANOCA and impaired MFR. Thus, treatments are often empirical and complicated due to the multifactorial pathophysiology and overlapping phenotypes that often coexist. Notably, in patients with coronary artery disease (CAD), guidelines[5,6] strongly recommend exercise-based cardiac rehabilitation (CR), which includes comprehensive supervised exercise training, health education, and patient counseling for cardiovascular risk reduction. The 2020 European Society of Cardiology guidelines[5] suggested that patients

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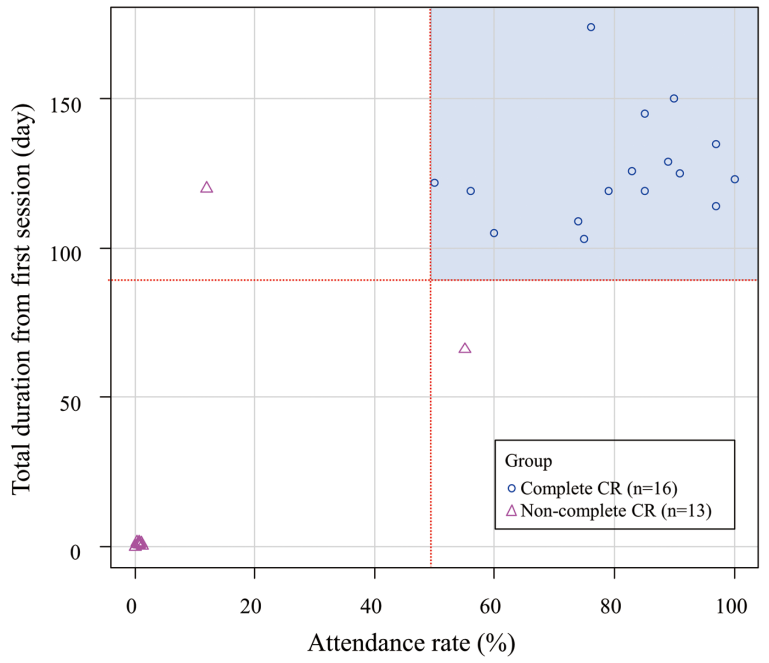

Figure 1. Relationship between attendance rate and the total duration since the first session stratified by group. CR, cardiac rehabilitation.

with ischemia and non-obstructive CAD should adhere to the same exercise recommendations as those for long-standing CAD. However, the efficacy and feasibility of this recommendation have not been fully evaluated in patients with ANOCA and impaired MFR.

The aim of this pilot study was to investigate whether a supervised 5-month CR program improves PET-derived MFR, symptom status, and exercise capacity in patients with ANOCA and impaired MFR compared with patients who did not complete the program, while also evaluating the feasibility and safety of the program.

Methods

Study Population

In this single-center retrospective observational study, we included 32 consecutive patients with ANOCA and impaired MFR assessed using ^{13}N-ammonia myocardial perfusion PET at our heart center between November 2018 and November 2022. A 5-month exercise-based CR program, along with appropriate medical interventions, including comprehensive patient education, lifestyle modifications, and management of cardiovascular risk factors, was proposed in our outpatient department at the first diagnosis. All study participants underwent myocardial perfusion PET examination, assessment of symptom status using the Seattle Angina Questionnaire (SAQ)-7,[7] and assessment of exercise capacity using cardiopulmonary exercise testing (CPX) at baseline and the 5-month follow-up. Three patients refused these follow-up visits and were excluded. The remaining 29 patients were included in the study and divided into 2 groups depending on whether they completed the CR program (complete CR group; n=16) or not (non-complete CR group; n=13), as shown in **Figure 1**. CR completion was predefined as attending >50% of the scheduled total sessions and having a duration of >90 days from the first to the last session within the 5-month CR program. Attendance was evaluated using medical records. The attendance rate was determined by dividing the total number of completed CR sessions by the total number of scheduled CR sessions, which were individually set before starting the 5-month CR program. Sessions were scheduled twice weekly based on consensus among attending physicians, physical therapists, and participating patients. ANOCA was defined as having rest/effort angina and no significant stenosis in an epicardial coronary artery of ≥2 mm diameter (<50% coronary diameter stenosis or >0.80 fractional flow reserve), assessed using coronary computed tomography (CT) angiography or invasive coronary angiography (**Figure 2A**).[2] Impaired MFR was defined as MFR <2.5.[1,3] Demographic, risk factor, and medication use data were obtained from medical records.

This study was performed in accordance with the Declaration of Helsinki and the ethical principles in the Belmont Report, and was approved by the Institutional Review Board of Sapporo Kojinkai Memorial Hospital (Approval no. 20228). The requirement for informed consent was waived due to the retrospective study design.

Exercise-Based CR Program

National health insurance is mandatory in Japan, and CR has been covered for treating stable CAD since 1996. We conducted a supervised CR program for the study participants based on the guidelines of the Japanese Circulation Society.[6] Briefly, the guideline-oriented exercise therapy consisted of endurable exercises, including warm-up, stretching, moderate-to-high-intensity aerobic exercise, and resistance training (**Figure 2B**). Exercise training was based on the CPX results, and an individualized program was created for each patient. Aerobic exercise was performed for 20–30 min/day with exercise intensity limited to

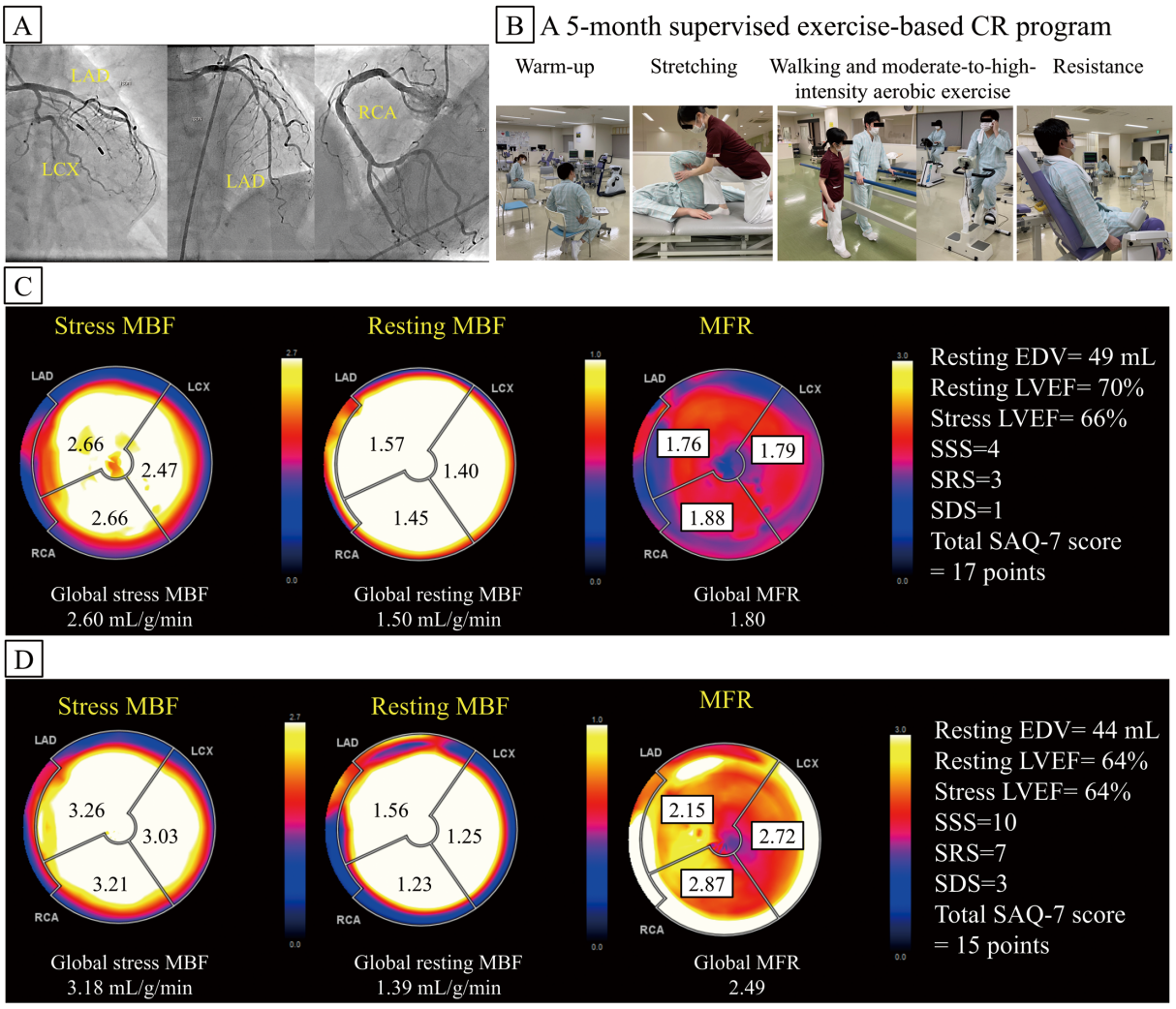

Figure 2. Representative case of a symptomatic 81-year-old woman in the complete cardiac rehabilitation (CR) group. (**A**) Invasive coronary angiography showed no significant stenosis in each coronary artery, with a fractional flow reserve of 0.85 in the left anterior descending coronary artery (LAD). LCX, left circumflex coronary artery; RCA, right coronary artery. (**B**) A 5-month supervised exercise-based CR program is implemented for a total of 122 days, with a 50% attendance rate. (**C**,**D**) Myocardial perfusion positron emission tomography (PET), including polar map analysis of quantitative myocardial perfusion imaging (**Left**, stress myocardial blood flow [MBF]; **Middle**, resting MBF; **Right**, myocardial flow reserve [MFR]) in each coronary territory and PET-derived indices, were assessed and compared between baseline (**C**) and follow-up (**D**), with a considerable improvement in global stress MBF (2.60 vs. 3.18 mL/g/min) and global MFR (1.80 vs. 2.49). EDV, end-diastolic volume; LVEF, left ventricular ejection fraction; SAQ-7, Seattle Angina Questionnaire; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score.

70–85% of the peak heart rate (HR) at which the ST was depressed by 1 mm or at 10-beats/min lower HR. The intensity was aimed at the anaerobic threshold (i.e., 40–60% of peak oxygen uptake), Karvonen's formula ([maximum HR − resting HR] × [0.4−0.6] + resting HR), and a rating of perceived exertion of 12–13 on the Borg scale. Because baseline exercise capacity and personal training goals varied across patients, the number of training hours was not stipulated in the program. Finally, multidisciplinary guidance on ANOCA management, including home-based regular exercise, was provided to all participating patients and/or their families regardless of their participation in CR.

MBF and MFR Measurements

Stress/resting MBF and MFR were quantified in all patients at baseline and at the 5-month follow-up. The detailed methods used for MBF quantification at rest and during hyperemia have been described elsewhere.[8] Briefly, single-day ^{13}N-ammonia PET using a PET/CT scanner (Biograph mCT Flow 64-4R PET/CT system; Siemens Healthcare, Erlangen, Germany) was performed at rest and during ATP-induced hyperemia for 5 min at a rate of 160 μg/kg/min, with 3 MBq/kg ^{13}N-ammonia injected over a 30-s period 3 min after starting ATP infusion. The resting scan was obtained following injection of 3 MBq/kg of ^{13}N-ammonia over a 30-s period 1 h after the stress scan.

Table 1. Baseline Characteristics Overall and in Patients According to Completion of CR

	Overall (n=29)	Complete CR (n=16)	Non-complete CR (n=13)	P value
Demographic characteristics				
Age (years)	75 [73–80]	74 [74–80]	75 [70–78]	0.50
Female sex	15 (52)	9 (56)	6 (46)	0.71
Body mass index (kg/m^2)	22.9 [21.8–24.0]	23.0 [22.3–25.9]	22.2 [21.8–22.9]	0.17
PET indication				
Effort angina	26 (90)	15 (94)	11 (85)	0.19
Rest angina	1 (3)	1 (6)	0 (0)	
Others	2 (7)	0 (0)	2 (15)	
Medical history				
Hypertension	20 (69)	11 (69)	9 (69)	1.0
Dyslipidemia	18 (62)	9 (56)	9 (69)	0.7
Diabetes	10 (35)	5 (31)	5 (39)	0.71
Prior PCI	6 (21)	2 (13)	4 (31)	0.36
Prior admission for HF	0 (0)	0 (0)	0 (0)	1.0
Chronic kidney disease	14 (48)	10 (63)	4 (31)	0.14
Current smoker	4 (14)	4 (25)	0 (0)	0.10
Medications				
Antiplatelet therapy	10 (35)	5 (31)	5 (39)	0.71
Calcium channel blockers	11 (38)	4 (25)	7 (54)	0.14
β-blockers	7 (24)	5 (31)	2 (15)	0.41
Cholesterol-lowering agents	13 (45)	7 (44)	6 (46)	1.0
ACEi/ARB	8 (28)	5 (31)	3 (23)	0.69
Nitrates	2 (7)	1 (6)	1 (8)	1.0
Laboratory values				
Hemoglobin (g/dL)	13 [11–14]	13 [11–15]	13 [11–14]	0.93
eGFR (pg/mL)	60 [53–66]	58 [53–65]	65 [59–66]	0.44
LDL-C (mg/dL)	97 [81–126]	93 [83–119]	105 [80–129]	0.74
HbA1c (%)	6.0 [5.9–6.8]	6.0 [5.7–6.6]	6.1 [5.9–6.8]	0.61
NT-proBNP (pg/mL)	166 [82–443]	163 [82–375]	173 [91–893]	0.77
Coronary assessment				
CCTA	21 (72)	11 (69)	10 (77)	0.69
Invasive coronary angiography	20 (69)	10 (63)	10 (77)	0.45
Fractional flow reserve	13 (45)	6 (38)	7 (54)	0.46
CR program attendance				
Attendance rate (%)	56 [0–85]	84 [75–90]	0 [0–0]	<0.001
Total no. sessions	18 [0–31]	31 [23–36]	0 [0–0]	<0.001
Total duration from first session (days)	109 [0–123]	123 [118–131]	0 [0–0]	<0.001

Unless indicated otherwise, data are presented as median [interquartile range] or n (%). ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCTA, coronary computed tomographic angiography; CR, cardiac rehabilitation; eGFR, estimated glomerular filtration rate; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention; PET, positron emission tomography.

Throughout each flow measurement, the electrocardiogram (ECG) was monitored continuously, and HR and blood pressure were measured at 1-min intervals. PET images were analyzed quantitatively using the Syngo MBF software package (Siemens Healthcare). Global MFR was calculated by dividing stress MBF by resting MBF. Semiquantitative assessments of myocardial perfusion (segmental perfusion scores) and left ventricular function were performed as described previously.[8] To correct the resting MBF for baseline work, the rate-pressure product (RPP) was calculated as HR×systolic blood pressure. Corrected resting MBF was then calculated as resting MBF multiplied by 10,000 divided by resting RPP. Corrected MFR was determined by dividing stress MBF by corrected resting MBF.[9]

Symptom Assessment

Symptom status was assessed using the SAQ-7,[7] which provides individual scores in 3 domains, namely physical limitation (Questionnaire 1a–c), angina frequency (Questionnaires 2 and 3), and quality of life (Questionnaires 4 and 5). The maximum scores (i.e., worst symptom status) in the physical limitation, angina frequency, and quality of life domains were set to 15 (5 points × 3), 12 (6 points × 2), and 10 (5 points × 2) points, respectively. Therefore, the maximum and minimum total scores were 37 and 7, respectively. None of the patients limited their activities for any reason other than those covered in Questionnaire 1.

Exercise Capacity Assessments

CPX was performed via a ramp protocol using a bicycle

Table 2. Baseline Physiological Parameters in Patients Who Did and Did Not Complete CR

	Overall (n=29)	Complete CR (n=16)	Non-complete CR (n=13)	P value
PET findings				
Resting MBF (mL/g/min)	1.06 [0.92–1.24]	1.04 [0.81–1.47]	1.08 [0.93–1.22]	0.87
Resting RPP (mmHg/[beats/min])	9,821 [7,524–13,616]	8,831 [7,551–11,369]	10,395 [7,198–13,851]	0.59
Corrected resting MBF (mL/g/min)[A]	0.94 [0.84–1.47]	1.15 [0.86–1.48]	0.93 [0.84–1.32]	0.51
Stress MBF (mL/g/min)	1.82 [1.40–2.17]	1.72 [1.34–2.15]	2.05 [1.51–2.40]	0.35
MFR	1.71 [1.49–1.94]	1.60 [1.43–1.98]	1.77 [1.67–1.89]	0.32
Corrected MFR[A]	1.60 [1.29–2.26]	1.54 [1.15–1.80]	1.61 [1.45–2.48]	0.13
Resting EDV (mL)	85 [73–117]	87 [76–122]	81 [66–107]	0.45
Resting LVEF (%)	66 [59–75]	67 [61–74]	66 [59–76]	0.70
Stress LVEF (%)	64 [57–72]	63 [56–70]	65 [59–73]	0.69
Summed rest score	4 [2–5]	4 [2–5]	2 [2–4]	0.24
Summed stress score	6 [3–8]	6 [4–10]	4 [3–6]	0.14
Summed difference score	2 [1–4]	2 [1–5]	2 [1–2]	0.27
Symptom assessment (SAQ-7)				
Total score (range 7–37)	17 [13–22]	16 [11–20]	22 [15–22]	0.10
Physical limitation domain (range 3–15)	6 [5–9]	6 [3–6]	9 [6–10]	0.005
Angina frequency domain (range 2–12)	5 [4–7]	6 [4–7]	4 [4–6]	0.82
Quality of life domain (range 2–10)	5 [3–7]	5 [3–6]	6 [5–7]	0.05
CPX findings				
Peak HR (beats/min)	107 [98–111]	107 [100–110]	107 [98–113]	0.80
Peak systolic blood pressure (mmHg)	171 [162–194]	184 [162–198]	170 [162–192]	0.70
Peak diastolic blood pressure (mmHg)	80 [74–89]	80 [75–91]	80 [69–88]	0.56
Peak $\dot{V}O_2$ (mL/kg/min)	13.7 [12.1–15.8]	14.2 [12.4–15.8]	13.2 [11.2–15.9]	0.43
Peak $\dot{V}O_2$/HR (mL/kg/min/[beats/min])	7.4 [6.4–9.5]	9.0 [6.7–9.6]	7.3 [6.0–8.6]	0.17
Peak work rate (W)	53 [42–63]	61 [44–69]	46 [41–60]	0.28

Unless indicated otherwise, data are presented as the median [interquartile range] or n (%). [A]Corrected resting myocardial blood flow (MBF) was calculated as resting MBF multiplied by 10,000 divided by resting rate-pressure product (RPP); corrected myocardial flow reserve (MFR) was calculated by dividing stress MBF by corrected resting MBF. CPX, cardiopulmonary exercise testing; EDV, end-diastolic volume; HR, heart rate; LVEF, left ventricular ejection fraction; SAQ-7, Seattle Angina Questionnaire-7; $\dot{V}O_2$, oxygen consumption. Other abbreviations as in Table 1.

ergometer to evaluate symptoms, ECG changes, arrhythmia, blood pressure, HR response, and exercise capacity. During the testing, patients were encouraged to achieve a peak respiratory exchange ratio of ≥1.1 or prespecified exercise-stopping criteria.[6] A symptom-limited CPX was performed at baseline and the end of the CR program. After an initial 2-min rest on a bicycle ergometer in the upright position, patients started pedaling at an intensity of 0 W for 1 min (warm-up) and then performed an incremental exercise test with a ramp protocol (10 or 15 W/min) until exhaustion. A 12-lead ECG was recorded continuously, and blood pressure was measured every minute using a sphygmomanometer. The expired gas was collected and continuously analyzed using an AE-300S gas analyzer (Minato, Osaka, Japan). The following parameters were measured during CPX: peak oxygen consumption ($\dot{V}O_2$), peak $\dot{V}O_2$/HR, and peak work rate (WR). The WR 1 min before reaching the anaerobic threshold was used for exercise prescription.[6]

Statistical Analyses

Unless stated otherwise, categorical data are presented as numbers and percentages, whereas continuous data are presented as the mean±SD or as the median with interquartile range (IQR) if normal distribution could not be assumed. Baseline clinical data were compared using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The significance of differences between baseline and follow-up was assessed using the Wilcoxon signed-rank test. Between-group differences in changes and percentage changes in physiological parameters from baseline to follow-up were evaluated using the Mann-Whitney U test. All tests were 2-sided, and statistical significance was defined as $P<0.05$. All statistical analyses were performed using Stata BE 18.0 (StataCorp, College Station, TX, USA) and R software version 4.3.1 (R Project for Statistical Computing, Vienna, Austria).

Results

Baseline Patient Characteristics

The final analysis included 29 patients (median age 75 years, 52% female), 16 and 13 in the complete and non-complete CR groups, respectively (**Figure 1**). In the non-complete CR group, 2 patients started the CR program but stopped midway due to temporary closure of the CR site, thus not meeting the definition of complete CR; the remaining 11 patients declined to participate in the CR program for individual reasons, including commuting distance, lack of time, and high cost. The median attendance rates were 84% and 0% in the complete and non-complete CR groups, respectively. No harmful events were documented in any patient during the CR sessions. **Figure 1** shows the relationship between the total duration from the first CR session and attendance rate. None of the baseline characteristics

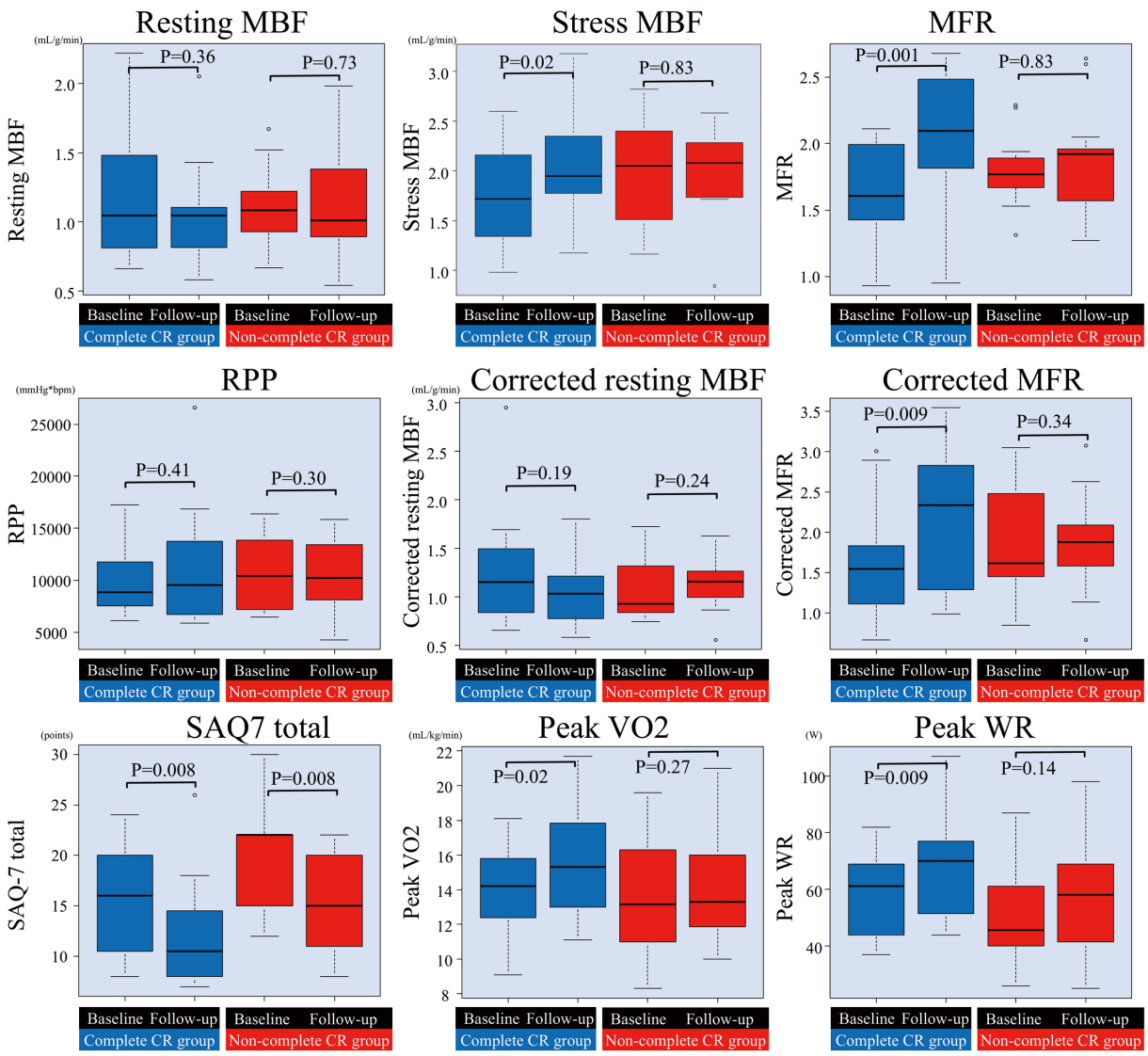

Figure 3. Changes in major physiological measurements from baseline to follow-up stratified by group. Corrected resting myocardial blood flow (MBF) was calculated as resting MBF multiplied by 10,000 divided by resting rate-pressure product (RPP); corrected myocardial flow reserve (MFR) was calculated by dividing stress MBF by corrected resting MBF. CR, cardiac rehabilitation; SAQ-7 total, total score on the Seattle Angina Questionnaire-7; $\dot{V}O_2$, oxygen consumption; WR, work rate.

differed significantly between the 2 groups, except for CR program attendance (**Table 1**). Similarly, no significant differences were found in medications between the 2 groups at follow-up. No significant differences were found in the baseline physiological parameters of PET-related indices, symptom assessments, and CPX findings, except for physical limitation scores, which were significantly lower in the complete CR than non-complete CR group (median 6 [IQR 3–6] vs. 9 [IQR 6–10] points, respectively; P=0.005; **Table 2**).

Changes in Physiological Parameters

The changes in major physiological measurements from baseline to follow-up are shown in **Figure 3**, and detailed changes in all measured indices in each of the 2 groups are presented in **Table 3**. The complete CR group exhibited a significant increase in stress MBF (median 1.72 [IQR 1.34–2.15] vs. 1.94 [IQR 1.80–2.30] mL/g/min; P=0.02) and MFR (1.60 [IQR 1.43–1.98] vs. 2.09 [IQR 1.83–2.48]; P=0.001) from baseline to follow-up, whereas resting MBF did not differ significantly between the baseline and follow-up PET examinations (1.04 [IQR 0.81–1.47] vs. 1.04 [IQR 0.88–1.17] mL/g/min; P=0.36). **Figure 2** shows a representative case from the complete CR group with considerable improvement in stress MBF and MFR from baseline to follow-up. In contrast, no change was noted in stress MBF (P=0.83), MFR (P=0.83), and resting MBF (P=0.73) in the non-complete CR group. The between-group difference was significant for MFR (P=0.01) but not for stress (P=0.14) or resting MBF (P=0.29). A slight, albeit not

statistically significant, decrease in resting RPP was noted in both groups; consequently, neither group exhibited significant changes in the corrected resting MBF. The complete CR group showed considerable improvement in corrected MFR from baseline to follow-up (P=0.009), but the non-complete CR group did not (P=0.34). No changes in other parameters, such as left ventricular ejection function and summed difference scores, were observed in either group. In addition, no significant difference was observed in body weight within each group or between the 2 groups from baseline to follow-up.

Regarding symptom assessments, the median total SAQ-7 score improved considerably from baseline to follow-up in both the complete CR (from 16 [IQR 11–20] to 11 [IQR 8–14] points; P=0.008) and non-complete CR (from 22 [IQR 15–22] to 15 [IQR 11–20] points; P=0.008) groups. Scores in the 3 domains (physical limitation, angina frequency, and quality of life) improved significantly at follow-up in both groups, except for the angina frequency score in the non-complete CR group (P=0.13). Regarding exercise capacity, there were marked improvements from baseline to follow-up in the complete CR group in peak $\dot{V}O_2$ (median 14.2 [IQR 12.4–15.8] to 15.3 [IQR 13.0–17.9] mL/kg/min; P=0.02), peak $\dot{V}O_2$/HR (9.0 [IQR 6.7–9.6] to 8.4 [IQR 6.9–10.9] mL/kg/min/(beats/min); P=0.04), and peak WR (61 [IQR 44–69] to 70 [IQR 52–77] W; P=0.009), but not in the non-complete CR group.

Table 3. Changes in Physiological Measurements

	No. patients	Baseline	Follow-up	Difference	P value (baseline vs. follow-up)	P value (CR vs. non-CR)
Myocardial perfusion (PET)						
Resting MBF (mL/g/min)						
Complete CR	16	1.04 [0.81, 1.47]	1.04 [0.88, 1.17]	−0.06 [−0.13, 0.10]	0.36	0.29
Non-complete CR	13	1.08 [0.93, 1.22]	1.01 [0.89, 1.38]	0.01 [−0.04, 0.19]	0.73	
Resting RPP						
Complete CR	16	8,831 [7,551, 11,369]	9,505 [6,687, 13,725]	−711 [−3,513, 2,296]	0.41	0.23
Non-complete CR	13	10,395 [7,198, 13,851]	10,206 [8,120, 13,416]	−2,183 [−3,864, −435]	0.30	
Corrected resting MBF[A] (mL/g/min)						
Complete CR	16	1.15 [0.86, 1.48]	1.03 [0.78, 1.20]	−0.07 [−0.48, 0.18]	0.19	0.08
Non-complete CR	13	0.93 [0.84, 1.32]	1.16 [0.99, 1.27]	0.19 [−0.01, 0.23]	0.24	
Stress MBF (mL/g/min)						
Complete CR	16	1.72 [1.34, 2.15]	1.94 [1.80, 2.30]	0.25 [0.04, 0.44]	0.02	0.14
Non-complete CR	13	2.05 [1.51, 2.40]	2.08 [1.73, 2.28]	0.03 [−0.36, 0.22]	0.83	
MFR						
Complete CR	16	1.60 [1.43, 1.98]	2.09 [1.83, 2.48]	0.41 [0.05, 0.62]	0.001	0.01
Non-complete CR	13	1.77 [1.67, 1.89]	1.92 [1.57, 1.96]	0.04 [−0.22, 0.26]	0.83	
Corrected MFR[A]						
Complete CR	16	1.54 [1.15, 1.80]	2.33 [1.34, 2.81]	0.43 [0.00, 0.94]	0.009	0.01
Non-complete CR	13	1.61 [1.45, 2.48]	1.88 [1.58, 2.09]	−0.15 [−0.35, 0.03]	0.34	
EDV (mL)						
Complete CR	16	87 [76, 122]	88 [77, 100]	0 [−4, 2]	0.40	0.02
Non-complete CR	13	81 [66, 107]	85 [71, 106]	5 [1, 8]	0.07	
Resting EF (%)						
Complete CR	16	67 [61, 74]	65 [59, 75]	−1 [−4, 1]	0.13	0.13
Non-complete CR	13	66 [59, 76]	69 [62, 69]	1 [0, 3]	0.55	
Stress EF (%)						
Complete CR	16	63 [56, 70]	61 [56, 68]	−2 [−5, 1]	0.36	0.78
Non-complete CR	13	65 [59, 73]	63 [61, 71]	−1 [−3, 0]	0.18	
Summed rest score						
Complete CR	16	4 [2, 5]	4 [3, 5]	0 [−1, 1]	0.36	0.68
Non-complete CR	13	2 [2, 4]	3 [1, 4]	0 [−1, 1]	0.83	
Summed stress score						
Complete CR	16	6 [4, 10]	8 [5, 10]	1 [0, 3]	0.19	0.70
Non-complete CR	13	4 [3, 6]	5 [2, 8]	0 [0, 2]	0.55	
Summed difference score						
Complete CR	16	2 [1, 5]	4 [1, 5]	1 [0, 2]	0.17	0.84
Non-complete CR	13	2 [1, 2]	2 [1, 4]	0 [0, 2]	0.29	

(**Table 3** continued the next page.)

	No. patients	Baseline	Follow-up	Difference	P value (baseline vs. follow-up)	P value (CR vs. non-CR)
Symptom status (SAQ-7)						
Total score (range 7–37)						
Complete CR	16	16 [11, 20]	11 [8, 14]	−2 [−8, 0]	0.008	0.94
Non-complete CR	13	22 [15, 22]	15 [11, 20]	−4 [−7, −1]	0.008	
Physical limitation domain (range 3–15)						
Complete CR	16	6 [3, 6]	3 [3, 5]	0 [−2, 0]	0.03	0.06
Non-complete CR	13	9 [6, 10]	6 [3, 9]	−2 [−3, 0]	0.008	
Angina frequency domain (range 2–12)						
Complete CR	16	6 [4, 7]	3 [3, 5]	−1 [−4, 0]	0.006	0.23
Non-complete CR	13	4 [4, 6]	4 [2, 6]	0 [−2, 0]	0.13	
Quality of life domain (range 2–10)						
Complete CR	16	5 [3, 6]	4 [3, 4]	0 [−2, 0]	0.03	0.44
Non-complete CR	13	6 [5, 7]	4 [3, 6]	−2 [−2, 0]	0.02	
Exercise capacity (CPX)						
Peak $\dot{V}O_2$ (mL/kg/min)						
Complete CR	14	14.2 [12.4, 15.8]	15.3 [13.0, 17.9]	1.9 [0.1, 3.9]	0.02	0.43
Non-complete CR	11	13.2 [11.2, 15.9]	13.3 [11.9, 16.0]	1.2 [−0.4, 2.8]	0.27	
Peak $\dot{V}O_2$/HR (mL/kg/min/[beats/min])						
Complete CR	14	9.0 [6.7, 9.6]	8.4 [6.9, 10.9]	0.6 [0.0, 0.9]	0.04	0.93
Non-complete CR	11	7.3 [6.0, 8.6]	7.9 [6.5, 9.2]	0.6 [0.2, 1.1]	0.05	
Peak work rate (W)						
Complete CR	14	61 [44, 69]	70 [52, 77]	13 [4, 27]	0.009	0.13
Non-complete CR	11	46 [41, 60]	58 [42, 69]	6 [4, 12]	0.14	
Body weight (kg)						
Complete CR	16	60.5 [53.7, 64.5]	59.0 [54.7, 64.5]	−0.9 [−2.0, 1.0]	0.44	0.37
Non-complete CR	13	58.0 [53.0, 60.0]	58.0 [54.0, 63.0]	0 [−0.1, 0.3]	0.83	

Unless indicated otherwise, data are given as the median [interquartile range]. [A]Corrected resting MBF was calculated as resting MBF multiplied by 10,000 divided by resting RPP; corrected MFR was calculated by dividing stress MBF by corrected resting MBF. EF, ejection fraction; RPP, rate–pressure product. Other abbreviations as in Tables 1,2.

Discussion

This study investigated the effects of 5-month supervised exercise-based CR on the vasodilator capacity of the microcirculation, symptom status, and exercise capacity in patients with ANOCA and PET-derived impaired MFR. The major findings of this study are as follows: (1) stress MBF and MFR improved significantly in the complete CR group from baseline to the 5-month follow-up, but did not change in the non-complete CR group, and these results remained unchanged even after correcting for resting RPP; (2) both groups showed significant improvements in symptom status, as indicated by the total SAQ-7 score at the 5-month follow-up; and (3) exercise capacity improved significantly in the complete CR group, whereas no significant change was observed in the non-complete CR group. These findings support the effectiveness of exercise-based CR in patients with ANOCA and impaired MFR. To the best of our knowledge, this is the first study to provide evidence of significant improvements in impaired vasodilator capacity, assessed using myocardial perfusion PET, through an exercise-based CR program.

Exercise training is effective in CR, particularly in improving myocardial perfusion in patients with CAD, as reported previously.[10–13] A previous study[12] including obese or overweight patients reported that weight loss through exercise training improves MFR; however, our study demonstrated that exercise training improved MFR in non-obese patients even without weight loss. Notably, we found no significant difference in body weight between baseline and follow-up PET in either group, possibly because the majority of our patients were not obese or overweight. These findings suggest that aerobic interval training and a low-energy diet can enhance MFR independent of significant weight changes. A recent study[14] involving patients with ANOCA demonstrated improvement in coronary vasodilator response after 3-month aerobic high-intensity interval training, along with improved endothelial function, which aligns with our findings. That study assessed coronary flow velocity reserve using transthoracic Doppler echocardiography; however, its use may be limited by technical issues and operator variability.

In the present study, the improvement in MFR following the CR program was caused by stress MBF augmentation; resting MBF was unaltered, with no significant change in resting cardiac work, as indicated by the resting RPP. This implies that amplified coronary vascular capacity, and not merely reduced resting myocardial oxygen requirements, explains the improvement in MFR. In contrast, another study[10] suggested that cardiovascular conditioning, including regular controlled physical exercise, improved PET-derived MFR primarily due to a reduction in resting cardiac work, with a consequent improvement in resting MBF, in addition to an increase in stress MBF. However, in our patients, resting MBF was not reduced in either group because cardiac work or myocardial oxygen

consumption did not decline significantly at rest from baseline to follow-up. This was consistent with the fact that the resting MBF corrected by RPP did not change at follow-up in the complete CR group. Accordingly, we speculate that these discordant findings may be explained mainly by the fact that CMD is a heterogeneous condition comprising distinct endotypes with different pathogeneses at the microvascular level: structural and functional CMDs.[15] However, these discussions are beyond the scope of the present study. Of note, the absence of significant alterations in stress MBF and MFR in the non-complete CR group supports our hypothesis that changes in MBF and MFR can be attributed to our CR program.

Improvement in coronary vascular function via the CR program is likely to be mediated through multiple mechanisms,[13] including improved vasodilator response of the endothelium-dependent coronary microcirculation, favorable changes in impaired autonomic control of the coronary microcirculation, and improved microcirculation spasticity due to intrinsic changes in the vascular smooth muscle. Briefly, the initial disturbance in vascular function at the molecular level is confined to the endothelium, but commonly extends to the vascular smooth muscle cell layer of the coronary arteriolar vessels in case of more pronounced and long-lasting exposure to cardiovascular risk factors, thus causing impairment of endothelium-independent vascular function.[16] Under physiological stimuli, such as exercise, vascular endothelial cells modulate the appropriate dilatation of coronary arteries through the local release of vasodilator substances, particularly nitric oxide.[4,17] Nitric oxide also protects endothelium integrity through its anti-inflammatory properties by inhibiting fibrosis, platelet aggregation, and apoptosis and promoting angiogenesis. Thus, regular exercise training can improve both endothelial-independent and -dependent functions of the coronary vasculature.[14] Although adenosine is an endothelial-independent vasodilator that activates arteriolar smooth muscle cell receptors, improved endothelial function may also contribute to the augmentation in stress MBF because flow-mediated dilation can contribute to adenosine-induced hyperemia.[12,14] This can explain the considerable improvement in stress MBF and MFR observed after the CR program in the present study.

The present findings of improved functional capacity and symptomatic status agree with those of previous studies[11–14,17] on the effects of exercise training in symptomatic patients with non-obstructive CAD. These beneficial effects of CR were extended in our study, with positive effects on patients with ANOCA and PET-derived impaired MFR. Notably, the symptom status improved significantly in both groups, whereas exercise capacity showed a significant improvement only in the complete CR group. These unique findings can largely be attributed to the positive effects of multidisciplinary approaches in both groups, including home-based regular exercises, additional medications, lifestyle modifications, and patient education, although these interventions were not fully assessed in our study. Furthermore, the improvement in symptom status without changes in MFR in the non-complete CR group suggests that symptoms in ANOCA patients may not be solely explained by impaired MFR. There is a possibility that ANOCA patients could have CMD resulting from increased microvascular resistance or microvascular spasm, and/or epicardial spasm, all of which could be improved using multidisciplinary approaches.

Study Limitations

This study has some limitations. First, this was a single-center retrospective observational study with relatively small sample size. Thus, multicenter studies with larger sample sizes should be designed to verify our novel findings. Second, selecting patients undergoing CR can be a confounding factor. Although many of the physiological characteristics were similar between the 2 groups, patients who follow the recommended CR may be more inclined to adopt other healthy behaviors than those who decline the recommended CR. Third, information on changes in treatment regimens during the follow-up period, such as changes in prescription, medication adherence, and lifestyle modifications, was not included in the analysis. Some studies have shown changes in PET-derived myocardial perfusion caused by drug therapies[18] and/or lifestyle changes.[19] Thus, we cannot conclude that changes in MFR were caused by CR alone. Fourth, we considered impaired PET-derived MFR as indicative of CMD; however, we did not fully investigate other definitions of CMD (e.g., microvascular spasm, increased microvascular resistance, or coronary slow flow phenomenon) in this study.[20] Therefore, further studies based on various definitions of CMD are needed. Finally, defining the complete CR group can be challenging, because no prior studies have used this definition. However, we considered it both practical and relevant, given that the median number of sessions for 5 months was 31 in the complete CR group, with an attendance rate of 84%, which was not a significant deviation from the 36 sessions recommended by the American College of Cardiology/American Heart Association guidelines.[21] Therefore, we could not explore the appropriate duration and content of CR programs and patient characteristics for implementing effective CR programs.

Conclusions

This study demonstrated the efficacy of a 5-month multidisciplinary supervised CR program in improving coronary microvascular function, symptom status, and exercise capacity in patients with ANOCA and CMD indicated by impaired PET-derived MFR. In contrast, patients who did not participate or dropped out of the CR program showed improvement only in their symptom status. The improvement in MFR following the CR program was primarily achieved by augmentation of stress MBF, whereas resting MBF was unaltered, with potentially unchanged resting myocardial oxygen demands. This study provides a basis for further recognition of CR as a promising treatment option for patients with ANOCA and CMD. A larger randomized study is warranted to test this hypothesis and validate our findings.

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IRB Information

This study was approved by the Institutional Review Board of Sapporo Kojinkai Memorial Hospital (Approval no. 20228).

Data Availability

The deidentified participant data will be shared on a request basis. Please contact the corresponding author directly to request data sharing. The entire dataset used will be available, including the study protocol. The data will be shared as soon as the IRB at Sapporo Kojinkai Memorial Hospital approves it, and will be available until end of March 2029. The data will be shared with anyone wishing to access it. Any analyses on the data will be approved and data will be shared as an Excel file via email.

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