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Beneficial effects of exercise training on physical performance in patients with vasospastic angina

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ABSTRACT

Aims: In vasospastic angina (VSA), coronary vasomotion abnormalities could develop not only in epicardial coronary arteries but also in coronary microvessels, where calcium channel blockers (CCBs) have limited efficacy. However, efficacy of exercise training for VSA remains to be elucidated. We thus aimed to examine whether vasodilator capacity of coronary microvessels is impaired in VSA patients, and if so, whether exercise exerts beneficial effects on the top of CCBs.

Methods: We performed 2 clinical protocols. In the protocol 1, we measured myocardial blood flow (MBF) using adenosine-stress dynamic computed tomography perfusion (CTP) in 38 consecutive VSA patients and 17 non-VSA controls. In the protocol 2, we conducted randomized controlled trial, where 20 VSA patients were randomly assigned to either 3-month exercise training group (Exercise group) or Non-Exercise group (n= 10 each).

Results: In the protocol 1, MBF on CTP was significantly decreased in the VSA group compared with the Non-VSA group (138 ± 6 vs 166 ± 10 ml/100 g/min, $P = 0.02$). In the protocol 2, exercise capacity was significantly increased in the Exercise group than in the Non-Exercise group (11.5 ± 0.5 to 15.4 ± 1.8 vs 12.6 ± 0.7 to 14.0 ± 0.8 ml/min/kg, $P < 0.01$). MBF was also significantly improved after 3 months only in the Exercise group (Exercise group, 145 ± 12 to 172 ± 8 ml/100 g/min, $P < 0.04$; Non-Exercise group, 143 ± 14 to 167 ± 8 ml/100 g/min, $P = 0.11$), although there were no significant between-group differences.

Conclusions: These results provide the first evidence that, in VSA patients, exercise training on the top of CCBs treatment may be useful to improve physical performance, although its effect on MBF may be minimal.

1. Introduction

Coronary vasomotion abnormalities play important roles in the pathogenesis of ischemic heart disease [1] and could develop not only in epicardial coronary arteries but also in coronary microvessels [2]. Indeed, it has recently been reported that the high prevalence of epicardial and microvascular spasm is noted in Caucasian patients with angina but angiographically non-obstructed coronary arteries [3]. We also previously demonstrated that one quarter of patients with vasospastic angina (VSA) have coronary microvascular spasm [4]. However, it remains to be examined whether vasodilator capacity of coronary microvessels is impaired in VSA patients.

Calcium channel blockers (CCBs) are widely used for patients with epicardial coronary spasm, although they have limited efficacy in patients with angina of microvascular origin [2]. Importantly, regular physical exercise improves exercise capacity and quality of life (QOL) in patients with atherosclerotic coronary artery disease (CAD) [5]. However, it remains to be examined whether regular physical exercise is also effective for functional CAD such as VSA. Notably, adenosine-stress dynamic computed tomography perfusion (CTP) is a non-invasive technique for absolute quantification of myocardial blood flow (MBF) that can evaluate impairment of coronary microcirculation in patients with significant stenosis [6].

In the present study, we thus performed 2 clinical protocols. In the protocol 1, we examined whether vasodilator capacity of coronary microvessels is impaired in VSA patients using adenosine-stress dynamic CTP. In the protocol 2, we examined whether regular exercise training ameliorates vasodilator capacity of coronary microvessels,

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exercise capacity assessed with cardiopulmonary exercise testing (CPET), and QOL in those patients.

2. Methods

The present study with 2 protocols was conducted following the ethical principles in the Declaration of Helsinki. The study protocols were approved by the Ethics Committee of Tohoku University Graduate School of Medicine (No. 2018-1-933 and No. 2018-2-041). Written informed consent was obtained from all patients before study entry. The detailed methods are available in the Supplementary materials.

2.1. Protocol 1

In the protocol 1, from March 2015 to January 2019, 79 patients with angina underwent adenosine-stress dynamic CTP within 1 month before and after coronary angiography (CAG) with coronary vasoreactivity testing (e.g. provocation testing for coronary spasm) at our Tohoku University Hospital. Of the 79 patients, we excluded a total of 24 patients for various reasons, and, finally 38 VSA patients and 17 non-VSA subjects were enrolled (Fig. 1). The detailed reasons for exclusion are shown in Fig. 1 and the Supplementary materials.

2.2. Protocol 2

In the protocol 2, from August 2016 to January 2019, 36 patients with angina underwent CPET and adenosine-stress dynamic CTP within 1 month before and after CAG with coronary vasoreactivity testing (e.g. provocation testing for coronary spasm) at our Tohoku University Hospital. Among the 36 patients, 10 were non-VSA patients and the remaining 26 VSA patients were eligible for this protocol (Fig. 1). All of the VSA patients were also included in the protocol 1. The detailed reasons for exclusion are mentioned in the Supplementary materials. After diagnostic coronary angiography, all the patients were randomly assigned to either the Exercise group with additional exercise training to the conventional therapies including CCBs or the Non-Exercise group treated with conventional therapies alone, in a 1:1 ratio, through stratification by sex, age, baseline systolic blood pressure, and smoking history. At study entry and 3 months, we repeated CPET and adenosine-stress dynamic CTP in all patients. The primary endpoint was defined as the extent of change in exercise capacity assessed with CPET. The secondary endpoints were defined as the extents of changes in MBF measured by adenosine-stress dynamic CTP, coronary perivascular adipose tissue (PVAT) volume, and QOL (Fig. 1).

2.3. Clinical and health status data

Health status was assessed twice at baseline and follow-up, using the Seattle Angina Questionnaire (SAQ) [7] and the 36-Item Short Form Health Survey (SF-36) [8]. Physical activity was assessed based on the International Physical Activity Questionnaire (IPAQ) [9].

2.4. Acetylcholine provocation testing

Acetylcholine (ACh) provocation testing was performed as previously reported [10,11].

2.5. Coronary physiological measurements

To evaluate vasodilator capacity of coronary microvessels, we then performed coronary physiological measurements for coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) in the left anterior descending coronary artery (LAD) during hyperemia induced by intravenous infusion of adenosine, as previously described [12–14]. In addition, we defined microvascular spasm (MVS) as previously reported [4]. In the present study, we defined coronary microvascular dysfunction as CFR ≤ 2.0 and/or IMR > 25 and/or MVS based on the diagnostic criteria proposed by the COVADIS (Coronary Vasomotor Disorders International Study) Group [15].

2.6. TIMI frame count

We measured TIMI frame count based on the previous study [16].

2.7. Cardiopulmonary exercise testing

CPET was performed on an upright cycle ergometer (BE-350 Well Bike, Fukuda Denshi, Tokyo, Japan) in the morning. Respiratory gas exchange variables were acquired continuously throughout the exercise test using breath-by-breath measurement system (AE310S, Minato Medical Science, Osaka, Japan).

2.8. CT data acquisition and reconstruction

All image acquisitions were performed by using a dual-source 2 × 128 detector-row CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). During a 3-min administration of adenosine triphosphate (Toa-Eiyo Tokyo, Japan) at 150 μg/kg/min, dynamic myocardial CTP was initiated with injection of 40 mL of iopamidol (Bayer Schering Pharma, Berlin, Germany) with an iodine concentration of 370 mgI/mL at a flow rate of 5 mL/s [6]. We also performed measurement of perivascular adipose tissue volume as previously reported [17].

2.9. Measurement of MBF with adenosine-stress dynamic CTP

The adenosine-stress dynamic CTP data were analyzed with commercially available perfusion software (Syngo VPCT body, Siemens Healthcare, Forchheim, Germany) as previously described [18].

2.10. Exercise training designs

In the protocol 2, patients were randomly assigned to either the Exercise group or the Non-Exercise group. Patients assigned to the Exercise group were expected to exercise, under close supervision, once a week for 30 min at the Tohoku University Hospital, where they exercised on a bicycle ergometer targeting for heart rate (HR) at anaerobic threshold (AT) level in the initial CPET [5]. In addition, they were provided with a bicycle ergometer and instructed to regularly exercise for 30 min or more at home, at least 3 times a week, targeting for HR at AT level for 3 months. Patients assigned to the Non-Exercise group were advised to perform regular activity according to current recommendations and were supervised by their general practitioner [5,19].

2.11. Statistical analysis

Continuous variables are expressed as mean ± standard error of mean (SEM) or medians and interquartile ranges (IQR) and categorical variables as numeral and percentages (%). Welch's *t*-test for normal distribution with unequal variances and Mann-Whitney *U* test for asymmetric distribution were used to compare mean differences in continuous variables. Fisher's exact test was used to compare frequencies for categorical variables. Correlations between continuous variables were analyzed using a linear regression model. Receiver-operating characteristic (ROC) curve analysis was used to determine the optimal MBF value for prediction of microvascular disorder in VSA in the protocol 1. In the protocol 1, the distributions of IMR was not normal. To improve the normality of the distributions, we used a natural logarithmic transformation of IMR. In the protocol 2, based on the results of the previous study [20], we expected that additional exercise training would achieve 3.0 ml/min/kg increase in

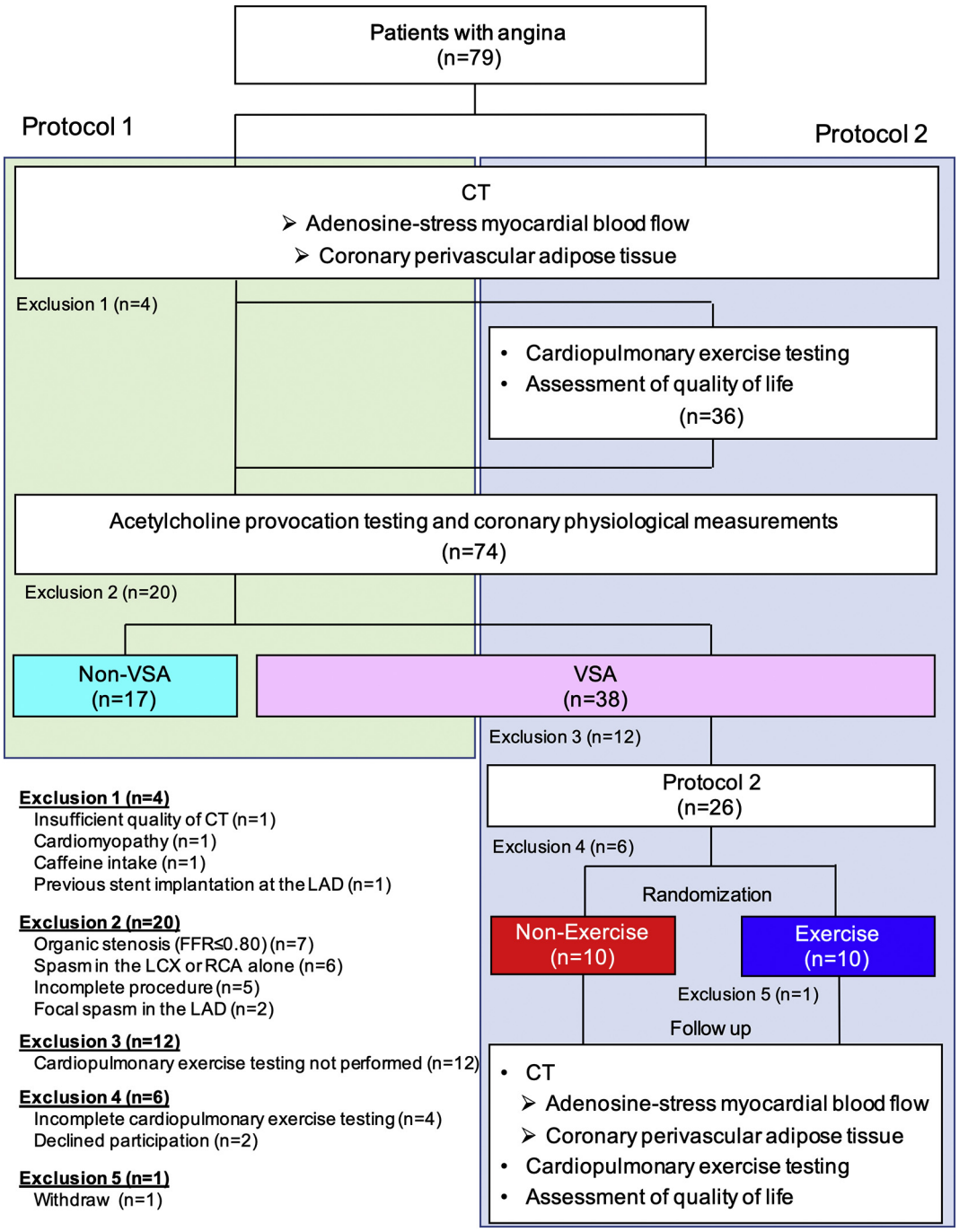

Fig. 1. Study flow chart. CT = computed tomography; FFR = fractional flow reserve; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery; VSA = vasospastic angina.

AT compared with conventional therapies alone. The sample size of 9 patients per treatment group was chosen in order to have 70% power to detect 3.0 ml/min/kg difference in AT with significance level 2.5% for one-sided test, assuming SD of 2.2 mg/min/kg and 10% possibility of loss to follow up. We used a power of 70% because of the low cardiac rehabilitation participation rate in Japan [21]. With an anticipated dropout rate of 10%, enrollment of 9 patients per treatment group was specified to provide an adequate number of patients for evaluation of the effects of CPET. The differences in exercise training effects and 95% confidence intervals were calculated with analysis of covariance (ANCOVA) for each variable of interest with that variable's baseline values as the covariate. Statistical analysis was performed with JMP Pro 11.0.0 (SAS institute, Cary, NC, USA). A P value of <0.05 was considered to be statistically significant.

3. Results

3.1. Protocol 1. Impaired vasodilator capacity of coronary microvessels in VSA patients

In the protocol 1, patient characteristics were comparable between the Non-VSA and the VSA groups (Table 1). The comprehensive CT protocol was successfully performed without any adverse events. The average radiation dose for CTP and CT coronary angiography (CTCA) was

Table 1
Baseline patient characteristics and treatments in the Protocol 1.

	Non-VSA (n = 17)	VSA (n = 38)	*P* value
Age, year	63.7 ± 2.7	62.7 ± 1.6	0.74
Male sex, n (%)	9 (53)	16 (42)	0.56
Body weight, kg	60.7 ± 2.9	60.2 ± 1.7	0.87
Body mass index, kg/m^2	22.3 ± 0.7	23.7 ± 0.5	0.14
Hypertension, n (%)	11 (65)	18 (47)	0.56
Diabetes mellitus, n (%)	2 (12)	2 (5)	0.58
LDL cholesterol, mg/dL	112.6 ± 7.7	111.5 ± 5.0	0.90
HDL cholesterol, mg/dL	58.1 ± 5.2	61.6 ± 2.2	0.30
Current smoker, n (%)	3 (18)	5 (13)	0.69
Former smoker, n (%)	4 (24)	8 (21)	>0.99
Positive family history of CVD, n (%)	5 (29)	4 (11)	0.12
LVEF, %	71.1 ± 2.0	69.2 ± 1.3	0.32
Cardiac markers			
hs-CRP, mg/dL	0.05 (0.02–0.07)	0.03 (0.01–0.07)	0.31
BNP, pg/mL	17.8 (5.8–27.4)	15.1 (8.7–22.0)	0.72
Troponin T, mg/L	0.005 (0005–0.007)	0.006 (0.003–0.008)	0.90
Medical treatments, n (%)			
CCB	10 (59)	26 (68)	0.55
Long-acting nitrate	2 (12)	9 (24)	0.47
Potassium channel opener	0 (0)	2 (5)	>0.99
ACE-I or ARB	6 (35)	11(29)	0.75
Beta-blocker	0 (0)	4 (11)	0.30
Statin	6 (35)	4 (11)	0.51
Anti-platelet	3 (18)	5 (13)	0.69

Categorical variables as n (%) and continuous variables are expressed as mean ± SEM.
ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BNP, brain natriuretic peptide; CCB, calcium channel blockers; CVD, cardiovascular disease; hs-CRP, high-sensitivity C-reactive protein; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction.

4.64 ± 1.1 mSv and 2.4 ± 0.8 mSV, respectively. The prevalence of organic stenosis < 50% in the LAD was also comparable between the 2 groups (Table 2). To examine vasodilator capacity of coronary microvessels, we measured MBF at the spastic LAD segment using adenosine-stress dynamic CTP. MBF was significantly reduced in the VSA patients compared with the non-VSA patients (Fig. 2A, D, G). In addition, cross-sectional CT images and 3-dimensional reconstructed CT images of coronary PVAT showed that coronary PVAT volume index was significantly increased at the spastic LAD segment in the VSA group than in the Non-VSA group, as we previously reported (Fig. 2B, C, E, F, H) [22]. Importantly, there was a significant negative correlation between MBF and the extent of coronary PVAT volume index at the spastic LAD segment (Fig. 2I).

Table 2
Coronary angiographic findings.

	Non-VSA (n = 17)	VSA (n = 38)	*P* value
Organic stenosis, n (%)			
25% in LAD	2 (12)	11 (29)	0.30
50% in LAD	1 (6)	5 (13)	0.65
25% in LCX	1 (6)	6 (16)	0.42
50% in LCX	0 (0)	1 (3)	>0.99
75% in LCX	1 (6)	0 (0)	0.31
25% in RCA	2 (12)	8 (21)	0.71
50% in RCA	0 (0)	1 (3)	>0.99
75% in RCA	0 (0)	1 (3)	>0.99
Acetylcholine provocation testing, n, (%)			
Multivessel spasm	0 (0)	30 (79)	<0.01
MVS	8 (47)	13 (34)	0.39
Physiological parameters			
IMR	15.6 (11.2–23.2)	14.6 (10.6–19.9)	0.54
CFR	3.05 (2.1–4.0)	2.8 (1.7–3.3)	0.34
Microvascular disease			
IMR > 25 and/or CFR ≤ 2.0 and/or MVS, n (%)	9 (53)	23 (61)	0.77

Categorical variables as n (%).
CFR indicates coronary flow reserve; IMR, index of microcirculatory resistance; MVS, microvascular spasm; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; VSA, vasospastic angina.

3.2. Correlation between MBF and physiological parameters and diagnostic accuracy of MBF for microvascular disorder in VSA patients

We further examined vasodilator capacity of coronary microvessels invasively, using TIMI frame count and IMR. There were significant negative correlations between MBF and TIMI frame count, and natural logarithm IMR (Fig. 2J, K). In addition, there was a trend for a positive correlation between MBF and CFR (Fig. 2L). Based on the receiver-operating characteristic (ROC) curve analysis, the optimal MBF value for prediction of microvascular disorder in VSA was 145.7 ml/100 g/min, and the area under the curve was 0.79 (95% confidence interval: 0.64 to 0.94, sensitivity 78% and specificity 80%) (Supplementary Fig. S1). With this value, the sensitivity and specificity for predicting microvascular disorder in VSA were 78% and 80%, respectively. Among the VSA patients, MBF was significantly higher in female than in male (Supplementary Fig. S2A). Importantly, there was significant negative correlation between MBF and age in female VSA patients (Supplementary Fig. S2B), but not in male VSA patients (Supplementary Fig. S2C). Using multivariable linear regression model, we assessed the impact of VSA on MBF value with adjustment for age and sex. We found that VSA had significantly negative correlation with MBF, even after adjustment. The estimate coefficient for VSA in the multivariable model was −32.1 (95% confidence interval: −52.7 to −11.5) (Table 3).

3.3. Protocol 2. Effects of exercise training on exercise capacity in VSA patients

In the protocol 2, one patient in the Exercise group declined to continue after the first week. Thus, a total of 19 patients completed the protocol (9 in the Exercise group, and 10 in the Non-Exercise group) (Fig. 1). Of the 19 patients, 2 failed to complete SF-36 questionnaire, and 1 in the Non-Exercise group lost a log book for his daily activity. No significant cardiovascular events occurred during the training sessions. Clinical characteristics and daily physical activity of the study subjects were comparable between the 2 groups at baseline and at 3 months (Supplementary Table S1).

Peak VO_2 was significantly improved only in the Exercise group, and AT was significantly increased both in the Exercise group and the Non-Exercise group, whereas peak VO_2/HR showed no significant difference between the 2 groups (Fig. 3A-F). There was significant between-group difference only in AT (adjusted difference in the average treatment effect between the Exercise group and the Non-Exercise group, 2.8 ml/min/kg; 95% confidence interval [CI], 1.1 to 4.4; $P < 0.01$) (Table 4).

3.4. Effects of exercise training on cardiac CT imaging in VSA patients

MBF was significantly increased only in the Exercise group (Supplementary Fig. S3A-D). However, there was no significant between-group difference in MBF (adjusted difference in the average treatment effect between the Exercise and the Non-Exercise groups, 4.1 ml/100 g/min; 95% confidence interval [CI], −19.1 to 27.4; $P = 0.71$) (Table 4). We have recently demonstrated that PVAT is one of the potential substrates of coronary spasm [22]. PVAT showed no significant difference between the 2 groups at baseline or follow-up, although there was significant between-group difference in PVAT (adjusted difference in the average treatment effect between the Exercise and the Non-Exercise groups, −3.4 cm^3/m^2; 95% confidence interval [CI], −6.0 to −0.7; $P = 0.02$) (Table 4).

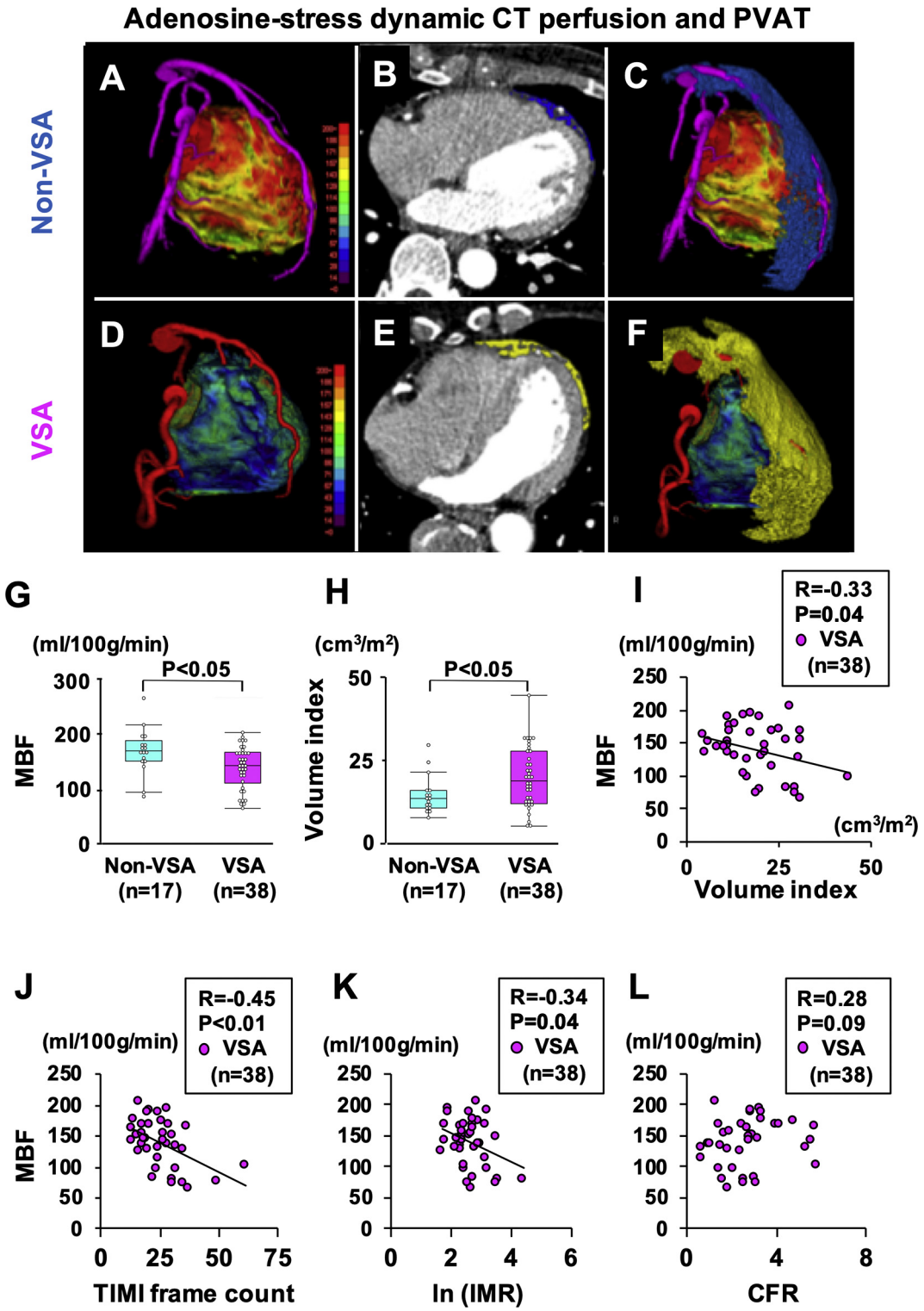

Fig. 2. CT images of adenosine-stress dynamic CTP and coronary PVAT volume. Representative 3-dimensional reconstructed CT images of adenosine-stress dynamic CTP, cross-sectional CTCA images, and coronary PVAT in a Non-VSA subject (A, B, C) and a VSA patient (D, E, F). Quantitative analysis of MBF in the VSA and the Non-VSA groups (G). Coronary PVAT volume index in the VSA and the Non-VSA groups (H). Correlations among the extent of MBF and that of coronary PVAT volume index (I), TIMI frame count (J), natural logarithm of IMR (K), and CFR (L). CFR = coronary flow reserve; CT = computed tomography; IMR = index of microcirculatory resistance; MBF = myocardial blood flow; PVAT = perivascular adipose tissue; TIMI = thrombosis in myocardial infarction; VSA = vasospastic angina.

3.5. Effects of exercise training on QOL in VSA patients

The number of angina attacks per month assessed with log book, in which patients documented their daily symptoms, was significantly reduced only in the Exercise group (P = 0.02), however there was no significant between-group difference in angina attacks (adjusted difference in the average treatment effect between the Exercise and the Non-Exercise groups, −3.8 per month; 95% confidence interval [CI], −8.7 to 1.0; $P = 0.11$) (Table 4). QOL was assessed with the SAQ and SF-36 questionnaires. The mean scores

Table 3
Multivariable linear regression model in the Protocol 1.

	Coefficient	Lower 0.95	Upper 0.95	*P* value
VSA	−32.087	−52.664	−11.511	0.003
Sex	−29.740	−49.066	−10.413	0.003
Age	−0.909	−1.877	0.059	0.065

VSA indicates vasospastic angina.

of the SAQ, SF-36, and IPAQ at baseline and 3 months are summarized in Supplementary Table S2. As compared with baseline, the SAQ score was comparable in both groups. Importantly, SF-36 of general health, vitality, and mental health were significantly increased only in the Exercise group. The SAQ score of angina frequency subscale tended to increase in the Exercise group compared with the Non-Exercise group (Supplementary Table S2). Furthermore, there was a significant positive correlation between the extent of change in SAQ of physical limitation score and that in peak VO_2 in the Exercise group but not in the Non-Exercise group ($R = 0.75$, $P = 0.02$).

4. Discussion

The major findings of the present study were as follows; (1) VSA patients have impaired vasodilator capacity of coronary microvessels compared with non-VSA patients, and (2) regular exercise training improves exercise capacity in VSA patients (Graphical abstract). To the best of our knowledge, this is the first study that provides the direct evidence of impaired vasodilator capacity of coronary microvessels and the beneficial effects of regular exercise training on physical performance in VSA patients.

4.1. Impaired vasodilator capacity of coronary microvessels in VSA patients

CTCA is a useful tool to rule out obstructive coronary artery disease, although it has limited capability to evaluate physiological significance of the coronary artery [23]. Adenosine-stress dynamic CTP is a recently developed technique to assess myocardial ischemia by quantification of MBF [6]. MBF reflects coronary microcirculation in the absence of obstructive coronary artery disease [24]. The present study demonstrates for the first time that VSA patients have reduced hyperemic response to adenosine as assessed by adenosine-stress dynamic CTP. Furthermore, there was good correlations among MBF and coronary physiological measurements such as IMR. These results indicate that adenosine-stress dynamic CTP is a useful imaging technique for evaluation of coronary microvascular dysfunction. In the present study, there was only a modest correlation between MBF and CFR. We consider that there are several reasons for this modest correlation between both parameters. First, CFR is generally calculated as the ratio between hyperemic MBF and baseline MBF. However, in the present study, we only measured hyperemic MBF to reduce radiation dose. Therefore, baseline MBF may be one of the reasons for the modest correlation between MBF and CFR. Second, the number of patients was obviously small.

In the present study, 53% of non-VSA patients also had impaired coronary microvascular function, and MBF was reduced only in the VSA patients. These results indicate that coexistence of epicardial coronary spasm and impaired coronary microvascular function may be associated with reduced MBF.

We have recently demonstrated that coronary PVAT is significantly increased in VSA patients and that the extent of coronary PVAT is correlated with that of coronary spasm [22]. Coronary PVAT may also play an important role in the regulation of coronary microcirculation. Combined assessments with CTCA and adenosine stress dynamic CTP provide both anatomical and functional information on coronary microcirculation [6].

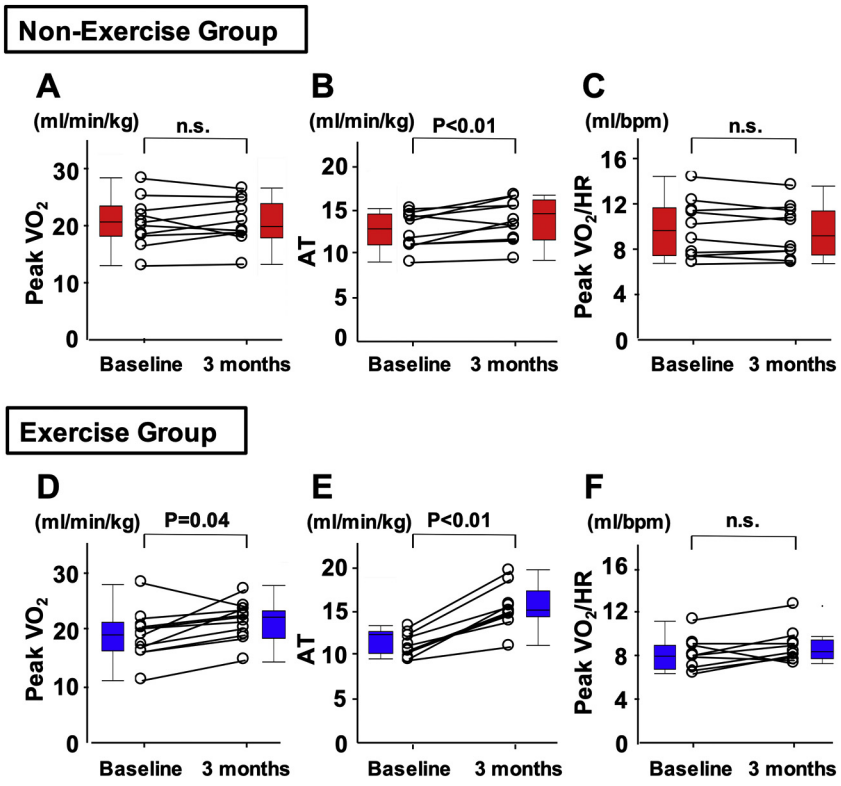

Fig. 3. The extents of changes in peak VO_2, AT and peak VO_2/HR at baseline and 3 months after randomization. Peak VO_2 was significantly improved only in the Exercise group. (A, D). AT was significantly improved both in the Exercise and the Non-Exercise groups (B, E). Peak VO_2/HR showed no significant difference between the Exercise and the Non-Exercise groups (C, F). AT = anaerobic threshold; HR = heart rate.

Table 4
Outcomes according to treatment group.

Variable	Non-Exercise		Exercise		Treatment comparison	
	Overall mean	Mean change from baseline	Overall mean	Mean change from baseline	Adjusted difference (95% CI)	*P* value
Peak VO_2 (ml/min/kg)						
Baseline	20.3 ± 1.4		18.7 ± 1.6			
3 months	20.7 ± 1.2	0.2 ± 0.6	21.4 ± 1.2	2.6 ± 1.2	1.8 (−0.6 to 4.2)	0.12
AT (ml/min/kg)						
Baseline	12.6 ± 0.7		11.5 ± 0.5			
3 months	14.0 ± 0.8	1.4 ± 0.3	15.4 ± 0.8	4.0 ± 0.7	2.8 (1.1 to 4.4)	<0.01
Peak VO2/HR (ml/min/kg/bpm)						
Baseline	9.8 ± 0.8		8.1 ± 0.5			
3 months	9.6 ± 0.7	−0.2 ± 0.2	8.8 ± 0.5	0.7 ± 0.4	0.7 (−0.2 to 1.7)	0.10
MBF (ml/100 g/min)						
Baseline	143.2 ± 13.5		145.3 ± 12.4			
3 months	167.2 ± 26.7	24.0 ± 13.7	171.8 ± 7.7	26.5 ± 10.6	4.1 (−19.1 to 27.4)	0.71
PVAT volume index (cm^3/m^2)						
Baseline	19.1 ± 2.2		14.9 ± 3.2			
3 months	19.9 ± 2.4	0.8 ± 0.7	12.8 ± 2.6	−2.0 ± 1.0	−3.4 (−6.0 to −0.7)	0.02
Angina attacks (per month)						
Baseline	13.4 ± 4.2		8.8 ± 3.6			
3 months	10.6 ± 3.4	−2.8 ± 1.9	3.7 ± 2.6	−5.1 ± 2.1	−3.8 (−8.7 to 1.0)	0.11

Continuous variables are expressed as mean ± SEM.
CI denotes confidence interval, AT, anaerobic threshold, HR, heart rate, MBF, myocardial blood flow, and PVAT, perivascular adipose tissue.

It has been reported that one-half of women with suspected myocardial ischemia have no obstructive coronary artery disease and that impaired coronary microvascular reactivity predicts all-cause mortality and MACE [25]. In the present study, there was a significant negative correlation between MBF and age in female VSA patients, but not in male VSA patients. We have previously reported that Rho-kinase plays a key role in the pathogenesis of coronary artery spasm [1] and that estrogen potently inhibits Rho-kinase expression in cultured human coronary vascular smooth muscle cell [26]. Thus, estrogen deficiency may reduce MBF via Rho-kinase expression in VSA patients. Impaired vasodilator capacity of coronary microvessels usually correlate with exercise-related symptoms. In the present study, although all patients with VSA had resting angina, patients with VSA + MVA had reduced exercise capacity compared with those with VSA alone. It has been reported that patients with Prinzmetal's variant angina have circadian variation of exercise capacity, where angina attacks with ST-segment elevation is frequently induced by exercise in the morning [27]. However, VSA patients without exercise-related symptoms may have reduced exercise capacity due to mainly coronary microvascular dysfunction. Thus, coronary microvascular dysfunction may be a new therapeutic target in VSA patients.

4.2. Beneficial effects of exercise training in VSA patients

Several beneficial effects of exercise training on atherosclerotic coronary artery disease can be raised. Exercise training ameliorates coronary responses to ACh in patients with asymptomatic coronary atherosclerosis [28]. Exercise training also improves myocardial perfusion in patients with obstructive coronary artery disease independently of changes in coronary lesions [29]. Physical activity is a useful predictor for prognosis of patients with coronary artery disease [30]. In the present study, exercise training exerted favorable effects in VSA patients with impaired vasodilator capacity of coronary microvessels.

CCBs are widely used for VSA patients, but they have limited efficacy in patients with microvascular angina [2]. Impaired microvascular function also predicts residual chest symptoms in women without obstructive coronary artery disease [25]. However, there was no evidence on the effect of exercise training on coronary vasomotion disorders, particularly VSA. It has been reported that exercise training in patients with non-obstructive coronary artery disease, such as coronary syndrome X, improves their exercise capacity and QOL [31]. The present study had several strengths as follows; First, we assessed coronary functional abnormalities using invasive diagnostic procedures (IDP). According to the CorMiCa trial, medical therapy stratified based on IDP improves angina in patients with non-obstructive coronary artery disease [32]. In the present study, exercise capacity was significantly increased not only in the Exercise group but also in the Non-Exercise group and daily activity assessed with IPAQ was also increased in both groups. The change of daily activity in both groups may have beneficial effect on impaired vasodilatation capacity of coronary microvessels in VSA patients. Second, we assessed the effects of exercise training using adenosine-stress dynamic CT perfusion. In the present study, we were able to demonstrate for the first time that IDP increased daily activity and that exercise training on the top of CCBs treatment had beneficial effect mainly on exercise capacity in VSA patients (Graphical abstract).

Exercise training has anti-inflammation effect and reduces adipocyte size [33]. Exercise training also ameliorates the adverse effect of PVAT on coronary vasomotor responses [34]. We have recently demonstrated that PVAT and perivascular inflammation play important roles in the pathogenesis of coronary artery spasm [22]. In the present study, PVAT volume was significantly reduced in the Exercise group than in the Non-Exercise group, suggesting that exercise training ameliorates coronary vasomotion abnormalities through alterations of PVAT.

4.3. Study limitations

Several limitations should be mentioned for the present study. First, since this study is a single-center study with a relatively small number of patients, future studies with a large number of patients are needed. This study was underpowered because we estimated sample size using a power of 70% due to the low cardiac rehabilitation participation rate in Japan [21]. Second, the MBF measurement with adenosine-stress dynamic CTP remains to be validated by other modalities, such as PET-CT or MRI. However, recent study demonstrated that MBFs measured by CTP and PET-CT are well correlated [35]. In addition, MBF in healthy volunteers was reported as 173 ± 33 ml/100 g/min [36], and MBF in the Non-VSA group (166 ± 10 ml/100 g/min) was similar to that in the present study. Importantly, MBF in the VSA group (138 ± 6 ml/100 g/min) was relatively lower than the normal range of MBF reported previously [36].

Thus, MBF in the VSA group may be reduced due to coronary microvascular dysfunction. Third, we excluded patients with focal spasm because of its potentially different pathophysiology from diffuse spasm [37,38]. Thus, further studies are needed to examine the possible involvement of impaired vasodilator capacity of coronary microvessels in patients with focal spasm. Forth, based on our previous study [38], we assessed coronary microvascular function only in the LAD because of its large perfusion area. Thus, it remains to be examined whether it is also the case for other coronary arteries (e.g. left circumflex and right coronary arteries).

5. Conclusions

The present study provides the first direct evidence that vasodilator capacity of coronary microvessels is impaired in VSA patients and that exercise training on the top of CCBs treatment may be useful to improve physical performance, although its effect on MBF may be minimal.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.12.003.

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