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Compensatory Increase in Heart Rate Is Responsible for Exercise Tolerance among Male Patients with Permanent Atrial Fibrillation

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Atrial fibrillation (AF) is an exacerbating factor for exercise tolerance due to the loss of atrial kick. However, many patients with permanent AF, which lasts for at least a year without interruption, and preserved left ventricular ejection fraction (LVEF ≥ 50%) are asymptomatic and have good exercise tolerance. In such cases, the possible mechanism that compensates for the decrease in cardiac output accompanying the loss of atrial kick is a sufficient increase in heart rate (HR) during exercise. We investigated the relationship between exercise tolerance and peak HR during exercise using cardiopulmonary exercise testing in 242 male patients with preserved LVEF, 214 with sinus rhythm (SR) and 28 with permanent AF. Peak HR was significantly higher in the AF group than the SR group (148.9 ± 41.9 vs. 132.0 ± 22.0 beats/min, p = 0.001). However, oxygen uptake at peak exercise did not differ between the AF and SR groups (19.4 ± 5.7 vs. 21.6 ± 6.0 mL/kg/min, p = 0.17). In multiple regression analysis, peak HR (β, 0.091; p < 0.001) and the interaction term constructed by peak HR and presence of permanent AF (β, 0.05; p = 0.04) were selected as determinants for peak VO_2; however, presence of permanent AF was not selected (β, −0.38; p = 0.31). Therefore, the impact of peak HR on exercise tolerance differed between the AF and SR groups, suggesting that a sufficient increase in HR during exercise is an important factor to preserve exercise tolerance among patients with AF.

Keywords: atrial fibrillation; diastolic function; exercise tolerance; heart rate; preserved left ventricular ejection fraction

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Introduction

Exercise tolerance is multifactorial (Hossack and Bruce 1982; Woo et al. 2006; Grewal et al. 2009); cardiac output (CO) is an important factor, along with a peripheral arteriovenous oxygen difference. Therefore, it is widely accepted that exercise tolerance in patients with atrial fibrillation (AF) is reduced because development of AF is accompanied by loss of atrial kick, resulting in decreased CO (Ostermaier et al. 1997). However, many patients with permanent AF and preserved left ventricular ejection fraction (LVEF ≥ 50%) are asymptomatic and have good exercise tolerance (Flaker et al. 2005; Myrstad et al. 2016). In such cases, the body may compensate for decrease in CO accompanying the loss of atrial kick. In general, to meet increasing oxygen demand during exercise, CO is increased by an augmentation in stroke volume and heart rate (HR) (Thompson 2005). Nevertheless, stroke volume typically reaches a plateau at 50%-60% of oxygen uptake at peak exercise (peak VO_2). Therefore, an increase in HR is needed to achieve a continuous increase in CO during exercise of moderate-to-high intensity. Thus, the importance of an increase in HR in patients with AF is not difficult to comprehend. However, the underlying mechanism that compensates exercise tolerance in such asymptomatic patients with AF and preserved LVEF has been partially elucidated. Accordingly, we examined the impact of permanent AF on exercise tolerance, as assessed by peak VO_2 using cardiopulmonary exercise testing (CPX). In addition, we investigated an increase in HR during exercise affected patients with permanent AF and preserved LVEF differently than those with sinus rhythm (SR).

Methods

Study population

This cross-sectional study assessed the impact of permanent AF on exercise tolerance of patients with preserved LVEF. The study patients included 464 consecutive patients who underwent CPX and

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comprehensive echocardiography for clinical evaluation, and who provided blood samples for B-type natriuretic peptide (BNP) measurement on the same day at the Nagoya City University Hospital from September 2008 to December 2017. The patients with permanent AF and those with SR as controls were selected for this study. Based on the duration of AF episodes, AF is classified into three categories: paroxysmal, persistent, and permanent AF. According to the J-RHYTHM Registry, which is a registered study of AF in Japan, the type of AF was paroxysmal in 37.1%, persistent in 14.4%, and permanent in 48.5% (Atarashi et al. 2011). Permanent AF was defined as AF present for at least a year with no interruption. In total, 432 patients (396 with SR and 36 with permanent AF) were finally enrolled. Reflecting clinical practice (Inoue et al. 2009), the AF group had a significantly lower proportion of females than did the SR group (11.8% vs. 33.3%, $p < 0.001$); therefore, we only analyzed male patients in this study. Furthermore, patients who were positive for ischemia during the exercise test were also excluded because cardiac ischemia could provide alteration of autonomic balance and could consequently alter HR. Therefore, a total of 242 male patients (66.9 ± 9.4 y; 214 with SR and 28 with permanent AF) were eligible for enrollment in this study. Patients with paroxysmal AF and persistent AF were excluded because some of them restored to SR by medication, cardioversion, or catheter ablation. Furthermore, patients with hemodynamically significant valvular disease classified as severe valvular disease on the basis of the echocardiography findings, decompensated heart failure (HF), acute coronary syndrome, pulmonary hypertension, adult congenital heart disease, chronic obstructive pulmonary disease, or other pulmonary disease were also excluded. In addition, because peak respiration exchange rate (RER) ≥ 1.0 was considered to indicate maximal effort, we excluded patients with peak RER of < 1.0 on exercise testing. Median duration of permanent AF was 60 months as per medical records. All patients with permanent AF had no apparent symptoms based on self-report. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or on treatment with antihypertensive drugs. Diabetes mellitus (DM) was defined as a fasting blood glucose level of > 126 mg/dL or treatment with blood glucose-lowering medicine. Hyperlipidemia was defined as low-density lipoprotein-cholesterol level of > 140 mg/dL or treatment with cholesterol-lowering medicine. All patients provided written informed consent prior to participation in the study. The study protocol was performed according to the regulations proposed by the Ethical Guidelines Committee of the Nagoya City University Graduate School of Medical Sciences (approval identification number: 832).

CPX

All patients underwent symptom-limited CPX with simultaneous expired ventilatory gas analysis by bicycle ergometry (Ergometer STB-3200; Nihon Kohden, Tokyo, Japan; AE-310S; Minato Medical Science, Osaka, Japan). CPX was performed at a constant cadence of 50 rpm according to the protocol of a 15 watts/min continuous ramp after a 3-min resting period. Resting HR was averaged during the 3-min resting period of CPX. Peak VO_2 was determined from the averaged during the last 30 seconds of CPX and was defined as the highest oxygen uptake value. The percent-predicted peak VO_2 was determined as a percentage of actual peak VO_2 in comparison with predicted peak VO_2 according to the data on healthy individuals in Japan (Itoh et al. 2013). The ventilatory anaerobic threshold (AT) was determined by V-slope analysis (Beaver et al. 1986). The VE/VCO_2 slope for the entire duration of exercise was calculated as the slope of the linear relationship between VE and VCO_2 from the start of exercise to just before the respiratory compensation (Sun et al. 2002). Peak HR was defined as HR at peak VO_2. Chronotropic response was expressed as the change in HR from rest to peak exercise. Age-predicted maximal HR was defined with the Astrand (220 − age) (Astrand 1960) and Brawner (164 − [0.7 × age]) (Brawner et al. 2004) formulas. Each formula was used to calculate chronotropic index reflecting the percentage of HR reserve used (change in HR from rest to peak exercise/age-predicted maximal HR − resting HR). Chronotropic incompetence was defined as a chronotropic index < 0.8 for patients not taking β-blockers and < 0.62 for patients taking β-blockers (Astrand formula) (Khan et al. 2005). The β-blocker correction was not used for chronotropic incompetence defined using the Brawner formula (Brawner et al. 2004).

Echocardiograhy

Each patient underwent comprehensive echocardiography with standard technique (Lang et al. 2005). All recordings were performed on ultrasound systems (Vivid 7; GE Healthcare, Vingmed Ultrasound AS, Horten, Norway). Values reported in patients with AF represent an average of ten beats (Nagueh et al. 1996). Early diastolic transmitral flow velocity (E) was recorded at the tip of the mitral leaflet. Using tissue Doppler imaging, mitral annular velocity during early diastole (e') was recorded with the sample volume placed on both the septal and lateral corners of the mitral annuls in the apical four-chamber view (Nagueh et al. 1997). Then, the E/e' ratio was calculated from these data.

Statistical analysis

Statistical analysis was performed with SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation for normally distributed variables and the median and interquartile range for non-normally distributed variables. Categorical variables are summarized as the frequency (%). For comparisons between the groups, continuous variables were compared by unpaired Student's *t*-test for normally distributed variables and Mann-Whitney *U*-test for non-normally distributed variables. Differences in prevalence between the groups were compared using the chi-square test. Relationships between variables were evaluated by univariate linear regression analysis. Multiple regression analysis was performed to identify the parameter that affects exercise tolerance. The variables entered into the model included age < 70 y, body mass index (BMI) < 24 kg/m^2, resting SBP ≥ 130 mm Hg, left atrium diameter (LAD) < 40 mm, average E/e' ratio < 10, peak HR, with permanent AF, and the interaction term constructed by peak HR and presence of permanent AF. The cut-off values of age, BMI, resting SBP, and LAD were derived from the median value of this study. The cut-off value of average E/e' ratio < 10 to identify preserved diastolic function was derived from the guidelines by the American Society of Echocardiography and European Association of Cardiovascular Imaging (Nagueh et al. 2016). Differences with a p value < 0.05 were considered statistically significant.

Results

Clinical characteristics

Patient clinical characteristics are presented in Table 1. Height and body weight were significantly larger in the AF

Table 1. Clinical characteristics of study groups, according to cardiac rhythm.

Characteristic	Sinus rhythm	Atrial fibrillation	p
Number	214	28	
Age (years)	66.7 ± 9.5	68.6 ± 8.9	0.32
Height (cm)	165.3 ± 6.5	168.3 ± 6.6	0.02
Weight (kg)	65.9 ± 11.1	70.7 ± 11.7	0.03
Body mass index (kg/m^2)	24.0 ± 3.3	24.8 ± 3.0	0.24
Hypertension (%)	55.6	78.6	0.02
Hyperlipidemia (%)	63.1	53.6	0.33
Diabetes mellitus (%)	25.7	46.4	0.02
Prior MI (%)	25.2	10.7	0.09
Cardiomyopathy (%)	8.4	3.6	0.37
Glucose (mg/dL)	117.8 ± 37.1	119.3 ± 41.8	0.84
Hemoglobin A1c (%)	6.1 ± 0.8	6.1 ± 0.7	0.76
eGFR (mL/min/1.73m^2)	67.4 ± 15.7	56.9 ± 18.2	0.001
BNP (pg/mL)	26.9 [IQR, 12.8-51.0]	139.7 [IQR, 82.8-361.9]	< 0.001
Medication			
β-blockers (%)	38.3	50.0	0.24
CCBs (%)	36.4	35.7	0.94
ACEIs/ARBs (%)	41.6	67.9	0.01
Statins (%)	53.7	35.7	0.07

Data are presented as mean ± SD, median (interquartile range) or percentages.
MI, myocardial infarction; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

group than those in the SR group, which are consistent with the previous studies (Wang et al. 2004; Rosenberg et al. 2012), However, BMI did not differ between the groups. The prevalence of hypertension and DM was higher in the AF group than in the SR group. The use of *β*-blockers was similar between the AF and SR groups (50.0% vs. 38.3%, p = 0.24). The number of patients who used *β*-blockers and the usage dose of each *β*-blockers were as follows: (1) Carvedilol: SR: n = 38, 8.9 ± 5.6 mg and AF: n = 11, 11.1 ± 7.4 mg, p = 0.29; (2) Bisoprolol: SR: n = 32, 3.0 ± 1.3 mg and AF: n = 3, 1.5 ± 1.0 mg, p = 0.053; (3) Atenolol: SR: n = 6, 25.0 ± 0.0 mg and AF: n = 0, N/A; (4) Metoprolol: SR: n = 5, 68.0 ± 30.3 mg and AF: n = 0, N/A; and (5) Celiprolol: SR: n = 1, 100.0 mg and AF: n = 0, N/A).

Echocardiography data

The results of echocardiography are shown in Table 2. The AF group had significantly greater LAD than the SR group. The AF group had significantly lower LVEF due to the larger LV end-systolic diameter. Reflecting these, the plasma BNP level was significantly higher in the AF group compared with that in the SR group. Although both transmitral E velocity and deceleration time of E wave had significant differences between the groups, no difference was found in the E/e' ratio that refers to LV filling pressure between them.

Table 2. Results of echocardiography data, according to cardiac rhythm.

Characteristic	Sinus rhythm	Atrial fibrillation	p
LVEF (%)	69.5 ± 8.3	64.0 ± 8.1	0.001
LVDd (mm)	47.3 ± 5.5	48.7 ± 7.6	0.23
LVDs (mm)	28.9 ± 6.4	31.6 ± 5.6	0.04
LAD (mm)	37.6 ± 6.3	48.3 ± 8.0	< 0.001
E (cm/sec)	63.2 ± 17.4	91.8 ± 18.6	< 0.001
DT (ms)	234.9 ± 59.5	159.7 ± 30.1	< 0.001
Septal E/e'	10.6 ± 4.5	10.9 ± 5.7	0.50
Lateral E/e'	8.3 ± 3.4	8.9 ± 4.2	0.58
Average E/e'	9.2 ± 3.4	9.9 ± 3.4	0.33

Data are presented as mean ± SD.
LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LAD, left atrium diameter; E, early diastolic transmitral flow velocity; DT, deceleration time of E wave; e', mitral annular velocity during early diastole.

CPX

The results of CPX are shown in Table 3. All patients surpassed their ATs. Their average peak RER was 1.22 (in the total cohort). Resting HR was significantly higher in the AF group than that in the SR group (71.6 ± 16.0 vs. 64.0 ± 10.7 beats/min, p = 0.001). Similarly, peak HR during exercise was higher in the AF group than that in the SR group (148.9 ± 41.9 vs. 132.0 ± 22.0 beats/min, p = 0.001). Peak VO_2 in each peak HR range is shown in Fig. 1. Peak HR in patients with AF totally shifted to the right side, which is in the higher HR range, compared to those in patients with SR. Reflecting the peak HR, percent-predicted HR was significantly higher in the AF group than in the SR group (98.8 ± 24.7% vs. 86.0 ± 13.2%, p < 0.001). Peak SBP was slightly but not significantly higher in the SR group than in the AF group. As a result, double product, which is an index of myocardial oxygen consumption calculated by peak HR * SBP, did not differ between the AF and SR groups (26,500 ± 8,200 vs. 25,500 ± 6,600 beats/min*mmHg, p = 0.53). On the other hand, peak O_2 pulse was significantly lower in the AF group compared with that in the SR group (9.4 ± 2.4 vs. 10.4 ± 2.6 mL/beats, p = 0.02). As a result, peak VO_2 did not differ between the patients with AF and those with SR (19.4 ± 5.7 vs. 21.6 ± 6.0 mL/kg/min, p = 0.17). Notably, prevalence of chronotropic incompetence calculated using each formula was equal between the groups.

Univariate and multiple regression analysis for peak VO_2

Peak VO_2 was significantly correlated with age (r = −0.36, p < 0.001), BMI (r = −0.19, p = 0.004), resting SBP (r = −0.16, p = 0.01), LAD (r = −0.14, p = 0.04), peak HR (total cases: r = 0.54, p < 0.001; SR group: r = 0.56, p < 0.001; AF group: r = 0.75, p < 0.001), and average E/e' ratio (r = −0.24, p < 0.001). Conversely, resting HR did not correlate with peak VO_2 (r = −0.02, p = 0.82; Table 4). Fig. 2 shows the relationship between peak HR and peak VO_2. It shows that a higher peak HR is needed to produce an extent of VO_2 in patients with AF than in patients with SR. The results of multiple regression analysis for Peak VO_2 are shown in Table 5. BMI < 24 kg/m^2 (β, 1.88; 95% CI, 1.98-21.8; p = 0.002), peak HR (β, 0.091; 95% CI, 1.05-1.14; p < 0.001), and the interaction term constructed by peak HR and presence of permanent AF (β, 0.05; 95% CI, 1.00-1.11; p = 0.04) were selected as determinants for peak VO_2. However, presence of permanent AF was not selected as a determinant for peak VO_2 (β, −0.38; 95% CI, 0.000013-35.6; p = 0.31).

Discussion

The main finding of this study was that the impact of peak HR on exercise tolerance differed between the AF and SR groups. Therefore, presence of permanent AF did not affect exercise tolerance in male patients with preserved LVEF when the ability of the heart to increase its rate was commensurate with the increase in activity. A sufficient increase in HR during exercise is important for preservation of exercise tolerance in patients with permanent AF and preserved LVEF.

Determinants of exercise tolerance

An association between the presence of AF and exer-

Table 3. Results of cardiopulmonary exercise testing.

Rest	Sinus rhythm	Atrial fibrillation	p
Heart rate (beats/min)	64.0 ± 10.7	71.6 ± 16.0	0.001
Systolic BP (mm Hg)	129.8 ± 16.5	127.6 ± 23.0	0.63
Diastolic BP (mm Hg)	71.6 ± 10.3	77.0 ± 11.4	0.01
Peak exercise			
Heart rate (beats/min)	132.0 ± 22.0	148.9 ± 41.9	0.001
Systolic BP (mm Hg)	190.8 ± 28.0	180.6 ± 20.5	0.07
Diastolic BP (mm Hg)	88.1 ± 15.3	88.6 ± 16.3	0.88
Double product (beats/min*mm Hg)	25,500 ± 6,600	26,500 ± 8,200	0.53
Percent predicted heart rate (%)	86.0 ± 13.2	98.8 ± 24.7	< 0.001
Anaerobic threshold (mL/kg/min)	12.3 ± 3.5	11.9 ± 2.8	0.53
Peak VO_2 (mL/kg/min)	21.6 ± 6.0	19.4 ± 5.7	0.17
Percent predicted peak VO_2 (%)	88.4 ± 27.4	80.6 ± 20.5	0.15
VE/VCO_2 slope	36.3 ± 6.7	37.8 ± 5.6	0.27
Peak RER	1.22 ± 0.10	1.27 ± 0.13	0.14
Peak O_2 pulse (mL/beats)	10.4 ± 2.6	9.4 ± 2.4	0.02
Exercise time (sec)	456 ± 105	475 ± 113	0.38
Peak work (watt)	116 ± 33	120 ± 36	0.57
Chronotropic incompetence with Astrand formula (%)	40.6	39.3	0.90
Chronotropic incompetence with Brawner formula (%)	12.2	7.1	0.43

Data represent mean ± SD or percentage.
Peak VO_2, oxygen uptake at peak exercise; BP, blood pressure; VE/VCO_2 slope, slope of minute ventilation to production of CO_2; REP, respiratory exchange ratio.

cise intolerance has been reported in patients with HF regardless of LVEF (Pardaens et al. 1997; Zakeri et al. 2014). A continuous increase in CO is needed for exercise of moderate-to-high intensity because CO decreases as a result of the loss of atrial kick that accompanies the development of AF. However, many patients with permanent AF (including athletes) are asymptomatic and have good exercise tolerance (Flaker et al. 2005; Myrstad et al. 2016). In such cases, the body may compensate for the decrease in CO that accompanies the loss of atrial kick (Peinado et al. 2010). Thus, we hypothesized that a key factor might be a sufficient increase in HR during exercise. The O_2 pulse accompanied by the loss of atrial kick was found to be significantly reduced in the AF group compared with the SR group in the present study, reflecting that within the same HR range, peak VO_2 was higher in the SR group than the AF group. In this context, the results of the present study are consistent with those of previous reports (Ostermaier et al. 1997; Pardaens et al. 1997; Zakeri et al. 2014) stating that exercise tolerance in patients with AF is reduced. On the other hand, peak HR during exercise testing was significantly higher in the AF group than the SR group because the distribution of peak HR was completely shifted to the higher range. Furthermore, the results of this study showed that the impact of peak HR on exercise tolerance differed between the AF and SR groups. This means that a higher

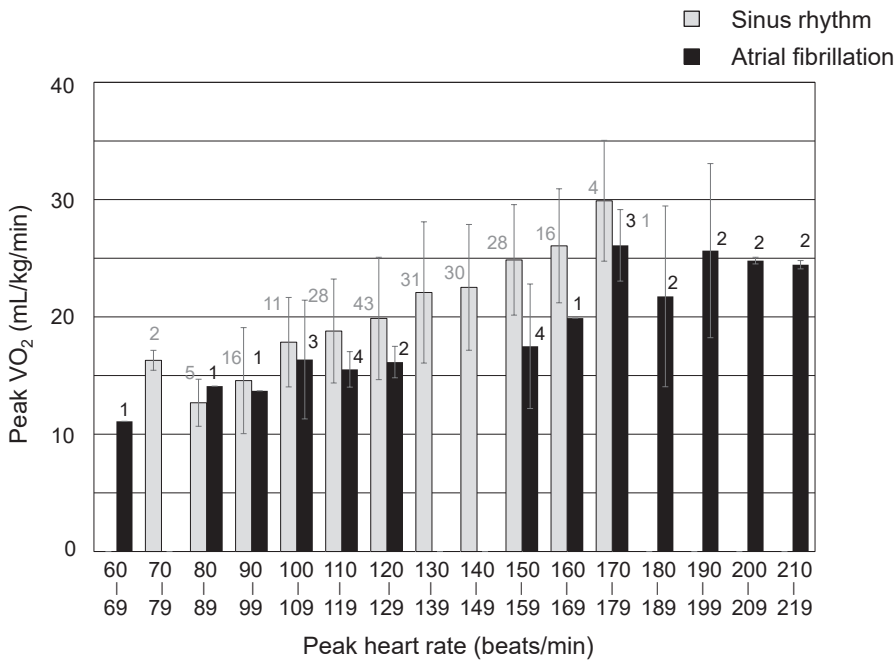

Fig. 1. The oxygen uptake at peak exercise (peak VO_2) in each peak heart rate (HR) range.
Peak VO_2 was higher in the sinus rhythm (SR) group than in the atrial fibrillation (AF) group within the same HR range. However, the distribution of peak HR in the AF group was shifted to the right side, which is in a higher HR range compared to that in the SR group. As a result, mean peak HR during exercise was higher in the AF group than in the SR group, and peak VO_2 did not differ between the groups. The number of patients in each HR range in each group is shown in the graph. Patients with SR are indicated in black text; patients with AF are indicated in gray text.

Table 4. Results of univariate regression analysis for peak VO_2.

	Univariate	
Variable	r	p
Age (years)	−0.36	< 0.001
Height (cm)	0.10	0.10
Weight (kg)	−0.09	0.16
Body mass index (kg/m^2)	−0.19	0.004
Resting systolic BP (mm Hg)	−0.16	0.01
Resting diastolic BP (mm Hg)	0.12	0.051
Resting HR (beats/min)	−0.02	0.82
Peak HR (beats/min) (total cases)	0.54	< 0.001
Peak HR (beats/min) (sinus rhythm)	0.56	< 0.001
Peak HR (beats/min) (atrial fibrillation)	0.75	< 0.001
LVEF (%)	0.05	0.46
LAD (mm)	−0.14	0.04
Average E/e' ratio	−0.24	< 0.001

Abbreviations as in Tables 1, 2, and 3.

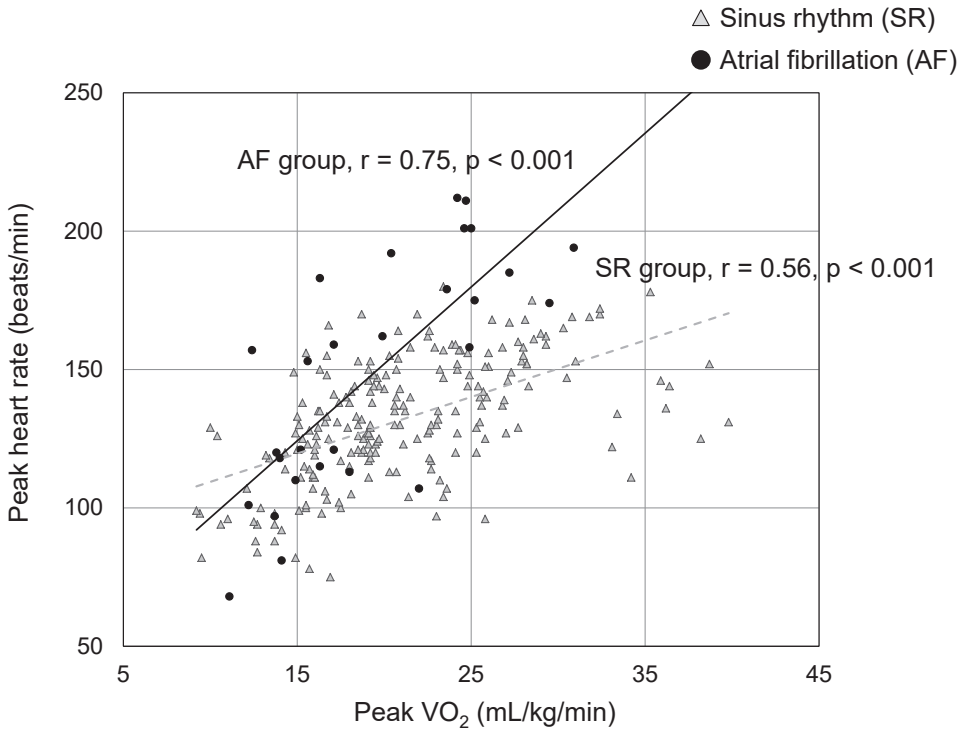

Fig. 2. The relationship between peak VO_2 and peak HR.
The inclination is steeper in the AF group than the SR group. A higher peak HR is needed to produce an extent of VO_2 in patients with AF than patients with SR.

Table 5. Results of multiple regression analysis for Peak VO_2.

Variable	β	*Standard error*	95% CI	Wald χ^2	p
Age < 70 years	1.25	0.65	0.98-12.3	3.70	0.54
Body mass index < 24 (kg/m^2)	1.88	0.61	1.98-21.8	9.46	0.002
Resting systolic BP ≥ 130 mm Hg	−1.15	0.60	0.10-1.03	3.64	0.056
LAD < 40 mm	0.25	0.67	0.34-4.78	0.14	0.71
Average E/e' < 10	0.68	0.65	0.55-7.13	1.09	0.30
Peak heart rate (beats/min)	0.09	0.02	1.05-1.14	16.3	< 0.001
Permanent atrial fibrillation	−3.83	3.77	0.000013-35.6	1.03	0.31
Interaction term	0.05	0.03	1.00-1.11	4.11	0.04

Abbreviations as in Tables 1, 2 and 3. The interaction term was constructed by peak HR and presence of permanent atrial fibrillation.

peak HR is needed to produce an extent of VO_2 in patients with AF. As a result of higher peak HR in patients with AF, no significant difference was observed in peak VO_2 between the groups in our study. Therefore, increased peak HR in the AF group compensates for the reduced exercise tolerance accompanied by the loss of atrial kick.

In this study, the chronotropic incompetence to exercise did not differ between the groups. Our data is consistent with the findings investigated in HF patients with preserved EF, in which the prevalence of chronotropic incompetence was similar in patients with AF and in those with SR (Zakeri et al. 2014). In the present study, the use of β-blockers was not different between the groups. However, peak HR did not differ between the groups, and exercise tolerance was reduced in the patients with AF than in those with SR in their study. On the other hand, an increase in HR during exercise was higher in the AF group than in the SR group, and no significant difference was found in exercise tolerance between the groups in the present study. Kato and colleagues (2016) reported that exercise tolerance in patients with AF was lower than that in patients with SR. In their study, however, the use of HR lower drugs was significantly higher in AF group compared with that in SR group. Ulimoen and colleagues (2014) investigated the influence of HR-lowering drugs on exercise tolerance in patients with permanent AF. Among them, in comparison with calcium channel blockers, exercise tolerance was significantly lower in patients using β-blockers, which decreased the maximum HR during exercise more (Ulimoen et al. 2014). These studies provided similar conclusions that hindering the increase in HR during exercise leads to a decrease in exercise tolerance. Thus, a sufficient increase in HR during exercise could be a compensatory mechanism for preserving exercise tolerance after the loss of normal atrial function in patients with permanent AF and preserved LVEF. Compared with the SR group, a similar use of β-blockers in the AF group may have led to a sufficient increase in HR in this study.

The other most important determinant of exercise tolerance of the cardiac side is the LV diastolic function. The heart with diastolic dysfunction could not deal with elevated atrial pressure during exercise without causing pulmonary congestion (Little et al. 2000). The association between the presence of AF and a reduced exercise tolerance was reported in patients with HF regardless of LVEF (Pardaens et al. 1997; Zakeri et al. 2014). This is because patients with HF have impaired LV diastolic function (LV relaxation) to a certain extent, but the present study patients had no HF. In contrast, diastolic dysfunction reportedly already exists in patients with AF (Tsang et al. 2002). In the present study, slight LV diastolic dysfunction in the patients with AF had been observed, but it was not significant. Furthermore, it has been reported that the elevated LV filling pressure expressed as E/e' ratio is closely related to exercise intolerance rather than impaired LV relaxation (Skaluba and Litwin 2004). In the present study, there was no significant difference in E/e' ratio between the groups. Moreover, peak DBP, which would affect LV filling pressure, also did not differ between the groups. Although the evaluation of LV filling pressure using echocardiography was performed only at rest, increased LV filling pressure accompanied by increase in HR and DBP during exercise was supposed to remain within the range where the heart could compensate without causing pulmonary congestion in both groups. These are other important reasons that similar exercise tolerance was observed between the groups.

Clinical implication

A previous study reported that strict control of resting HR is not necessary for management of permanent AF (Van Gelder et al. 2010). In this present study, the frequency of use and the dose of β-blockers did not differ between the groups, suggesting that HR management in the AF group was practical in the present study. Drugs used to lower resting HR may also prevent an increase in HR during exercise. Thus, this practical HR management at rest in this study, which has room for an HR increase during exercise, indicates preservation of exercise tolerance in patients with permanent AF. We believe that the present study provides new perspective to reconsider the HR control during exercise in patients with permanent AF and preserved LVEF.

Study limitations

This study had several limitations. First, this was a cross-sectional study conducted at a single institution that included a limited number of patients. Furthermore, we only analyzed male patients in this study. This may have led to selection bias. A prospective study with a larger number of patients should be conducted to confirm the present findings. Second, this study showed that a sufficient increase in HR during exercise is an important factor to preserve exercise tolerance in patients with AF. However, an appropriate HR during exercise in the patients with AF was not specifically shown in this study. Even so it is increased HR during exercise in the patients with AF shown in this study is suggested to be sufficient and appropriate because of no significant differences in peak VO_2 in the AF group compared with that in the SR group. Third, increasing peripheral arteriovenous oxygen difference was not investigated in this study. Since no differences were found in terms of patient backgrounds between the groups, we assumed that there is no difference in the peripheral arteriovenous oxygen difference. Hence, we need to clarify that this was an investigation on CO in patients with permanent AF. The final limitations were related to AF itself. The HR variability in cycle length affects various results. The E/e' ratio were obtained separately specifically during different beats. Thus, the assessments of E/e' ratio were not ideal. The permanent AF focused on this study is technically long-standing persistent AF. However, the mean duration of AF was 60 months, according to the medical record, and it clinically could be regarded as permanent AF. Being

asymptomatic as per self-report is questionable. However, similar exercise tolerance between the groups could indicate that AF patients were asymptomatic. The contribution of AF to exercise intolerance greatly differs among individuals. Thus, our results cannot be generalized to all patients with permanent AF and preserved LVEF. However, we believe our findings are useful for understanding the pathology of asymptomatic patients with permanent AF and preserved exercise tolerance.

Conclusions

The impact of peak HR on exercise tolerance differed between the AF and SR groups. Although presence of permanent AF does not affect exercise tolerance in male patients with preserved LVEF, sufficient increase in HR during exercise was more important in the AF group than the SR group to preserve exercise tolerance among male patients with AF and preserved LVEF.

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Conflicts of Interest

The authors declare no conflict of interest.

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