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Influence of atrial fibrillation on oxygen uptake and exercise tolerance in cardiovascular patients; close association with heart rate response

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ABSTRACT

To investigate the effect of atrial fibrillation (AF) on the oxygen uptake and exercise tolerance, we evaluated cardiopulmonary exercise test (CPET) data in AF patients and heart rate-matched controls with sinus rhythm (cSR) who received ambulatory cardiac rehabilitation. We compared CPET data between AF ($N = 27$) and cSR patients ($N = 106$) who had similar HRs at rest and the peak points. Oxygen uptake (VO_2)/kg and relative O_2 pulse (ml/bpm/kg) at rest and the anaerobic threshold (AT) level was not different between AF and cSR patients, but these parameters above the AT level were significantly lower in AF than in cSR patients. Concisely the parallel increase of relative O_2 pulse during exercise was blunted above the respiratory compensation level (Rc) in the AF group. In addition, the HR change during exercise was inversely correlated with the increase of the O_2 pulse above the AT level and this inverse correlation was more prominent in AF patients than in cSR patients. In conclusion, the value of VO_2 was significantly lower above the AT level in AF patients. The trend of O_2 pulse above the AT level was strongly associated with the detrimental response of HR increase and the response was markedly exaggerated in the AF patients.

1. Introduction

Atrial fibrillation (AF) is a major cardiac rhythm disturbance that is frequently encountered in clinical practice. Even though AF is common in patients with underlying cardiac diseases, it also occurs in those without and increases in prevalence with advanced age [1]. AF may be associated with the worsening of heart failure or the occurrence of thrombotic events, which significantly affect patients' prognoses [2]. However, it may also have detrimental effects on patients' daily lives because of reduced exercise tolerance [3]. Exertional dyspnea is a frequently observed complaint in patients with AF, with patients reporting a significant impairment in their quality of life (QoL) [4].

Rate control therapy, including both heart rate control and anticoagulant therapy, is unable to improve AF-derived exertional dyspnea. On the contrary, the development of new therapeutic strategies against AF, including catheter ablation, has clearly improved the symptomatology for each patient [5].

Exercise tolerance is a useful parameter that corresponds with and greatly influences QoL in patients. In the PIAF trial, it was believed that exercise tolerance was better with rhythm control than rate control; however, a clinically meaningful difference was not observed [6]. The STAF pilot study also showed no significant difference in exertional dyspnea between the two treatment strategies [7]. Furthermore, it was reportedly difficult to accurately determine the differences in exertional symptoms between sinus rhythm patients and AF patients [6,8].

An improvement in physical activity should be regarded as being imperative to the personalization of AF therapy, as symptoms could be determined by the balance between a patient's exercise capacity and daily physical activity. For appropriate personalization of therapy for AF patients, further investigation into exercise physiology in AF is warranted [9,10]. In particular, the effects of heart rate (HR) on exercise capacity, which, in AF patients are complicated, in part due to an exaggerated HR increase during exercise, itself may have a significant impact on exercise tolerance [11,12]. Cardiopulmonary exercise testing (CPET) is the standard criterion for assessing exercise capacity and has proven beneficial for evaluating the exercise capacity in patients with various extents of cardiac dysfunction.

The primary aim of our study was to examine the influences of cardiac hemodynamics, such as oxygen uptake by AF, independent of the effect of HR increase during exercise.

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2. Method

2.1. Study population

We obtained data on 934 cases of CPET from 422 patients undergoing ambulatory cardiac rehabilitation for heart failure or ischemic heart disease between 2009 and 2015 at the University of Tokyo Hospital (Fig. 1). Exclusion criteria were a history of heart transplant; severe illnesses other than heart disease, such as malignant tumors; or the presence of any clinical comorbidity that might interfere with exercise performance. Patients were also excluded if they (a) were < 45 years of age or > 80 years of age, (b) were unable to achieve an adequate pedal rotation speed or had a maximum respiratory exchange ratio < 1.05 during CPET, (c) performed CPET by the minority protocol which is different from the main protocol mentioned below, (d) had an HR at rest of >110 bpm, or (e) showed the presence of moderate valvular disease, which was thought to be the cause of the patient's symptoms. If the patients performed CPET more than once, the highest value of peak oxygen consumption (VO_2/kg) was selected for this study.

The AF group ($N = 27$) comprised those subjects with an AF rhythm at the time of CPET, whereas the subjects with a sinus rhythm (SR) were defined as the SR group ($N = 228$). From the SR group, the HR-matched controls whose heart rates at rest and peak exercise were matched with those of the AF group were selected ($N = 106$) and defined as the cSR group. CPET parameters in the AF group were compared with those in the cSR group.

Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was reviewed and approved by the University of Tokyo Institutional Review Board (2650).

2.2. Cardiopulmonary exercise testing

Symptom-limited CPET was performed on an electromagnetically braked upright cycle ergometer (Corival, Load, Holland) with a metabolic gas analyzer (AE-300S; Minato Medical Science, Osaka, Japan). After 4 min of rest on the cycle ergometer, exercise commenced at 20 watt for a 4 min-warm up; then, the work rate was increased by 1 watt every 6 s. During CPET, blood pressure was measured by an automatic, indirect cuff manometer (FB-300; Fukuda Denshi, Tokyo, Japan) every min. HR and electrocardiography (ECG) were monitored using an exercise electrocardiogram (ML-9000; Fukuda Denshi, Tokyo, Japan). The criteria for discontinuation of CPET were (i) if pedal rotations were delayed; (ii) if the patient reached maximum symptom-limited performance determined by a Borg score of ≥17; (iii) when 85% of age-predicated maximal HR was achieved; or (iv) if there was evidence of ST-T changes in ECG or if any cardiac event, such as arrhythmia or chest pain, occurred. Expired gases were continuously measured in all subjects on a breath-by-breath basis. The anaerobic threshold (AT) was determined by gas-exchange criteria as the point of nonlinear increase in ventilation equivalents for oxygen.

2.3. CPET parameters

The values of VO_2 and HR at rest (Rest; average of 4 min of rest on the cycle ergometer), warm up (Wu; average of 3–4 min after exercise commenced), AT, the respiratory compensation point (Rc), and the exercise peak (Peak) were all measured and recorded during CPET. Peak VO_2 was defined as the average value obtained during the last 20 s of incremental exercise or the average of 20 s around the highest value obtained during the CPET. O_2 pulse, which was calculated by

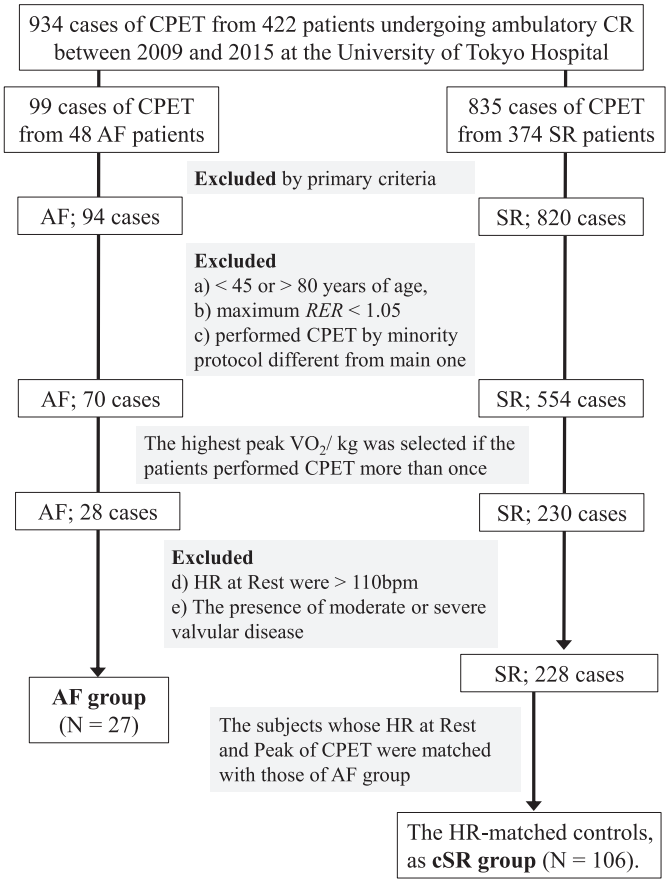

Fig. 1. Enrollment criteria and flow chart of the study. CR, cardiac rehabilitation; CPET, cardiopulmonary exercise test; AF, atrial fibrillation; SR, sinus rhythm; cSR, heart rate-matched controls with sinus rhythm; RER, respiratory exchange ratio; HR, heart rate; VO_2, oxygen uptake; N, number of patients.

Table 1
Baseline characteristics of patients in the AF and cSR groups.
N, number of patients; AF, atrial fibrillation; HR, heart rate; SR, sinus rhythm; BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; RAS, renin–angiotensin system; ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme. Data are presented as the mean ± SD or number (%) of patients.

Variable	Patients with AF ($N = 27$)	HR-matched controls with SR ($N = 106$)	*P* value
Gender (women/men)	(6/21)	(26/80)	0.80
Age (years)	68.4 ± 8.0	65.2 ± 8.4	0.07
weight (kg)	67.7 ± 12.0	64.3 ± 11.3	0.17
BMI (kg/m^2)	25.0 ± 3.3	23.6 ± 3.1	0.04*
Diagnosis			
Hypertension	24 (88.9)	81(76.4)	0.16
CAD (%)	15 (55.6)	77 (72.6)	0.08
PCI	10	65	
CABG	3	13	
Cardiomyopathy	4 (14.9)	5 (4.7)	0.15
Valvular heart disease	9 (33.3)	8 (7.5)	0.001**
Diabetes mellitus (%)	12 (44.4)	47 (44.3)	0.99
Medication (%)			
Calcium channel blockers	10 (37.0)	47 (44.3)	0.64
Non-dihydropyridine	4 (14.8)	4 (3.8)	0.03*
RAS blockers	21 (77.8)	71 (67.0)	0.28
ARB	13 (48.1)	44 (41.5)	
ACE inhibitor	8 (29.6)	30 (28.3)	
Beta blockers	17 (63.0)	51 (48.1)	0.17
Statins	16 (59.3)	74 (69.8)	0.42
Diuretics	12 (44.4)	19 (17.9)	0.004**
Digoxine	12 (44.4)	0 (0)	<0.001**

** $P < 0.001$.
* $P < 0.05$.

dividing VO_2 by HR, was obtained at Rest, Wu, AT, Rc, and Peak point during CPET.

The minute ventilation/carbon dioxide production relation slope (VE/VCO_2 slope), the slope of the increase in ventilation to the increase in CO_2 output, was calculated during incremental exercise using least squares linear regression.

Percent-predicted VO_2/kg at AT and Peak were calculated according to published age and sex-normalized values for healthy Japanese of the same age and sex [13].

2.4. Examinations

Standard echocardiographic imaging was performed for the evaluation of left ventricular (LV) ejection fraction (EF), diameters of the left ventricle and left atrium (LA), and assessment of right ventricular systolic pressure (RVSP). The presence or absence of valvular heart disease was also evaluated. The brain natriuretic peptide (BNP) and hemoglobin levels were measured within 1 month before or after CPET.

2.5. Statistical analysis

Data are presented as the mean ± standard deviation. All calculations were made using the JMP statistical software package v.11.0 (SAS institute Inc., Tokyo, Japan) and the PASW Statistics 18 (SPSS Inc., Chicago, IL, USA).

The prevalence of any underlying disease, the indices obtained from echocardiography, and the indices obtained from CPET were compared between the AF and cSR groups using unpaired *t*-test, Mann–Whitney *U* test, or Fisher's exact test, where appropriate. Categorical variables are expressed as absolute numbers with percentages. Comparisons of the trends in VO_2 and HR during exercise between the AF and cSR groups were achieved using two-way ANOVA with repeated measurements. One-way repeated ANOVA was used to compare the values of VO_2 and HR during exercise between each timing in each group. Comparisons of the variables between the AF and cSR groups were performed using Student's *t*-test with Bonferroni correction. Comparisons of the variables between adjacent time points in each group were performed using Student's *t*-test with Bonferroni correction. A *P* value <0.05 was considered statistically significant. Two correlations were compared by *Z*-score, calculated by Fisher r-to-z transformation.

3. Results

3.1. Baseline characteristics

The patients in the AF group included 21 men (77.8%) with a mean age of 68.4 ± 8.0 years (Table 1). The cSR group included 80 men (75.5%) with a mean age of 65.2 ± 8.4 years. Although the patients in the AF group were older on average compared with the cSR group, the difference was not statistically significant. Regarding the cardiovascular background, the proportion of patients with ischemic heart disease was high in the cSR group, whereas the proportion of patients with valvular disease was high in the AF group. Calcium channel blockers, renin–angiotensin system blockers, beta blockers, and statins were prescribed

Table 2
Cardiopulmonary exercise testing, laboratory data, and echocardiography parameters of patients in the AF and cSR groups.
N, number of patients; AF, atrial fibrillation; HR, heart rate; SR, sinus rhythm; Rest, average of 4 min of rest; AT, anaerobic threshold; Peak, exercise peak;
VO_2, oxygen uptake; %AT; percent-predicted VO_2/kg at AT; %Peak; percent-predicted VO_2/kg at Peak; VE/VCO_2 slope; the minute ventilation/carbon dioxide production relation slope; Hb, hemoglobin; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LAD, left atrial dimension; RVSP, right ventricular systolic pressure. Data are presented as the mean ± SD.

Variable	Patients with AF (N = 27)	HR-matched controls with SR (N = 106)	*P* value
CPET parameters			
Peak watts	87.9 ± 14.9	93.7 ± 22.9	0.22
Heart rate (bpm)			
at Rest	78.4 ± 13.4	78.5 ± 10.2	0.98
at AT	109 ± 17.5	106.6 ± 11.6	0.40
at Peak	139.1 ± 19.8	134 ± 13.7	0.12
Systolic/diastolic blood pressure (mmHg)			
at Rest	116 ± 26/72 ± 14	123 ± 21/73 ± 12	0.13/0.56
at AT	144 ± 21/79 ± 12	161 ± 24/80 ± 13	0.001**/0.61
at Peak	165 ± 27/83 ± 13	191 ± 28/86 ± 15	<0.001**/0.43
VO_2 (ml/min)			
at Rest	222 ± 41.7	223 ± 44.8	0.91
at AT	751.4 ± 122.8	770 ± 175.5	0.61
at Peak	1056 ± 190.1	1134.2 ± 287.6	0.18
VO_2/kg (ml/kg/min)			
at Rest	3.3 ± 0.5	3.5 ± 0.6	0.12
at AT	11.2 ± 1.3	12.1 ± 2.4	0.06
at Peak	15.7 ± 2	17.7 ± 3.3	0.004**
O_2 pulse (ml/bpm)			
at Rest	2.9 ± 0.75	2.87 ± 0.6	0.82
at AT	7.02 ± 1.42	7.34 ± 1.68	0.36
at Peak	7.76 ± 1.92	8.53 ± 2.2	0.10
Relative O_2 pulse (ml/bpm/kg × 100)			
at Rest	4.4 ± 1.2	4.5 ± 0.9	0.45
at AT	10.5 ± 2.2	11.3 ± 2.2	0.09
at Peak	11.6 ± 2.5	13.2 ± 2.3	0.001**
%AT (%)	69.2 ± 8.8	76 ± 12.4	0.06
%Peak (%)	67.0 ± 9.5	73.7 ± 13.8	0.02*
VE/VCO_2 slope	30.6 ± 5.1	29.4 ± 5.6	0.33
Laboratory data and cardiac indices			
Hb (g/dl)	13.7 ± 1	13.3 ± 1.6	0.30
BNP (pg/ml)	144.3 ± 88.1	55.1 ± 57.5	<0.001**
LVEF (%)	59.8 ± 10.2	60.8 ± 12.4	0.68
LVDd (mm)	49.0 ± 5.5	48.5 ± 6.1	0.68
LVDs (mm)	33.0 ± 7	32.3 ± 7.8	0.7
LAD (mm)	49.5 ± 7.2	37.0 ± 7.1	<0.001**
RVSP (mmHg)	30.3 ± 5.9	23.5 ± 11.1	0.004**

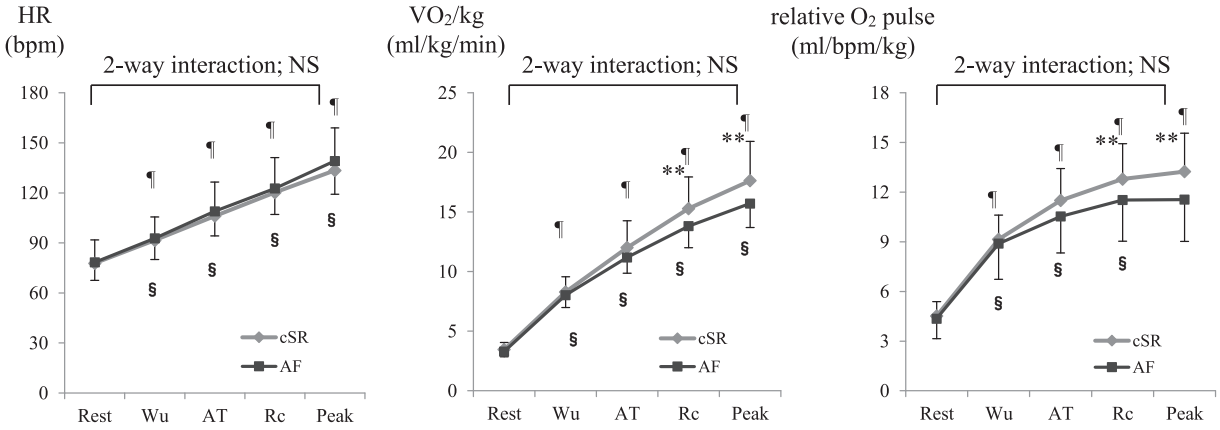

Fig. 2. Changes in the HR, VO2/kg, and relative O2 pulse in the AF and cSR groups during exercise. ¶, statistically significant change from the previous time point of exercise in the cSR group; §, statistically significant change from the previous time point of exercise in the AF group; **, statistically significant difference between the AF and cSR groups; AF, atrial fibrillation; cSR, heart rate-matched controls with sinus rhythm; HR, heart rate; VO_2, oxygen uptake; Rest, average of 4 min of rest; Wu; average of 3–4 min after exercise commenced; AT, anaerobic threshold; RC, respiratory compensation point; Peak, exercise peak.

to patients in the AF group as well as to patients in the cSR group. However, non-dihydropyridine calcium channel blocker, diuretics and digoxin were used frequently in the AF group (Table 1). Amiodarone was prescribed to one patient in cSR group.

3.2. Differences in VO_2/kg between AF and cSR groups at each point of exercise

The HR at Rest, Wu, AT, Rc, and at Peak were not significantly different between the AF and cSR groups (Table 2 and Fig. 2). The systolic blood pressure at AT and Peak in the AF group were significantly lower than those in the cSR group. Peak watts in the AF group were lower than that in the cSR group, but the difference was not significant. In terms of VO_2/kg, the values of VO_2/kg increased during exercise in both groups; however, there was a significantly different trend between AF and cSR. In addition, VO_2/kg at Rest, Wu and AT were not significantly different between the AF and cSR groups, whereas VO_2/kg at Peak was significantly impaired in the AF group. Similarly, there was a significant difference between the AF and cSR groups in the relative O_2 pulse, which is exemplified by VO_2 per HR standardized by body weight.

According to the time course of VO_2/kg and relative O_2 pulse during exercise, the values of VO_2/kg were increased during exercise in both groups. In contrast, relative O_2 pulse was increased in accordance with the exercise time in the cSR group, whereas relative O_2 pulse at Rc and Peak in the AF group had no difference. Therefore, the slope of relative O_2 pulse along the increase of exercise was blunted for the AF group compared with that of the cSR group.

Other than CPET parameters, the BNP level was significantly higher in the AF group than in the cSR group (Table 2). Left atrial dimension (LAD) and RVSP were significantly higher in the AF group than in the cSR group. There were no differences in LVEF between the AF and cSR groups.

3.3. Blunted increase in relative O_2 pulse in the AF group

We continued our investigation by examining the trend of the O_2 pulse in the AF group (Fig. 3, Table 3). O_2 pulse trend ratio was calculated by O_2 pulse at Peak/O_2 pulse at AT, and AF patients were divided into two groups according to O_2 pulse trend ratio (median = 1.1). High O_2 pulse trend (high-O_2p trend) had the O_2 pulse trend ratio > 1.1, whereas low O_2 pulse trend (low-O_2p trend) had the O_2 pulse trend ratio < 1.1. In the low-O_2p trend group, the HR at Rest was comparatively low compared with the high-O_2p trend group. HR change from Rest to Peak (HR reserve) was significantly higher in the low-O_2p trend group as compared with that of high-O_2p trend group. In contrast, the O_2 pulse was comparatively increased below the Rc level in the low-O_2p trend

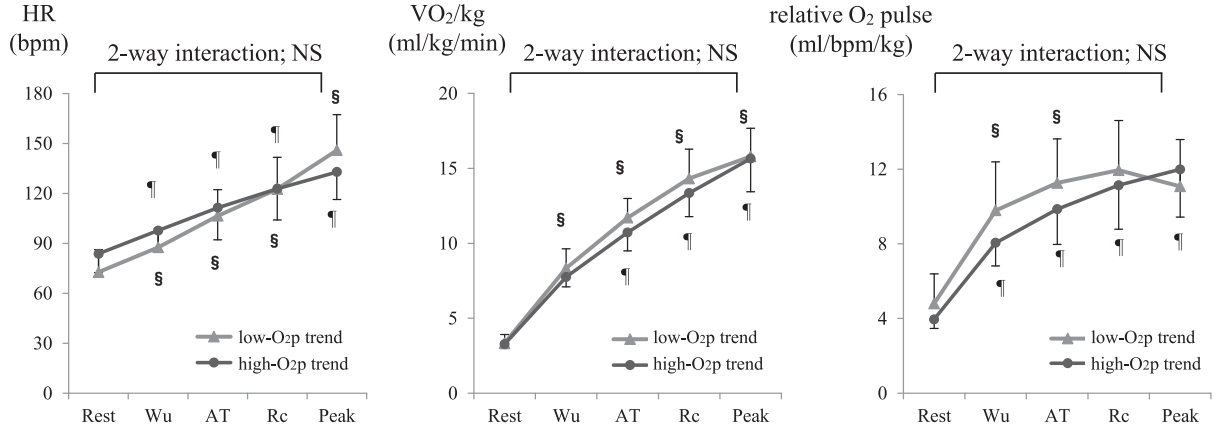

Fig. 3. Changes in the HR, VO2/kg, and relative O2 pulse in AF patients after divided into two groups according to O2 pulse trend ratio. ¶, statistically significant change from the previous time point of exercise in the high O_2 pulse trend group; §, statistically significant change from the previous time point of exercise in the low O_2 pulse trend group; The horizontal axis shows each point during CPET. AF, atrial fibrillation; cSR, heart rate-matched controls with sinus rhythm; HR, heart rate; VO_2, oxygen uptake; Rest, average of 4 min of rest; Wu; average of 3–4 min after exercise commenced; AT, anaerobic threshold; RC, respiratory compensation point; Peak, exercise peak.

Table 3
Characteristics of AF patients after they were divided into two groups according to O_2 pulse trend ratio calculated by O_2 pulse at Peak/O_2 pulse at AT (median = 1.1).
N, number of patients; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; RAS, renin–angiotensin system; Rest, average of 4 min of rest; AT, anaerobic threshold; Peak, exercise peak; VO_2, oxygen uptake; %AT; percent-predicted VO_2/kg at AT; %Peak; percent-predicted VO_2/kg at Peak; VE/VCO_2 slope; the minute ventilation/carbon dioxide production relation slope; HRR, heart rate reserve; %HRR, percentage of heart rate reserve; Hb, hemoglobin; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LAD, left atrial dimension; RVSP, right ventricular systolic pressure. Data are presented as the mean ± SD or number of patients.

Variable	Low O_2 pulse trend group ($N = 13$)	High O_2 pulse trend group ($N = 14$)	*P* value
Clinical characteristics			
Gender (women/men)	(4/9)	(2/12)	0.57
Age (years)	69.4 ± 6.2	67.6 ± 9.5	0.57
Weight (kg)	66.1 ± 13.6	69.2 ± 10.5	0.52
BMI (kg/m^2)	24.9 ± 3.9	25.1 ± 2.9	0.87
Diagnosis			
Hypertention	12	12	0.56
CAD	7	8	0.83
Valvular heart disease	5	4	0.89
Diabetes mellitus	5	7	0.83
Medications			
Calcium channel blockers	7	3	0.24
Non-dihydropyridine	4	2	0.30
RAS blockers	11	10	0.72
Beta blockers	6	11	0.18
Statins	7	9	0.87
Diuretics	7	5	0.58
Digoxin	5	7	0.83
CPET parameters			
Peak watts	86.1 ± 16.3	89.6 ± 13.8	0.54
Heart rate (bpm)			
at Rest	72.7 ± 13.5	83.7 ± 11.4	0.03*
at AT	106.5 ± 15.8	111.4 ± 19.3	0.48
at Peak	145.9 ± 21.4	132.9 ± 16.6	0.09
Systolic/diastolic blood pressure (mmHg)			
at Rest	119 ± 18/73 ± 13	114 ± 33/71 ± 15	0.62/0.79
at AT	151 ± 21/79 ± 12	137 ± 19/78 ± 12	0.07/0.94
at Peak	175 ± 29/85 ± 14	155 ± 22/82 ± 12	0.05/0.51
VO_2 (ml/min)			
at Rest	217.2 ± 42.6	226.5 ± 41.9	0.57
at AT	769.5 ± 155.8	734.6 ± 84.3	0.47
at Peak	1037.3 ± 223.6	1073.4 ± 159.5	0.63
VO_2/kg (ml/kg/min)			
at Rest	3.3 ± 0.6	3.3 ± 0.3	0.75
at AT	11.7 ± 1.3	10.7 ± 1.2	0.053
at Peak	15.8 ± 1.9	15.6 ± 2.2	0.86
O_2 pulse (ml/bpm)			
at Rest	3.1 ± 0.9	2.7 ± 0.5	0.23
at AT	7.3 ± 1.5	6.8 ± 1.3	0.34
at Peak	7.2 ± 1.8	8.3 ± 2	0.16
Relative O_2 pulse (ml/bpm/kg × 100)			
at Rest	4.8 ± 1.6	4.0 ± 0.5	0.07
at AT	11.3 ± 2.4	9.9 ± 1.9	0.10
at Peak	11.1 ± 2.5	12.0 ± 2.6	0.36
%AT (%)	71.3 ± 8	65.5 ± 7.4	0.06
%Peak (%)	67.9 ± 9.3	66.2 ± 9.88	0.65
VE/VCO_2 slope	30.3 ± 5.5	30.8 ± 4.9	0.80
HR reserve (bpm)	73.2 ± 18.9	49.1 ± 12.3	0.001**
%HRR (%)	96.4 ± 29.3	74.0 ± 22.9	0.04*
Laboratory data and cardiac indices			
Hb (g/dl)	13.2 ± 1.1	14.1 ± 0.8	0.02*
BNP (pg/ml)	142.3 ± 99.4	146.2 ± 79.1	0.91
LVEF (%)	58.9 ± 8.9	60.5 ± 11.4	0.70
LVDd (mm)	49.1 ± 4.9	48.9 ± 6.2	0.93
LVDs (mm)	32.8 ± 5.9	33.1 ± 8	0.91
LAD (mm)	48.5 ± 5.9	50.4 ± 8.3	0.51
RVSP (mmHg)	30.0 ± 6.5	30.5 ± 5.3	0.82

group, whereas, above the Rc level, there was no increase in the O_2 pulse in the low-O_2p trend group. In the high-O_2p trend group, the increase in the O_2 pulse was somewhat low below the Rc level compared with that of the low-O_2p trend group, whereas the O_2 pulse at peak in the high-O_2p trend group exceeded that in the low-O_2p trend group. From these results, blunted increase in relative O_2 pulse in the AF group was associated with HR increase during exercise.

We compared the contributions of the HR change (from Rest to Peak/from Rest to AT/from AT to Peak) during exercise on the value of O_2 pulse trend ratio (= O_2 pulse at Peak/O_2 pulse at AT) between the AF and cSR groups (Fig. 4). There was a significant inverse-correlation between the HR change and the O_2 pulse trend ratio in AF patients, whereas the association was comparatively weak in the cSR group. These inverse correlations between O_2 pulse trend ratio and the HR change from Rest to Peak as well as those from AT to Peak were significantly different by *Z*-score analysis between AF and cSR groups.

4. Discussion

The exercise capacity of AF patients is greatly affected by the HR response. In the present study, we identified HR-matched controls with SR who had a similar HR trend to AF patients during exercise and, we demonstrated that the value of VO_2/kg is significantly lower in AF patients above the AT level. This study ultimately suggests that exercise impairment in the setting of AF is developed above the exercise level of the AT point after standardization of HR [14,15]. The results of this study show that adverse effects on the hemodynamics due to AF become apparent with a load exceeding the AT level. Regarding the hemodynamic derangement of AF, rhythm irregularity and loss of atrial contribution to LV filling impair cardiac output in AF patients [3]. Exercise capacities in AF patients have been shown to be impaired by multiple pathways, such as endothelial dysfunction or neurohumoral factors [16,17]. In addition, hemodynamic effects derived from AF change according to the exercise level.

Our results were similar to those of Elshazly et al. [18], in which the value of VO_2 below the AT point was similar between AF and SR patients. HRs at baseline and peak were higher in AF patients in Elshazly's study as compared with ours. In our study, the hemodynamic trend in AF was verified even after the deleting the effect derived from exaggerated HR response in the AF group. Atrial emptying is mainly performed by conduit flow, which is induced by LV longitudinal contraction in light exercise [19]. This is closely associated with LV properties rather than intrinsic LA function. These findings suggest that the impact of left atrial abnormalities in AF patients is comparatively smaller than the effect derived from LV factors. In contrast, during moderate exercise atrial emptying is induced mainly by atrial contraction and is therefore greatly affected by the presence of AF [19]. These mechanistic insights correspond well to the findings that exercise derangement in AF patients was demonstrated above the level of moderate exercise in the present study.

However, there are some contradictory findings regarding the relationship between exercise load and the contribution of atrial function. Linde-Edelstam et al. demonstrated that the importance of atrial contraction to ventricular filling diminishes in accordance with increasing blood flow velocity as the exercise work load increases [20]. Furthermore, left atrial pressure determines the contribution of atrial contraction to LV filling, and the elevation of pulmonary capillary wedge pressure was reported to diminish the power of atrial contraction on the cardiac output [17]. These studies suggest that multiple factors affect the contribution of atrial-derived factors on the cardiac output. Further investigations should be conducted to better understand the mechanism underlying decreased O_2 pulse in AF patients.

Another interesting aspect of this manuscript is the close association between the HR response and increase in the O_2 pulse above the AT level. The inverse association between HR change, which is a marker of chronotropy, and the increase in the O_2 pulse above the AT level is

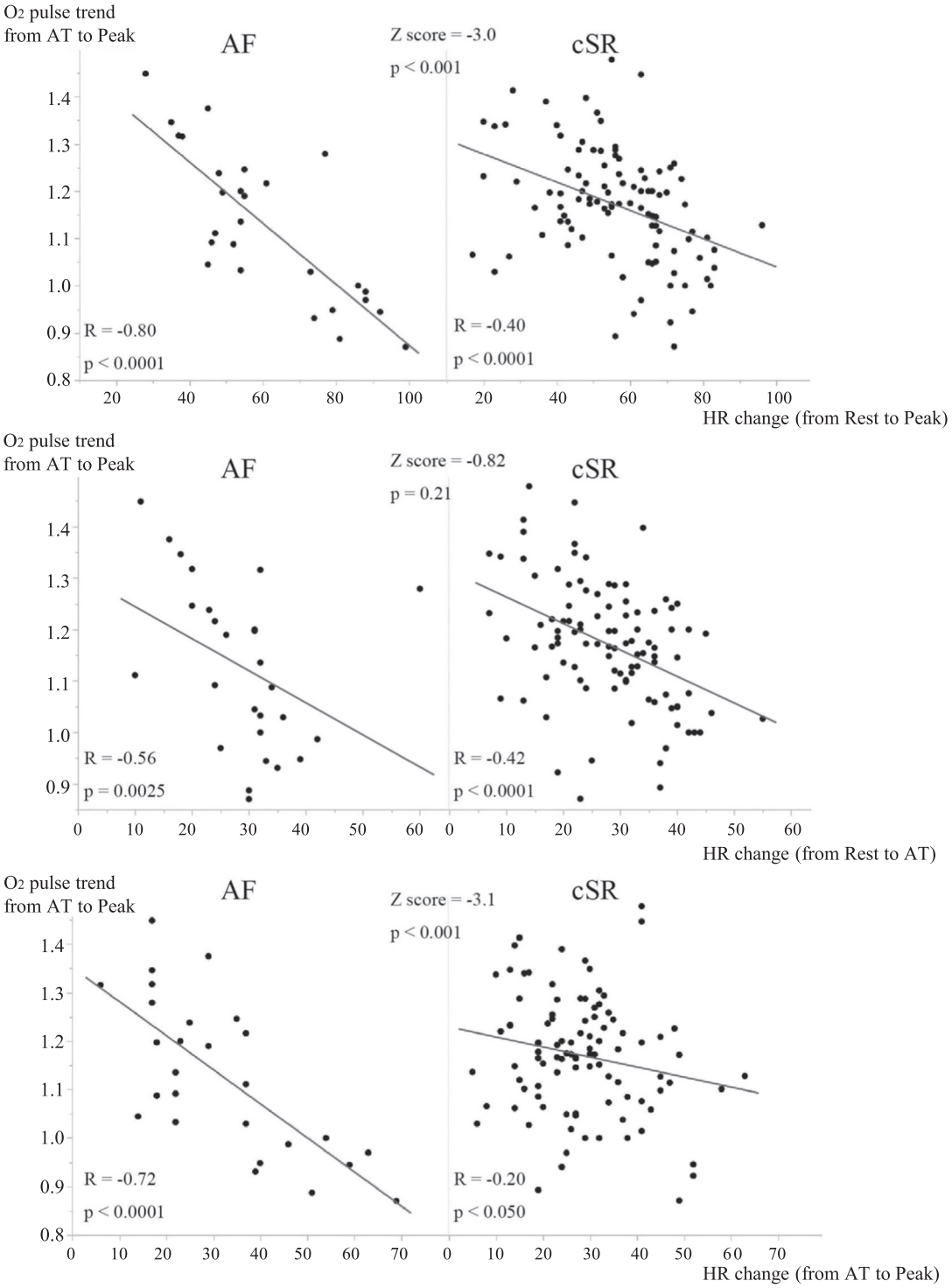

Fig. 4. Correlative relationships between the O_2 pulse trend ratio (O_2 pulse at Peak/O_2 pulse at AT) and HR change from Rest to Peak, Rest to AT and AT to Peak.

strikingly enhanced in AF patients. The HR change during exercise could predict the trend of the O_2 pulse at the submaximal stage. In addition, there were two different groups with different trends in the O_2 pulse in AF patients; one wherein VO_2 is maintained above the AT level by increasing HR and one wherein VO_2 is maintained by increasing the stroke volume. The blunted increase in the O_2 pulse above the AT level corresponded to the enhanced response of chronotropy, maintaining the value of VO_2/kg. However, there were no differences in laboratory data, echocardiographic parameters, and medication profiles.

Several studies have demonstrated the association between HR or HR response and exercise capacity [21,22]. The enhanced HR response in AF patients has been demonstrated in previous studies [14,23] and has been reported to be due to an increased sympathetic drive triggered to maintain cardiac output. However, increasing HR does not always improve exercise tolerance or symptoms in AF patients [24]. Indeed, the degree of exaggerated chronotropic response evoked an unfavorable effect on cardiac output above the moderate intensity of exercise and the unfavorable effect was more enhanced in AF patients. In this study, there was no significant

difference in HR trend between AF and cSR patients, which could demonstrate the different association of HR response and the change of cardiac output between AF and cSR patients in more sophisticated manner. However, the relationship between exercise capacity and HR response is more complicated in AF patients. The determinant factors of chronotropy in AF patients had been warranted more concisely [25,26]. Another possible determining factor of chronotropy in AF is atrial function, such as atrial appendage emptying velocity or atrial contractile function. In order to verify it, the more detailed evaluation of atrial function should be performed.

The findings of the current study suggested that, aerobic exercise is generally performed as a main protocol of cardiac rehabilitation, in which the change of O_2 pulse during exercise had similar behavior between patients with sinus rhythm and AF. However, the exercise capacity is significantly impaired above the level of AT and the change of HR reflected the burden of exercise in a more exaggerated manner in patients with AF than patients with sinus rhythm.

5. Study limitations

There are several limitations in the present study, which includes a small study population without healthy controls. In addition, the patient population was limited to those receiving cardiac rehabilitation, which could evoke referral bias because patients referred for cardiac rehabilitation are not representative of the general community population. In selecting cSR patients, there was some possibility that they were different from SR patients and the difference of chronotropic competency may be a candidate to segregate the cSR group from a general SR group, which, however, is above the scope of this study. The elucidation of basic characteristics of these classifications is also warranted. Because the disease severity in our patients was mild and the study population included only Japanese patients, the results should be carefully interpreted when applied to different populations. The voluntary participation of the study patients in ambulatory cardiac rehabilitation may introduce some bias in the present study. In addition, the study design was limited regarding the evaluation of the effect of medications. Among them, the medication of beta blockers should be carefully considered because it might significantly affect the behavior of HR. However, there were no significant differences in HR trend, VO_2/kg trend during exercise in AF patients in this study.

6. Conclusion

Hemodynamic derangement during exercise derived from AF was developed above the moderate intensity exercise such as AT and the VO_2 was significantly lower in AF patients than HR-matched control above AT. Additionally, the HR change during exercise was inversely correlated with the increase of O_2 pulse. Especially the inverse correlation between the increase of O_2 pulse and HR change above AT was significantly enhanced in AF patients. It may be beneficial for AF patients to be reevaluated for exercise tolerance so that the quality and usefulness of rhythm control can be better determined.

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Conflict of interest statement

The authors report no relationships that could be construed as a conflict of interest.

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