Full research paper

European Journal of Preventive Cardiology

ESC European Society of Cardiology

European Journal of Preventive Cardiology
0(00) 1–10

DOI: 10.1177/2047487319859974
journals.sagepub.com/home/cpr
SAGE

Exercise-based cardiac rehabilitation for patients with catheter ablation for persistent atrial fibrillation: A randomized controlled clinical trial

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Abstract

Aims: The efficacy and safety of cardiac rehabilitation for patients with persistent atrial fibrillation who restored sinus rhythm after catheter ablation remains unclear. The aim of the present study was to evaluate the effects of cardiac rehabilitation on exercise capacity, inflammatory status, cardiac function, and safety in patients with persistent atrial fibrillation who had catheter ablation.

Methods: In this randomized controlled study, 61 patients treated with catheter ablation for persistent atrial fibrillation (male, 80%; mean age, 66 ± 9 years) were analyzed. Thirty patients underwent cardiac rehabilitation (rehabilitation group), whereas the remaining 31 patients received usual care (usual care group). The rehabilitation group underwent endurance and resistance training with moderate intensity, at least three times per week for six months. Six-minute walk distance, muscle strength, serum high-sensitivity C-reactive protein, plasma pentraxin 3, left ventricular ejection fraction and atrial fibrillation recurrence were assessed at baseline and at six-month follow-up.

Results: In the rehabilitation group, significant increases in the six-minute walk distance, handgrip strength, leg strength and left ventricular ejection fraction and significant decreases in high-sensitivity C-reactive protein and plasma pentraxin 3 concentrations were observed at six-month follow-up compared with baseline (all $p < 0.05$). No significant changes were observed in the usual care group. During the six-month follow-up period, the number of patients with atrial fibrillation recurrence was six (21.4%) in the rehabilitation group and eight (25.8%) in the usual care group (risk ratio, 0.83; 95% confidence interval, 0.33 to 2.10).

Conclusions: Cardiac rehabilitation improved exercise capacity without increasing the risk for atrial fibrillation recurrence. It may also be effective in managing systemic inflammatory status and systolic left ventricular function in patients with persistent atrial fibrillation treated with catheter ablation.

Keywords

Atrial fibrillation, catheter ablation, cardiac rehabilitation, cardiac function, physical function, inflammatory status

Received 8 March 2019; accepted 6 July 2019

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Introduction

Atrial fibrillation is widely known as the most common cardiac arrhythmia and is associated with morbidity, mortality and healthcare costs.[1] Due to the aging population and increased prevalence of atrial fibrillation among older people, the number of atrial fibrillation patients is expected to increase significantly in the near future. In atrial fibrillation patients, reduced atrial contraction and irregular pulse lead to decreased cardiac output, resulting in decreased physical capacity and quality of life (QoL).[2] Catheter ablation for atrial fibrillation is an invasive therapy to eliminate symptoms and is expected to reduce stroke incidence and death.[3] Approximately one-third of atrial fibrillation ablation procedures are currently performed in patients with persistent atrial fibrillation.[4] Maintenance of sinus rhythm after successful catheter ablation improves exercise capacity and QoL even in patients that were asymptomatic and had unrecognized impairment in their physical performance and QoL.[5]

Recently, cardiac rehabilitation based on exercise training has become part of the standard care for patients with heart disease. The benefits of long-term cardiac rehabilitation are well described in patients with myocardial infarction, coronary artery bypass grafts and heart failure.[6] A recent study reported that an endurance training reduced atrial fibrillation burden among patients after catheter ablation for paroxysmal atrial fibrillation.[7] Long-term endurance training improves exercise capacity and left ventricular ejection fraction (LVEF) and attenuates systemic inflammation in patients with heart failure and/or atrial fibrillation.[6] On the other hand, studies on cardiac rehabilitation among patients with persistent atrial fibrillation are limited. Patients with persistent atrial fibrillation may be vulnerable in exercise training because of the exposure to unstable hemodynamics. Studies are needed to investigate whether exercise training can be safely implemented and effectively increase exercise capacity among patients with persistent atrial fibrillation who restored sinus rhythm after catheter ablation.

We conducted a randomized controlled clinical trial (RCT) to evaluate the effects of adding cardiac rehabilitation to usual care versus usual care alone on exercise capacity, cardiac function, inflammatory status and safety in persistent atrial fibrillation patients treated with catheter ablation.

Methods

This study was a single-center, six-month RCT comparing an exercise-based cardiac rehabilitation program with a control group. The study took place at the department of Rehabilitation and Cardiovascular Medicine at Shizuoka Medical Center in Shizuoka. This study was performed with approval from the Ethics Committee of Shizuoka Medical Center (26-17). All patients were informed about the study and provided written consent. The CONSORT guidelines were followed during the course of the research.[8]

Participants

Consecutive patients who were diagnosed with atrial fibrillation from September 2014 to December 2016 by clinicians according to the criteria of the European Society of Cardiology and treated with first or second catheter ablation were screened for inclusion. Patients with age $\geq$ 40 years, persistent atrial fibrillation and no atrial fibrillation recurrence during blanking period after catheter ablation were eligible to participate. Blanking period of only one month was applied after catheter ablation in this study because early participation in cardiac rehabilitation was considered more meaningful for persistent atrial fibrillation patients, who may have lower exercise capacity. Persistent atrial fibrillation was defined as recurrent atrial fibrillation that was not self-terminating, with an episode lasting over seven days or requiring termination by either electrical or pharmacological cardioversion. Exclusion criteria were patients who were unable to understand the study due to severe cognitive impairment, those who engaged in intense physical exercise or sports several times a week prior to catheter ablation, those who had reduced left ventricular systolic function (LVEF $<$ 40%) and those who suffered an acute exacerbation of heart failure, cancer or comorbid conditions that may affect or impede the performance of the evaluation or intervention within the past three months.

Study protocol

Patients who did not show atrial fibrillation recurrence during the blanking period after catheter ablation were randomized 1:1 to exercise-based cardiac rehabilitation plus usual care (rehabilitation group) versus usual care (control group) by independent physician using a computer-generated randomization table. All patients received baseline assessments of electrocardiography (ECG), echocardiography, blood parameters, physical function and exercise capacity. Patients in the rehabilitation group then received the exercise-based rehabilitation program in addition to usual care for six months, whereas patients in the control group received only usual care for six months. After six months, patients completed the same assessments as those performed at baseline.

Exercise-based cardiac rehabilitation program and usual care

Patients in the rehabilitation group participated in a supervised exercise program one to two times weekly at the hospital and were also instructed to do an unsupervised moderate intensity walking exercise for 30 min 2–3 times per week during the study period. The supervised exercise program was a combination of endurance and resistance training, including ergometer cycling or treadmill walking, and machine-based strength training. Each session was 60 min, including 5-min warm-up and 5-min cool-down. For endurance training, to ensure reproducibility and maximal benefit without exposing subjects to undue risk, the prescribed exercise had intensity and time set at moderate (anaerobic threshold measured by cardiopulmonary exercise testing) and 30 min, respectively.[9] For resistance training, patients used machines to perform 2–3 sets of a series of two upper-extremity, one trunk and five lower-extremity exercises (chest press, rowing, abdominal, leg extension, leg curl, hip abduction, hip adduction and leg press) with intensity of 40% to 60% of one repetition maximum.[9] Patients in the control group were advised to continue their usual lifestyle for six months. Patients in both groups followed usual care for atrial fibrillation patients treated with catheter ablation, which included a limited visit to a cardiologist at the hospital for one-, three- and six-month follow-up.

Study outcomes

The primary outcome was predefined as the change in exercise capacity. Secondary outcomes were cardiac function, inflammatory status and safety.

Exercise capacity and physical function. To evaluate exercise capacity, six-minute walk distance (6MWD) was measured in accordance with guidelines established by the American Thoracic Society.[10] Patients were told to walk as fast and for as long as possible, while stopping and resting or reducing their walking speed if they felt palpitations, fatigue or shortness of breath.

Symptom-limited cardiopulmonary exercise testing via a ramp protocol using cycle ergometer (BE-255, Fukuda Denshi Co., Tokyo, Japan) was performed for the rehabilitation group to assess exercise capacity and prescribe an endurance training program. Peak oxygen uptake (peak $\dot{V}O_2$), peak load, peak respiratory exchange ratio and anaerobic threshold were measured with an aero monitor (AE-310S, Minato Ikagaku Co., Tokyo, Japan).

Handgrip strength was measured twice for each hand, using a standard adjustable-handle JAMAR dynamometer (Bissell Healthcare Co., Grand Rapids, Michigan, USA). The average maximal value measured was used as a parameter of handgrip strength (kg).

As a parameter of leg strength, maximal isometric knee extensor strength was assessed twice for each leg using a hand-held dynamometer (μTas F-1, Anima, Tokyo, Japan) with patients sitting on a chair with their hips and knees flexed at a 90° angle.[11] Leg strength was calculated as the average value of the maximal strength in both legs divided by body weight (kg) and was expressed as a percentage of body weight.

Blood test and inflammatory status. Serum low-density and high-density lipoprotein cholesterol concentrations, estimated glomerular filtration rate, plasma brain natriuretic peptide level and hemoglobin A1c were measured by a blinded medical technologist. Serum high-sensitivity C-reactive protein (hs-CRP), plasma pentraxin 3 (PTX3) and Interleukin-6 (IL-6) were measured as parameters of inflammation.[12]

Cardiac structure and function. Echocardiography was performed during supine rest in the left lateral position using a Vivid Five scanner with a 2.5-MHz phased array probe (GE Vingmed Ultrasound, Horten, Norway) by a blinded medical technologist. Left ventricular end-systolic diameter (LVDs), left ventricular end-diastolic diameter, LVEF, left atrial diameter (LAD), interventricular septum were measured by the modified Simpson biplane method. Mitral annulus velocity during diastole (e′) were measured by pulsed tissue Doppler images in the septal, lateral, anterior and posterior points and averaged. Mitral flow velocity (E) was measured by averaging three cycles.

Safety. All patients were scheduled to visit the outpatient clinic for one-, three- and six-month follow-up. Atrial fibrillation recurrence was assessed by a cardiologist using a 12-lead ECG. Additional ECG recordings were obtained when patients' symptoms such as palpitations, discomfort, dizziness or shortness of breath were suggestive of atrial fibrillation. In addition, 24-h ECG monitoring was performed at baseline and at six months to detect paroxysmal atrial fibrillation and other arrhythmia. Atrial fibrillation recurrence was defined as documented atrial fibrillation lasting $\geq$30 s on ECG during the study period.[13,14] In addition, we assessed cardiovascular adverse events, including myocardial infarction, unstable angina, stroke and serious adverse arrhythmia, during the intervention period.

Sample size calculation for the primary outcome

Sample size calculation was based on a significance level of 0.05, power of 0.80, and previous data on the primary outcome, change in 6MWD.[14] The sample size was determined to be 31 patients in each group. The sample size was calculated using the statistical software EZR, which is freely available online (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html).

Statistical analysis

Student's unpaired *t* test or Fisher's exact test was used to compare differences in patient characteristics between the two groups. A two-way analysis of variance for repeated measures was used to compare parameters for exercise capacity, inflammatory status and cardiac function measured at baseline and follow-up of the study. A Tukey's post-hoc analysis was conducted if an *F* ratio was significant. Dichotomous variables were analyzed using risk ratio (RR) with 95% confidence interval (CI). Crude survival curves were constructed using the Kaplan–Meier method to describe the incidence of atrial fibrillation recurrences over time and log-rank tests were applied to evaluate differences between groups. All continuous data were expressed as mean ± standard deviation (SD), and a p value < 0.05 was considered statistically significant. All analyses were performed using SPSS 19.0 for Windows (SPSS Statistics, IBM, Tokyo, Japan).

Results

A total of 315 patients underwent catheter ablation for atrial fibrillation. Among them, a total of 68 were deemed eligible and accepted to participate in this trial. The 68 patients were randomized into two groups and then assessed for baseline status. Compliance to the cardiac rehabilitation program was excellent (93.3%) and only two patients in the rehabilitation group discontinued the study. One patient suffered a thoracic compression fracture not related to exercise training, and the other developed hypothyroidism during the intervention period. We excluded these two patients from this study (Figure 1). There were no other cardiovascular adverse events in either group.

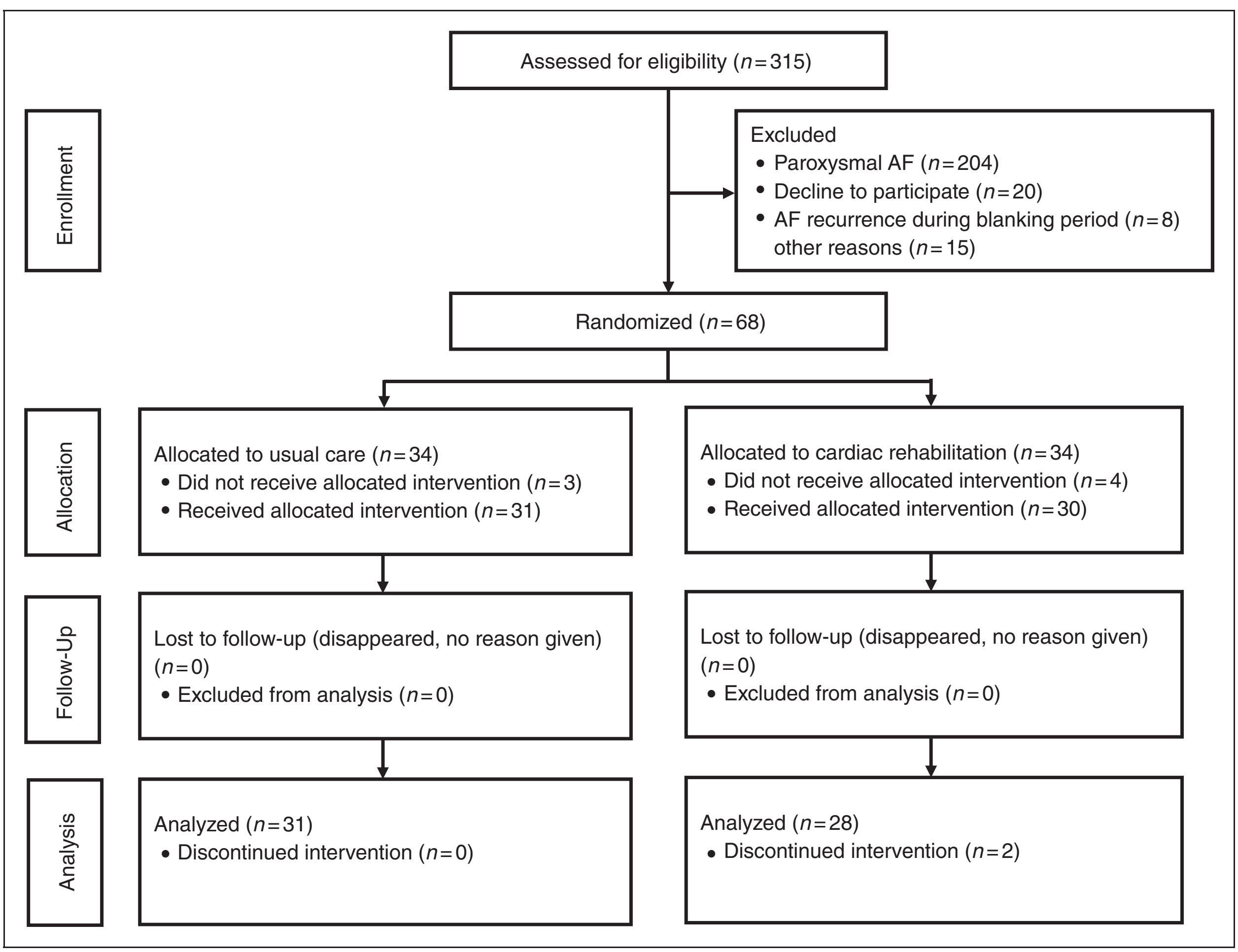

Figure 1. The CONSORT flow diagram.
AF: atrial fibrillation.

Table 1. Patient baseline characteristics.

	Usual care $n=31$	Cardiac rehabilitation $n=28$
Male sex, *n* (%)	28 (90)	20 (71)
Age, years	65 ± 8	67 ± 10
Body mass index, kg/m^2	23.9 ± 3.2	23.8 ± 2.6
Smoking, *n* (%)		
Non-smoker/former smoker/current smoker	13 (42)/ 13 (42)/ 5 (16)	13 (46)/ 13 (46)/ 2 (8)
Type of AF, *n* (%)		
Persistent	31 (100)	28 (100)
Long-standing persistent AF (AF lasting ≥ 1 year)	6 (19)	5 (18)
Comorbidities, *n* (%)		
Hypertension	18 (58)	20 (71)
Diabetes mellitus	7 (23)	5 (18)
Dyslipidemia	11 (35)	11 (39)
Chronic kidney disease	5 (16)	6 (21)
Angina	3 (10)	3 (11)
Chronic heart disease	6 (19)	6 (21)
Chronic obstructive pulmonary disease	2 (6)	2 (7)
Cerebrovascular accident	2 (6)	1 (4)
Treatment, *n* (%)		
Sodium channel blocker	1 (3)	0 (0)
Beta-blocker	8 (26)	9 (32)
Amiodarone	1 (3)	1 (4)
Calcium channel blocker	8 (26)	5 (18)
Digoxin	1 (3)	0 (0)
Warfarin	4 (13)	2 (7)
DOAC	27 (87)	26 (93)
Diuretics	2 (6)	6 (21)
ARB or ACEI	8 (26)	11 (39)
Statin	7 (23)	6 (21)
CHA_2DS_2VASc score, *n* (%)		
0	7 (23)	4 (14)
1	7 (23)	7 (25)
≥2	17 (55)	16 (57)
Number of ablation procedure, *n* (%)		
First	27 (87)	26 (93)
Second	4 (13)	2 (7)

AF: atrial fibrillation; DOAC: direct oral anticoagulant; ARB: angiotensin 2 receptor blocker; ACEI: angiotensin-converting-enzyme inhibitor.

Patient baseline characteristics are shown in Table 1. There were no significant differences in patient baseline characteristics between the two groups.

Changes in exercise capacity and physical function are shown in Table 2 and Figure 2(a). Significant interactions were detected in the 6MWD, handgrip strength and leg strength ($F=5.07$, $p<0.05$; $F=16.24$, $p<0.01$; $F=81.03$, $p<0.01$, respectively). The 6MWD, handgrip strength and leg strength increased significantly after the study period in the rehabilitation group compared with baseline ($p<0.01$, $p<0.05$ and $p<0.01$, respectively). The peak $\dot{V}O_2$, peak load and anaerobic threshold increased significantly after the study period in the rehabilitation group compared with baseline ($p<0.01$, $p<0.05$ and $p<0.05$, respectively).

The effects of rehabilitation on echocardiography, inflammatory status and other parameters are shown in Table 3 and Figure 2(b) to (d). Significant interactions were detected in LVEF, LVDs, hs-CRP and PTX3 ($F=4.55$, $p<0.05$; $F=42.79$, $p<0.01$; $F=4.02$, $p<0.05$; $F=5.03$, $p<0.05$, respectively). The LVEF increased ($p<0.05$) and LVDs, hs-CRP and PTX3 decreased ($p<0.05$, $p<0.05$, $p<0.01$, respectively) significantly after the study in the rehabilitation group compared with baseline.

A total of 14 patients (23.7%) developed atrial fibrillation recurrence: six (21.4%) in the rehabilitation group and eight (25.8%) in the control group (RR, 0.83; 95% CI, 0.33 to 2.10). Kaplan–Meier analysis was performed for time to atrial fibrillation recurrence after catheter ablation in each group (log rank test $p=0.716$) (Figure 3).

Discussion

Persistent atrial fibrillation is associated with a significantly increased risk of thromboembolism and death compared with paroxysmal atrial fibrillation.[15] Early detection and new therapies to prevent atrial fibrillation progression are needed. Cardiac rehabilitation is reported to be effective to alleviate atrial fibrillation symptoms and reduce atrial fibrillation burden among non-permanent atrial fibrillation patients.[7] However, the efficacy of cardiac rehabilitation for persistent atrial fibrillation patients remains unknown. This study is the first to demonstrate that cardiac rehabilitation improves exercise capacity, and may also be effective in managing inflammatory status and cardiac function without increasing risk for atrial fibrillation recurrence in patients treated with catheter ablation for persistent atrial fibrillation.

Atrial fibrillation patients have decreased cardiac output secondary to reduced atrial contraction, tachycardia, or irregular rhythms, resulting in decreased physical function and QoL.[16] Therefore, it may be important to increase exercise capacity and physical function for atrial fibrillation patients treated with catheter ablation. The present study showed that six months of cardiac rehabilitation significantly increased

Table 2. Effects of cardiac rehabilitation on physical function and exercise capacity.

	Usual care $n = 31$		Cardiac rehabilitation $n = 28$	
	Baseline	Follow-up	Baseline	Follow-up
Physical function				
Hand grip, kg	33.4 ± 9.5	32.7 ± 8.6	31.9 ± 8.9	$33.3 \pm 8.1^{\dagger\dagger *}$
Leg strength, %BW	0.55 ± 0.15	0.52 ± 0.13	0.54 ± 0.17	$0.60 \pm 0.16^{\dagger\dagger **}$
Exercise capacity				
6MWD, m	551 ± 84	565 ± 95	545 ± 123	$596 \pm 95^{\dagger **}$
Peak $\dot{V}O_2$, mL/kg per min	—	—	17.8 ± 3.4	$19.8 \pm 4.6^{**}$
Peak load, W	—	—	105 ± 30	$124 \pm 33^{*}$
PER	—	—	1.19 ± 0.07	1.17 ± 0.05
AT, mL/kg per min	—	—	11.1 ± 1.1	$12.4 \pm 2.4^{*}$

Change from baseline to follow-up within each group, $^{*}p < 0.05$, $^{**}p < 0.01$; interaction, $\dagger p < 0.05$, $\dagger\dagger p < 0.01$.
%BW: percent body weight; 6MWD: six minute walk distance; $\dot{V}O_2$: oxygen uptake; PER: peak respiratory exchange ratio; AT: anaerobic threshold.

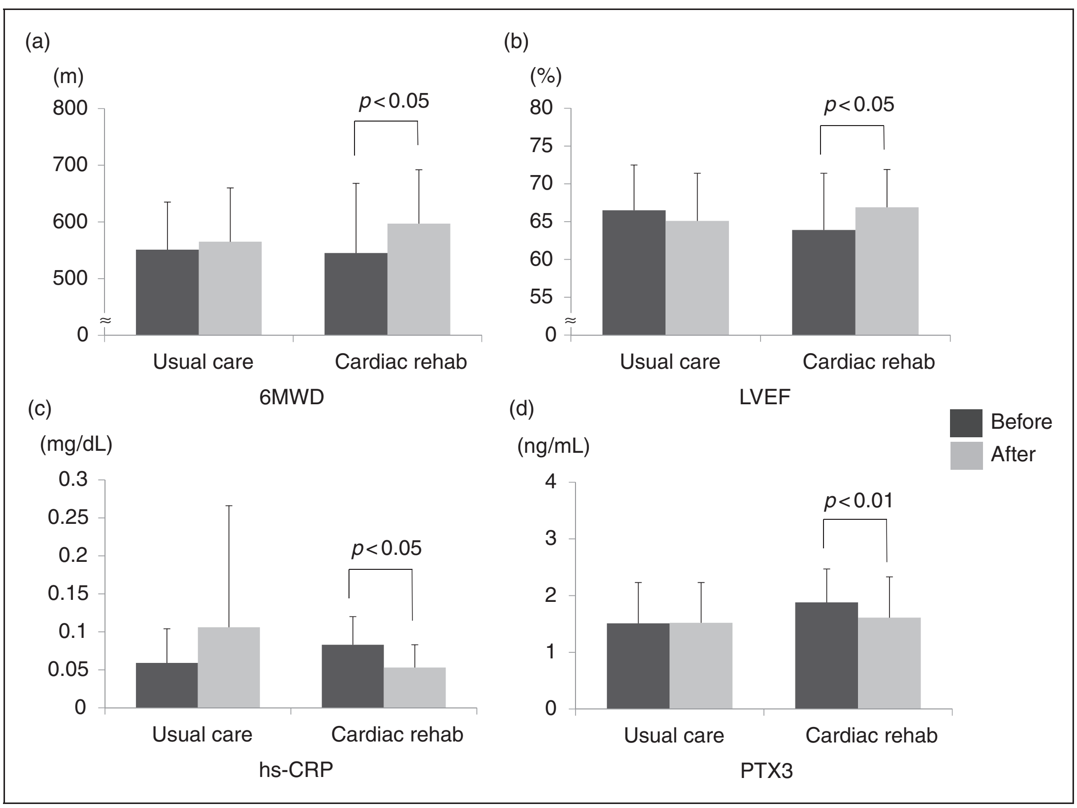

Figure 2. Changes in (a) 6MWD, (b) LVEF, (c) hs-CRP and (d) PTX3 from baseline to follow-up.
rehab: rehabilitation; 6MWD: six-minute walk distance; LVEF: left ventricular ejection fraction; hs-CRP: high-sensitivity C-reactive protein; PTX3: pentraxin 3.

6MWD and upper and lower limb strength compared with the control. In addition, cardiac rehabilitation also increased peak $\dot{V}O_2$, peak load and anaerobic threshold from baseline to follow-up. A recent RCT showed that exercise capacity measured by peak $\dot{V}O_2$ increased significantly by rehabilitation in atrial fibrillation patients treated with catheter ablation.[17] Moreover, a meta-analysis of RCTs showed that peak $\dot{V}O_2$ increased significantly by exercise training in permanent atrial fibrillation patients.[6] These publications are consistent with the results of our study showing that exercise training improved physical function and exercise

Table 3. Effects of cardiac rehabilitation on patient characteristics, echocardiography, inflammatory status and others.

	Usual care $n=31$		Cardiac rehabilitation $n=28$	
	Baseline	Follow-up	Baseline	Follow-up
Weight, kg	69.0 ± 4.8	69.4 ± 11.4	65.3 ± 10.4	65.2 ± 10.7
HR, beats/min	70 ± 12	70 ± 10	69 ± 9	67 ± 8
Echocardiography				
LVEF, %	66.5 ± 6	65.1 ± 6.3	63.9 ± 7.5	$66.9 \pm 5.0^{\dagger *}$
LVDd, mm	48.9 ± 3.8	49.1 ± 3.3	48.0 ± 4.6	48.4 ± 3.9
LVDs, mm	31.2 ± 4.4	31.7 ± 4.5	32.3 ± 8.1	$30.3 \pm 3.6^{\dagger\dagger *}$
LAD, mm	38.3 ± 5.1	36.9 ± 5.3	40.3 ± 4.2	39.3 ± 4.9
IVS, mm	10.3 ± 1.6	10.2 ± 1.5	10.1 ± 1.1	10.2 ± 1.3
E/e′	10.8 ± 5.4	10.1 ± 2.9	10.6 ± 3.3	10.3 ± 2.6
Inflammatory status				
hs-CRP, mg/dL	0.059 ± 0.045	0.106 ± 0.163	0.083 ± 0.037	$0.053 \pm 0.031^{\dagger *}$
PTX3, ng/mL	1.51 ± 0.72	1.52 ± 0.71	1.88 ± 0.59	$1.61 \pm 0.72^{\dagger **}$
IL-6, pg/mL	1.64 ± 0.63	1.92 ± 1.12	1.77 ± 0.85	1.71 ± 0.92
Other blood markers				
HDL-C, mg/dL	50 ± 10	52 ± 11	55 ± 10	55 ± 12
LDL-C, mg/dL	109 ± 24	110 ± 26	126 ± 24	120 ± 23
HbA1c, %	5.9 ± 0.5	5.8 ± 0.6	5.8 ± 0.2	5.7 ± 0.3
eGFR, mL/min per 1.73 m^2	64.7 ± 9.8	68.9 ± 13.1	61.8 ± 9.8	64.7 ± 10.4
BNP, pg/mL	53.6 ± 72.4	46.4 ± 53.6	54.5 ± 44.9	54.7 ± 51.9

Change from baseline to follow-up within each group, $*p < 0.05$, $**p < 0.01$; interaction, $\dagger p < 0.05$, $\dagger\dagger p < 0.01$.
HR: heart rate; LVEF: left ventricular ejection fraction; LVDd: left ventricular end-diastolic diameter; LVDs: left ventricular end-systolic diameter; LAD: left atrial diameter; IVS: interventricular septum; E: mitral flow velocity; e′: mitral annulus velocity during diastole; hs-CRP: high sensitivity C-reactive protein; PTX3: pentraxin 3; IL-6: interleukin-6; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: hemoglobin A1c; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

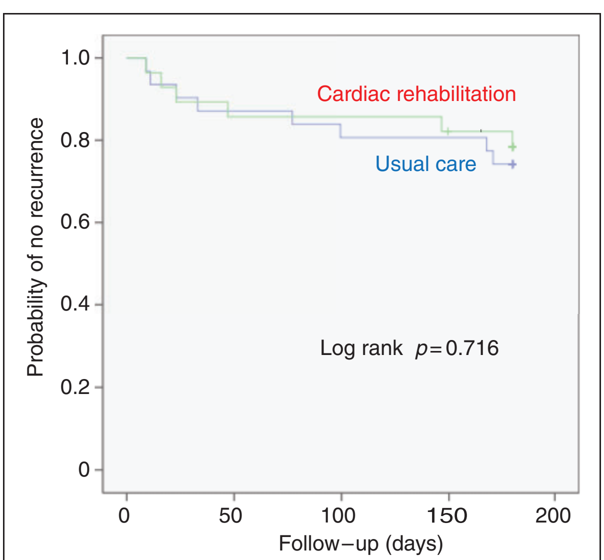

Figure 3. Kaplan–Meier graph showing atrial fibrillation recurrence over 180 days of follow-up.

capacity in patients with persistent atrial fibrillation that received catheter ablation. The underlying mechanisms responsible for the increase in exercise capacity are probably related to improvements in cardiac output and factors that improve oxygen uptake in peripheral skeletal muscle.[6] On the other hand, there was no change in 6MWD in usual care subjects. Yagishita et al. reported that exercise capacity significantly increased after six months of catheter ablation compared with before catheter ablation in asymptomatic atrial fibrillation patients with preserved ejection fraction.[5] Differences in patient characteristics and timing of exercise capacity measurement may have caused this discrepancy. The patients in the present study were older and had higher rates of chronic disease such as diabetes mellitus or cerebrovascular disease than in the previous study.

The present study also demonstrated that cardiac rehabilitation decreased hs-CRP and PTX3, which shares a structural homology with CRP, reflecting improved inflammatory status. Elevated inflammatory status leads to atrial remodeling by the release of activated substances, including oxygen free radicals and proteases.[18] A previous study showed that high CRP levels were associated with very late recurrence of atrial fibrillation after ablation.[19] Long-term endurance training has been reported to decrease circulating inflammatory cytokines and serum hs-CRP in patients with chronic heart failure.[20] In addition, physical activity could decrease resting levels of some inflammatory cytokines, including IL-6, and, ultimately, CRP production, by reducing obesity and leptin and increasing adiponectin and insulin sensitivity.[21] However, IL-6 levels were not significantly impacted by cardiac rehabilitation in the present study. Though these inconsistencies are difficult to explain, this may be related to lower levels of circulating IL-6 and the characteristics of the patient populations enrolled in this study. Some studies demonstrated that regular exercise training with moderate intensity did not improve IL-6 level in patients with heart failure or normal weight adults.[22,23] Given that subjects in our study were mostly normal weight (mean body mass index: 23.9 and 23.8 kg/m^2 in the usual care and cardiac rehabilitation group, respectively), our results are consistent with these studies. Therefore, cardiac rehabilitation may be effective at managing systemic inflammation status in patients treated with catheter ablation.

In the present study, cardiac rehabilitation significantly increased LVEF by 3% with LVDs decreased by 2 mm. This change is consistent with a recent meta-analysis showing that exercise training significantly improved LVEF by 4.8% in patients with atrial fibrillation.[6] Exercise training is known to improve myocardial substrate utilization by increasing insulin-stimulated myocardial glucose uptake, resulting in increased left ventricular (LV) function.[24] On the other hand, in a study that did not implement exercise trainings after catheter ablation, patients with preserved LV function, $\geq$50% LVEF, did not show an increase in LVEF within six months after catheter ablation.[25] In addition, patients in the usual care group tended to have decreased LVEF from baseline to follow-up in the present study. Adding an exercise-based cardiac rehabilitation program to usual care may be helpful in preserving or improving systolic LV function after catheter ablation. Additionally, some studies show that LAD is also a strong predictor for atrial fibrillation recurrence.[18] In our study, there was no significant change for LAD from baseline to follow-up. Improving LAD by cardiac rehabilitation may be difficult because patients with persistent atrial fibrillation often have advanced left atrial fibrosis.[26]

The occurrence of atrial fibrillation facilitates the continuation and recurrence of atrial fibrillation. The progression from paroxysmal atrial fibrillation to persistent atrial fibrillation has recently gained increasing attention. In the present study, cardiac rehabilitation did not increase the risk for atrial fibrillation recurrence and cardiovascular events. This may suggest that cardiac rehabilitation is safe for patients with persistent atrial fibrillation treated with catheter ablation. Greater exercise capacity and low inflammatory status are known to decrease atrial fibrillation burden after catheter ablation.[27] In addition, long-term aggressive management of cardiac risk factors reduced atrial fibrillation recurrence in paroxysmal and persistent atrial fibrillation patients after catheter ablation.[28] The European Society of Cardiology guideline recommends daily moderate physical activity for atrial fibrillation prevention. Although this guideline is not specifically about preventing atrial fibrillation recurrence after catheter ablation, benefits of physical activity, including better glucose and lipid control, improved endothelial function and lower systemic inflammation, are expected to apply to patients with persistent atrial fibrillation treated with catheter ablation as well.[29] Therefore, long-term cardiac rehabilitation including moderate physical activity might reduce atrial fibrillation recurrence after catheter ablation.

Study limitations

This study has several limitations. First, the single-center design and the relatively small number of participants are major limitations. Despite the absence of statistically significant differences in patient characteristics between the two groups, the effect of randomization might not have been perfect because of the small sample size. In addition, log-rank tests in this study might have the probability of making a type II error. On the other hand, the primary outcome of the present study was exercise capacity and sample size for the primary outcome was calculated using 6MWD data from a previous study. In addition, it was difficult to enroll statistically enough patients to demonstrate a difference in atrial fibrillation recurrence because patients with paroxysmal atrial fibrillation were not eligible and our exclusion criteria were strict. Second, the patients were not blinded for the exercise intervention. This might have affected the patients' everyday lifestyle (e.g. other activity and diet). Third, there is a possibility for detection bias regarding atrial fibrillation recurrence because atrial fibrillation recurrence was assessed only three times using a 12-lead ECG and twice using a 24-h ECG during the study. Using an implanted loop recorder to continuously assess atrial fibrillation recurrence would have been ideal. Fourth, the lack of information on QoL is another limitation in the present study because QoL is becoming an increasingly important measure when evaluating interventions for atrial fibrillation patients. Fifth, a short-term follow-up period of six months is also a limitation in this study. Pathak et al. demonstrated that aggressive risk factor management improved the long-term success of atrial fibrillation ablation.[28] Therefore, a longer follow-up might have reinforced the value of the study. Sixth, as the values of LVEF and inflammatory markers at baseline and follow-up were within the normal range in both groups, it is unclear whether changes in these parameters by cardiac rehabilitation have clinical significance, such as atrial fibrillation recurrence or their prognosis in the future. Finally, given that our study included only patients with persistent atrial fibrillation, it is unknown whether cardiac rehabilitation will have the same effect among non-persistent atrial fibrillation patients. Because of these limitations, our findings require confirmation from larger samples, multicenter studies, possibly using an outcome measurement without detection bias.

Conclusion

The present study demonstrated that cardiac rehabilitation improved exercise capacity without increasing the risk for atrial fibrillation recurrence. It may also be effective in managing the systemic inflammatory status and systolic LV function in patients with persistent atrial fibrillation treated with catheter ablation.

Author contribution

MK and MO contributed equally to this work.

Acknowledgements

The authors thank Yayoi Fukutomi and Keiko Sugimoto for assistance in patient follow-up.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this research was supported by JSPS KAKENHI (grant number 18K17693).

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