ORIGINAL ARTICLE

Korean J Intern Med 2023;38:872-878
https://doi.org/10.3904/kjim.2023.075

Exercise capacity and risk of incident atrial fibrillation in healthy adults

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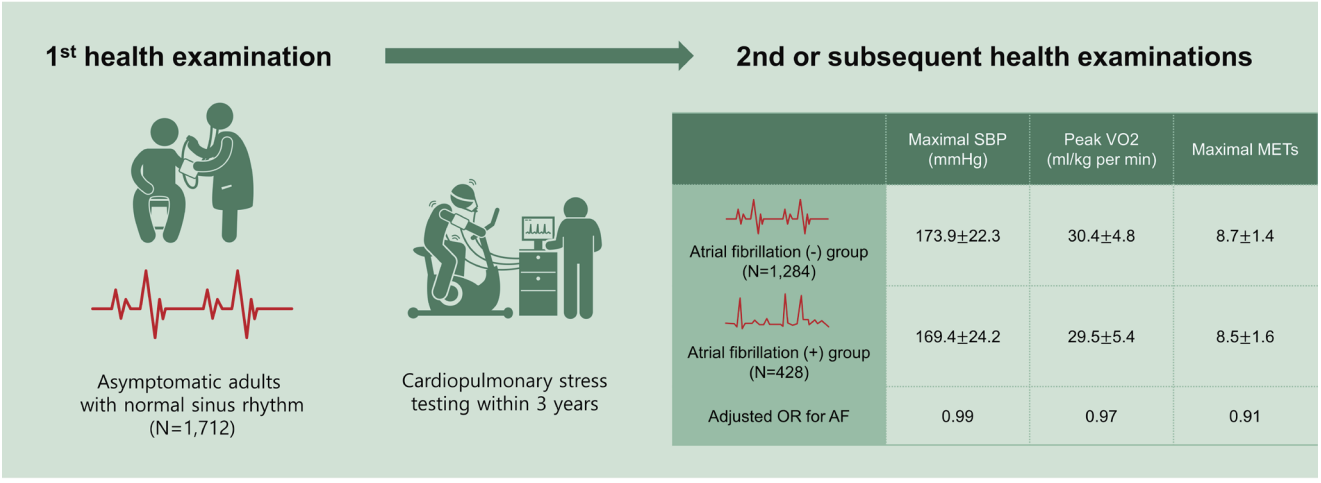

Conclusion We demonstrated that poorer exercise capacity was associated with the development of AF in a healthy population. A prospective, systematic trial is necessary to confirm that appropriate exercise training will be beneficial in preventing the development of AF in such patients.

Background/Aims: Atrial fibrillation (AF) is a common arrhythmia and is associated with cardiovascular morbidity and mortality. It is important to identify and control the modifiable risk factors of AF. We aimed to examine the association of exercise capacity with the risk of incident AF within 3 years in healthy subjects.

Methods: We evaluated asymptomatic adults who had undergone more than two consecutive health checkups. We included subjects who exhibited normal sinus rhythm on the first health examination and who developed AF on the second or subsequent health examinations. Subjects who underwent cardiopulmonary exercise testing within 3 years before the diagnosis of AF were examined.

Results: The study population in the analyses included 428 cases (mean age 58.4 ± 7.6 yr, male 95.6%). There were significant differences in maximal systolic blood pressure (SBP; case 169.4 ± 24.2 vs. control 173.9 ± 22.3 mmHg), peak VO_2 (29.5

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

± 5.4 vs. 30.4 ± 4.8 mL/kg per minute), and maximal metabolic equivalents (METs; 8.5 ± 1.6 vs. 8.7 ± 1.4) between the two groups. In the multivariable logistic models, adjusted odds ratios were 0.99 for maximal SBP (95% confidence interval [CI] 0.98–0.99), 0.97 for peak VO_2 (95% CI 0.95–0.99), and 0.91 for maximal METs (95% CI 0.83–0.98).

Conclusions: We demonstrated that poorer exercise capacity was associated with the development of AF in a healthy population. A prospective, systematic trial is necessary to confirm that appropriate exercise training will be beneficial in preventing the development of AF in such patients.

Keywords: Atrial fibrillation; Cardiopulmonary exercise testing; Exercise capacity

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia with increasing incidence [1]. AF is associated with considerable morbidity and mortality including heart failure (HF) and stroke [2]. Therefore, screening for AF is important, and various screening tools have been suggested [3]. Nonetheless, it remains under-diagnosed due to asymptomatic patients. In addition, systematic screening of AF exhibited low-cost effectiveness [4]. Ultimately, it is important to identify patients who are at high risk of AF.

Obesity, high blood pressure, and alcohol consumption are associated with incident AF [5-7]. These conditions are modifiable risk factors resulting in adverse atrial remodeling and potential HF if left uncontrolled. Physical activity is associated with the development of AF, and AF patients exhibit a decrease in exercise capacity [8]. A decrease in cardiorespiratory fitness is associated with an increased risk of AF [9]. Cardiopulmonary exercise testing (CPX) is a non-invasive indicator for assessing the cardiovascular and pulmonary components of exercise responses. The impact of exercise capacity according to CPX on the risk of AF in healthy individuals remains unknown. Therefore, we aimed to examine the association of exercise capacity with the risk of incident AF in healthy subjects within a 3-year study period.

METHODS

This was a retrospective study that utilized a health promotion center database. The population who visited the healthcare center for comprehensive health evaluations between January 2008 and December 2020 were enrolled. We compared patients who exhibited new-onset AF to the AF-free control population. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center in the Republic of Korea (IRB number: 2021-04-022-001). IRB approved a request to waive the need for informed consent. The research presents no more than minimal risk of harm to the subjects and involves no procedures for which written consent is required.

Study population

We evaluated asymptomatic adults older than 18 years of age who had undergone more than 2 consecutive health checkups. We included subjects who exhibited normal sinus rhythm on the first health examination and who developed AF by electrocardiogram (ECG) on the second or subsequent health examinations. The timing of AF diagnosis was defined as the index time. We excluded subjects who exhibited persistent AF or pacing rhythm, and who were diagnosed with AF at the first health examination or identified with AF in our electronic health records system according to the diagnostic code before the index time. Subjects who underwent CPX within 3 years before the diagnosis of AF were examined. An AF-free control population, matched for age and sex, was randomly selected from the same database as the case population. We examined covariates including basic demographic data, comorbidities, and results of the health checkups (Fig. 1).

Cardiopulmonary exercise testing

Exercise testing was performed in an exercise laboratory supervised by an exercise physiologist. The subjects underwent maximal, symptom-limited metabolic treadmill (Quinton Q4500; Cardiac Science Corp., Bothell, WA, USA) exercise testing using the Bruce or modified Bruce protocol according to age and exercise capacity. Measurements of ventilator gases during exercise were performed using Trueone 2400 (Parvo Medics, Sandy, UT, USA). Subjects underwent

12-lead ECG, and heart rate and systolic and diastolic blood pressures (SBP, DBP) were measured at baseline, during each stage, and in the recovery phase. In addition, oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) values were obtained. Finally, the following calculations were performed [10]:

1. Peak oxygen consumption (pVO_2) was defined as maximum oxygen consumption calculated using established equations based on age and sex. Aerobic capacity was defined as peak VO_2.
2. Metabolic equivalents (METs) were used to represent exercise capacity.
3. Peak rate pressure product (RPP) represents myocardial oxygen consumption which was calculated by multiplying SBP with heart rate.

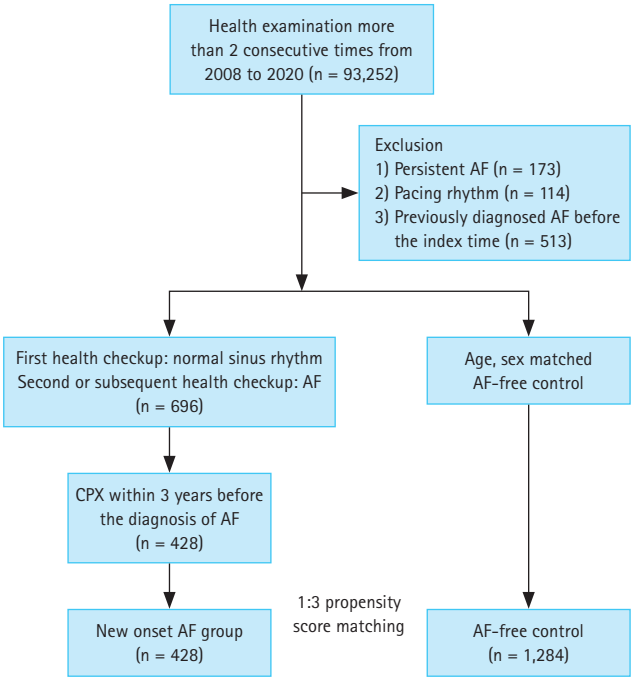

Figure 1. Flow chart of study inclusion. AF, atrial fibrillation; CPX, cardiopulmonary exercise testing.

Statistical analyses

The baseline characteristics are presented as the mean ± standard deviation for continuous variables and as frequency with percentage for categorical variables. Continuous variables were compared using the unpaired t-test, while categorical variables were compared using either the χ^2 test or Fisher's exact test as appropriate. The AF and control groups were matched at a 1:3 ratio according to age and sex. We performed logistic regression and calculated univariate odds ratios (ORs) for the risk factors. In addition, the risk of new-onset AF was assessed using a multivariable logistic regression model including hypertension, diabetes, and BMI and is presented as adjusted OR and 95% confidence interval (CI). p values < 0.05 were considered statistically significant. All statistical analysis was performed using SAS software, Version 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

In total, 93,252 patients who had undergone health examination more than two consecutive times from 2008 to 2020 were screened; 800 patients were excluded according to the exclusion criteria. Overall, 696 patients developed

Table 1. Baseline characteristics

Variable	Total (n = 1,712)	AF (n = 428)	No AF (n = 1,284)	*p* value
Age (yr)	58.2 ± 7.4	58.4 ± 7.6	58.1 ± 7.4	0.643
Sex, male	1,644 (96.0)	409 (95.6)	1,235 (96.2)	0.668
Body weight (kg)	71.0 ± 9.5	73.7 ± 9.3	70.1 ± 9.3	< 0.001
BMI (kg/m^2)	24.6 ± 2.7	25.2 ± 2.7	24.4 ± 2.7	< 0.001
Medical history				
Hypertension	551 (32.2)	163 (38.1)	388 (30.2)	0.002
Stroke	35 (2.0)	11 (2.6)	24 (1.9)	0.467
Diabetes	229 (13.4)	53 (12.4)	176 (13.7)	0.599
Thyroid disease	68 (4.0)	11 (2.6)	57 (4.4)	0.189

Values are presented as mean ± standard deviation or number (%).
AF, atrial fibrillation; BMI, body mass index.

https://doi.org/10.3904/kjim.2023.075

new-onset AF during the second or subsequent health checkups. Among these, 428 underwent CPX within 3 years before the diagnosis of AF. Finally, the study population in the analyses included 428 cases (mean age 58.4 ± 7.6 yr, male 95.6%) with 1,284 controls (mean age 58.1 ± 7.4 yr, male 96.2%). Body mass index (BMI) was higher in the case group (25.2 ± 2.7 vs. 24.4 ± 2.7 kg/m^2) as was hypertension (40.6% vs. 31.8%) compared to the control. The baseline

Table 2. Cardiopulmonary exercise testing parameters and logistic regression analysis for new-onset AF with age- and sex-matched controls

Variable	Parameter		Crude OR (95% CI)	Adjusted OR[a)] (95% CI)
	AF (n = 428)	No AF (n = 1,284)		
Baseline HR (BPM)	63.1 ± 11.8	63.6 ± 9.6	0.99 (0.98–1.01)	0.99 (0.98–1.00)
Maximal HR (BPM)	148.4 ± 18.5	147.6 ± 13.4	1.00 (1.00–1.01)	1.01 (1.00–1.01)
Delta HR (BPM)	85.3 ± 18.1	84.0 ± 15.1	1.01 (1.00–1.01)	1.01 (1.00–1.02)
Baseline SBP (mmHg)	124.3 ± 14.2	123.9 ± 14.4	1.00 (0.99–1.01)	0.99 (0.99–1.00)
Maximal SBP (mmHg)	169.4 ± 24.2	173.9 ± 22.3	0.99 (0.99–1.00)	0.99 (0.98–0.99)
Delta SBP (mmHg)	45.1 ± 20.4	50.0 ± 17.8	0.99 (0.98–0.99)	0.99 (0.98–0.99)
Baseline DBP (mmHg)	83.4 ± 9.5	82.9 ± 8.7	1.01 (0.99–1.02)	1.00 (0.98–1.01)
Maximal DBP (mmHg)	78.2 ± 10.5	77.7 ± 9.8	1.01 (0.99–1.02)	1.00 (0.99–1.01)
Delta DBP (mmHg)	-5.2 ± 8.2	-5.2 ± 7.8	1.00 (0.99–1.01)	1.00 (0.99–1.01)
RPP	233.3 ± 47.4	243.3 ± 43.6	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Peak VO_2 (mL/kg per min)	29.5 ± 5.4	30.4 ± 4.8	0.96 (0.94–0.99)	0.97 (0.95–0.99)
METs	8.5 ± 1.6	8.7 ± 1.4	0.89 (0.82–0.96)	0.91 (0.83–0.98)

AF, atrial fibrillation; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; METs, metabolic equivalents; OR, odds ratio; RPP, peak rate pressure product; SBP, systolic blood pressure.
[a)]Body mass index, hypertension, and diabetes were included in the multivariate model.

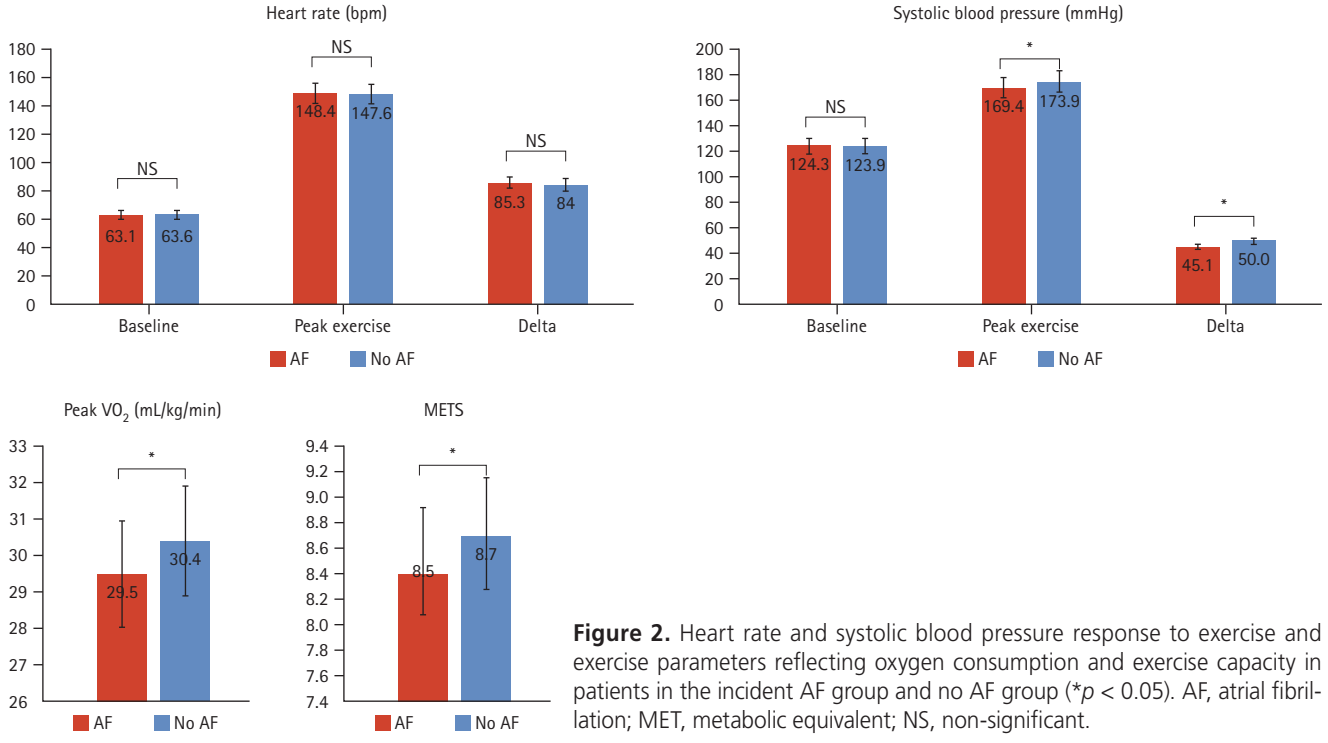

Figure 2. Heart rate and systolic blood pressure response to exercise and exercise parameters reflecting oxygen consumption and exercise capacity in patients in the incident AF group and no AF group (*$p < 0.05$). AF, atrial fibrillation; MET, metabolic equivalent; NS, non-significant.

characteristics of the patients are summarized in Table 1. In logistic regression analysis, the OR for body weight was 1.04 (95% CI 1.03–1.05) and 1.10 (95% CI 1.06–1.15) for BMI.

Cardiopulmonary exercise testing parameters

Exercise parameters are summarized in Table 2. Most of the parameters were within the normal range. There were significant differences in maximal SBP (case 169.4 ± 24.2 vs. control 173.9 ± 22.3 mmHg), peak VO_2 (29.5 ± 5.4 vs. 30.4 ± 4.8 mL/kg per minute), and maximal METs (8.5 ± 1.6 vs. 8.7 ± 1.4) between the two groups (Fig. 2). In the univariate analysis, the crude ORs were 0.99 for maximal SBP (95% CI 0.98–1.00), 0.96 for peak VO_2 (95% CI 0.94–0.99), and 0.89 for maximal METs (95% CI 0.82–0.96). In the multivariable logistic model, adjusted OR was 0.99 for maximal SBP (95% CI 0.98–0.99), 0.97 for peak VO_2 (95% CI 0.95–0.99), and 0.91 for maximal METs (95% CI 0.83–0.98).

DISCUSSION

We examined the prognostic value of exercise parameters associated with incident AF in health checkup subjects. In our analysis, we demonstrated that poorer exercise capacity was associated with the development of AF. In the adjusted model, every 1 MET increase was associated with a 9% risk reduction of incident AF, and a 1 mL/kg/min increase in peak VO_2 was associated with a 3% risk reduction of incident AF.

Cardiopulmonary exercise testing

CPX is a combination of standard exercise testing and the measurement of ventilator gas exchange amounts for assessing exercise capacity in patients suspected of having cardiovascular or pulmonary disease [11]. Several reports have indicated that AF is associated with a decrease in exercise capacity. Several studies have also shown that peak VO_2 is decreased in patients with AF, especially in HF [12,13]. Most studies analyzed patients with cardiovascular disease including AF or HF. In our study, we evaluated healthy subjects who had never been diagnosed with AF, and the parameters of exercise testing were within normal limits in those subjects and the AF groups. We suggest that a subtle decrease in exercise capacity is prognostic of the future development of AF in a healthy population. In heart rate and DBP response during exercise, no significant differences in baseline, maximal, and delta heart rates were observed between the two groups. Subjects who developed AF within 3 years exhibited similar baseline SBP but 5 mmHg lower maximal and delta SBP. Hemodynamic responses to exercise depend on cardiac output and peripheral resistance. Therefore, SBP typically increases with exercise, while DBP remains the same or decreases [10]. In other words, an inadequate increase in SBP during exercise reflects impaired contractile reserve and circulatory impairment. In a previous study, peak SBP was 10 mmHg lower in patients with AF compared to those without AF [14]. These results indicate that exercise performance progressively decreases in patients with subsequent AF development. We excluded CPX data more than 3 years prior to the occurrence of AF, assuming that the change in exercise capacity or atriopathy would be reflected within 3 years. Subjects who were included in our study underwent CPX for health checkups and not for suspicion of other cardiac diseases or complaints. Therefore, our study may represent the prognostic effectiveness of CPX in a healthy population.

Risk factors of AF

Obesity, especially with lean body mass, and alcohol consumption are known risk factors for AF [5,15]. Recently, body weight fluctuation, dynamic changes in hemoglobin levels, and blood pressure variability have been suggested to be associated with increased risk of incident AF [16-18]. Lifestyle modifications and a multifaceted educational intervention are needed to prevent or optimize treatment of AF. Higher physical activity is also associated with lower AF incidence [19]. However, competitive athletes or endurance-type activities including marathon runners exhibit increased risk for developing AF [20]. Therefore, regular exercise at the appropriate intensity may have a protective effect against AF and can be a modifiable risk factor [21]. We demonstrated the relationship between exercise capacity and incident AF within 3 years in a healthy population. This suggested the possibility that exercise training may protect against the development of AF. Further systematic prospective studies are needed to confirm this finding.

Limitations

This is a retrospective, single-center study from a health checkup database. We excluded subjects who were previously diagnosed with AF according to our electronic health records system. Nevertheless, it is possible that some subclinical AF patients might have been included in both

https://doi.org/10.3904/kjim.2023.075

groups. Selection bias may exist because not all subjects underwent all of the exams. In addition, some variables were not included in the analysis. For example, we could not analyze echocardiography or medications due to the absence of data. We attempted to adjust for other risk factors of AF but could not identify and adjust for all confounding variables.

Conclusion

This study demonstrated that a mild decrease in exercise capacity or other exercise parameters is associated with incident AF in a healthy population. A prospective, systematic trial is necessary to confirm that appropriate exercise training will be beneficial in preventing AF.

KEY MESSAGE

1. Poor exercise capacity was associated with the development of AF in a healthy population.

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Received : February 14, 2023
Revised : May 22, 2023
Accepted : August 3, 2023

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Ju Youn Kim: conceptualization, data curation, formal analysis, methodology, writing - original draft, writing - review & editing; Soo Jin Cho: data curation, visualization; Juwon Kim: visualization; Tae-Wan Chung: visualization; Seung-Jung Park: visualization; Kyoung-Min Park: visualization; June Soo Kim: visualization; Young Keun On: conceptualization, methodology, writing - review & editing, visualization, project administration

Conflicts of interest
The authors disclose no conflicts.

Funding
None

https://doi.org/10.3904/kjim.2023.075