





ORIGINAL RESEARCH

Improvement of Maximal Exercise Performance After Catheter-Ablation of Atrial Fibrillation and Its Prognostic Significance for Long-Term Rhythm Outcome

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BACKGROUND: Rhythm control may improve functional capacity in patients with atrial fibrillation (AF). Long-term exercise tolerance improvement and its prognostic implications following catheter-ablation (CA) of paroxysmal and nonparoxysmal AF are underreported.

METHODS AND RESULTS: Consecutive patients underwent cardiopulmonary exercise testing just before and 12 months after their index CA of AF. Follow-up 24-hour Holter recordings were obtained at 6-month intervals post-CA, and any atrial arrhythmia >30 seconds detected after 3 months postprocedure was considered AF recurrence. Of 110 patients (mean age 57.5±10.6 years, 77.2% males) with paroxysmal AF (n=66) or nonparoxysmal AF (n=44), the 12-month exercise tolerance improved significantly in those who maintained sinus rhythm during the first 12 months post-CA (n=96), but not in patients with AF recurrence (n=14). After CA, the 12-month respiratory exchange ratio at maximal workload significantly increased in patients with paroxysmal AF, whereas those with nonparoxysmal AF significantly reduced their heart rate during the 12-month cardiopulmonary exercise testing (all $P\leq 0.001$). During the follow-up of 42.8±7.8 months, a total of 29 patients (26.3%) experienced recurrent AF. On multivariate analysis including patients without recurrent AF at 12 months after CA, the extent of work time improvement at follow-up cardiopulmonary exercise testing was independently associated with the rhythm outcome beyond 12 months postprocedure (hazard ratio of 0.936 [95% CI, 0.894–0.979] for each 10 seconds increase in the work time following ablation, $P=0.004$).

CONCLUSIONS: CA of AF was associated with recovery of exercise intolerance in patients with paroxysmal AF or nonparoxysmal AF. Inability to improve exercise capacity at 12 months post-CA was an independent risk factor for later AF recurrence.

Key Words: atrial fibrillation ■ cardiopulmonary exercise testing ■ catheter-ablation of atrial fibrillation ■ exercise tolerance ■ pulmonary vein isolation

Approximately 50% of patients with atrial fibrillation (AF) experience symptoms that cause significant deterioration of their exercise performance and quality of life (QoL),^{1,2} and the restoration

of sinus rhythm is followed by recovery in exercise tolerance.³

Catheter-ablation (CA) of AF is more effective than antiarrhythmic drugs (AADs) for maintaining sinus

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CLINICAL PERSPECTIVE

What Is New?

- This study demonstrated a significant recovery of exercise intolerance after (successful) catheter-ablation of nonparoxysmal atrial fibrillation (which is mediated mainly by reduction in heart rate) and after ablation of paroxysmal atrial fibrillation (which is probably driven by an improvement in left atrial booster pump function).
- Among the patients who were arrhythmia-free at 12 months after ablation, inability to improve their exercise capacity postablation was an independent risk factor for later atrial fibrillation recurrence.

What Are the Clinical Implications?

- Our findings suggest that the cardiopulmonary exercise test could be used as a risk assessment tool in patients undergoing catheter-ablation of atrial fibrillation, facilitating a more optimal selection of patients for the procedure and long-term rhythm monitoring strategy, which may influence a treatment decision about the antiarrhythmic drugs and oral anticoagulation use late after the procedure.

Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drug
AT	atrial tachycardia
CA	catheter-ablation
CPET	cardiopulmonary exercise test
HR	heart rate
LRAA	late recurrence of atrial arrhythmia
NPAF	nonparoxysmal atrial fibrillation
PAF	paroxysmal atrial fibrillation
PV	pulmonary vein
RER	respiratory exchange ratio
VAT	ventilatory anaerobic threshold
VO₂	oxygen uptake

rhythm and arrhythmia-related symptom relief.⁴ Data on the effects of CA of AF on maximal exercise performance are scarce and restricted to highly selected cohorts with long-standing persistent AF.^{5,6}

Generally, the inability to increase exercise performance following appropriate therapeutic or rehabilitation programs is associated with worse outcomes among patients with complex cardiovascular disease (eg, survivors of myocardial infarction, patients with heart failure, etc).^{2,7} However, prognostic value of the exercise tolerance improvement after CA of AF is not well characterized.

The aim of this study was to evaluate (1) the improvement in exercise tolerance 12 months post-CA

among consecutive patients undergoing CA of AF, and (2) impact of the 12-month exercise tolerance improvement post-CA on long-term rhythm outcome.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

This prospective single-center study considered consecutive patients (n=170) who underwent CA for symptomatic AF refractory to at least 1 Class IC or III AAD between October 2014 and March 2016 at the Cardiology Clinic, Clinical Centre of Serbia; 39 patients were excluded from further analysis because of a history of previous CA for AF (n=35) and 4 patients declined participation. Of the remaining 131 patients, baseline cardiopulmonary exercise testing (CPET) was contraindicated or inconclusive in 21 patients because of uncontrolled atrial tachyarrhythmia (n=12), known severe coronary artery disease (n=3), previous syncope (n=2), orthopedic diagnosis limiting physical performance (n=2), or patient's inability to cooperate during the test (n=2). Thus, the final study group included 110 patients. The study flow-chart is presented in Figure 1. The study protocol was approved by the hospital ethics committee and all patients provided written informed consent to participate in the study.

Pre-Ablation Work-Up

All patients received oral anticoagulant therapy for >6 weeks before CA.⁴ The use of AADs was stopped at least 3 to 5 days before the admission, while amiodarone was ceased >1 month before CA. Beta-blocker use was continued throughout the periprocedural period.

Paroxysmal AF (PAF), persistent AF, and long-standing persistent AF were defined as an AF episode lasting <7 days, 7 days to 1 year, or >1 year, respectively. The term nonparoxysmal AF (NPAF) included both persistent and long-standing persistent AF.⁴

Data on previous comorbidities, AF history, drug therapy, and the CA procedure were collected from hospital records and dedicated CA database. After admission, but before the CA, all patients completed the 36-Item Short Form Health Survey (SF-36) questionnaire¹ and underwent routine transthoracic echocardiography, chest computed tomography, 24-hour Holter monitoring, and the baseline CPET.

QoL Assessment

QoL was evaluated by a self-completed SF-36 questionnaire, comprising 36 items assessing 8 health

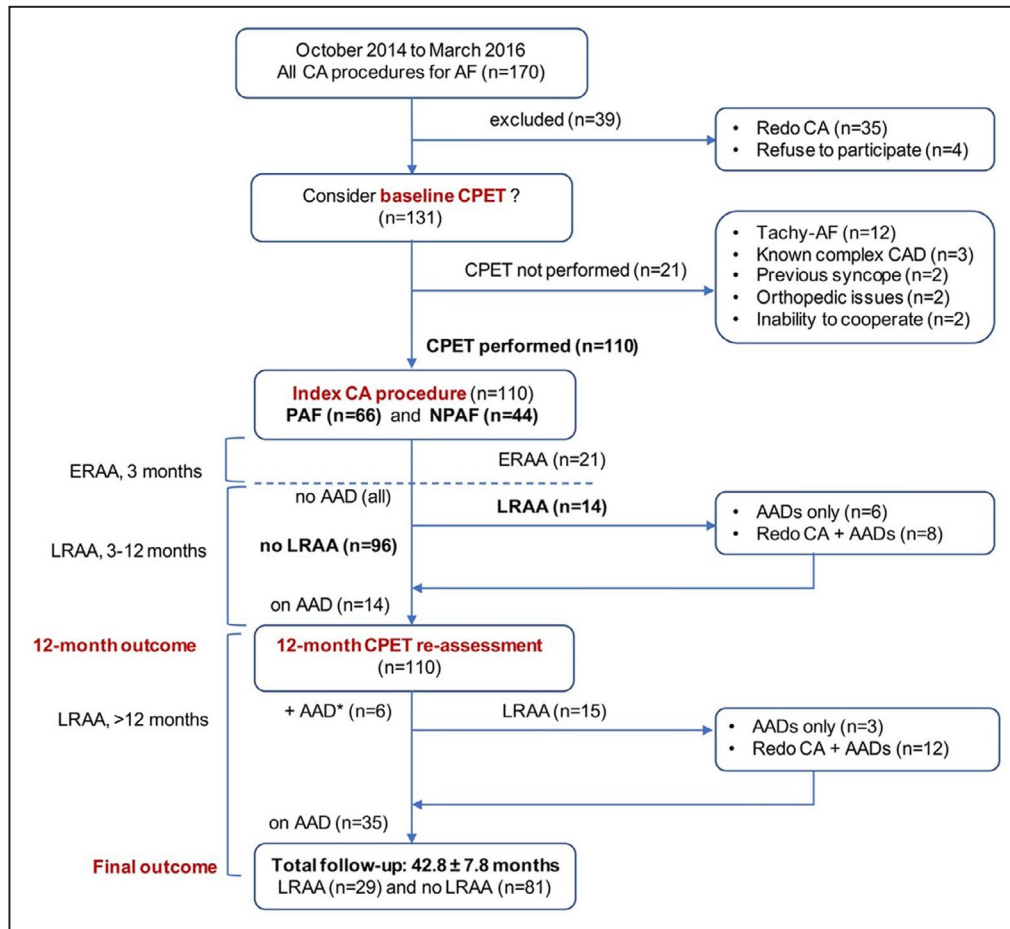


Figure 1. Study flow-chart and rhythm outcome after ablation of AF.

AAD indicates anti-arrhythmic drug; AF, atrial fibrillation; CA, catheter-ablation; CAD, coronary artery disease; CPET, cardiopulmonary exercise testing; ERAA, early recurrence of atrial arrhythmia; LRAA, late recurrence of atrial arrhythmia; NPAF, nonparoxysmal atrial fibrillation; and PAF, paroxysmal atrial fibrillation. * six patients received antiarrhythmic drug for frequent atrial or ventricular premature ectopic beats (not for atrial fibrillation).

domains (physical functioning, role limitations because of physical problems, bodily pain, general health perception, role limitations because of emotional problems, vitality, mental health, and social functioning).¹ The first 4 and the last 4 of these components are merged into the Physical Component Score (PCS) and the Mental Component Score (MCS), respectively. A lower score indicated a greater disability, whereas a higher score depicted better QoL.¹

CPET Protocol

CPET was performed on a semisupine ergo-bicycle using Ramp 15 protocol (15 W/min load increments).⁸ The maximal heart rate (HR) was calculated as 220 minus the patient’s age. Expiratory gases were collected on a breath-by-breath basis, and analyzed by metabolic cart (Schiller CS 200, Germany). Ventilatory

anaerobic threshold (VAT) was determined by the “V-slope” analysis of oxygen consumption (VO₂) versus carbon dioxide production. The values of VO₂ at VAT and at peak exercise (peak VO₂) are expressed as mL O₂/kg per min during the 30 seconds in which the examined event occurred and printed using rolling averages every 10 seconds. The predicted peak VO₂ was defined according to current recommendations.⁷ The predicted peak O₂ pulse was calculated as the predicted peak VO₂/predicted maximal HR.⁸ Ventilatory efficiency versus CO₂ output slope (ventilatory efficiency/carbon-dioxide production) was measured by excluding data points after the onset of maximal hyperventilation at the maximal effort (a higher value indicates a ventilatory/flow mismatch). The respiratory exchange ratio (RER) 1.0 was considered a satisfactory effort, while RER of 1.1 at the end of the CPET test was considered the achievement of the maximal effort.

Index CA Procedure

The ablation strategy for AF in our institution has already been described in detail elsewhere.⁹ Briefly, after the trans-septal access to the left atrium (LA), an anatomical LA map was created (Ensite Velocity/Precision; St. Jude Medical, St. Paul, MN), and fused with its computed tomography model. Radiofrequency point-by-point ablation was performed with the 4-mm externally irrigated tip ablation catheter (Cool-Flex; St. Jude Medical, St. Paul, MN) navigated by a deflectable long sheath (Agilis NT; St. Jude Medical, St. Paul, MN) with power limit of 25 to 30 W and flow rate of 17 mL/min. Local radiofrequency delivery was continued until a >80% reduction of atrial potential amplitude or for maximum of 20 to 30 seconds and 40 to 60 seconds at the posterior and anterior LA wall, respectively. Ipsilateral pulmonary veins (PVs, left and right) were encircled in pairs with a circumferential ablation line deployed 5 mm from anterior and 15 to 20 mm from posterior aspects of their ostia, respectively. During the ablation, residual electrical activity of PVs was evaluated with a duodecapolar circumferential mapping catheter.

Patients with PAF underwent a circumferential antral PV isolation, as a stand-alone ablation strategy. In patients with NPAF, the additional LA substrate modification was performed on top of PV isolation, consisting of the LA linear ablation (the roof line plus mitral isthmus ablation) and/or complex fragmented LA electrograms ablation. If typical atrial flutter was documented before CA, linear ablation of the cavo-tricuspid isthmus was deployed.^{4,9}

Clinical Follow-Up After CA

The AAD and oral anticoagulant that were used before the procedure were administered during the 3-month blanking period post-CA in all patients. Afterwards, AADs were discontinued in all patients, while oral anticoagulant was continued only in those with a CHA₂DS₂VASc score of >1.^{4,10}

The structured follow-up rhythm monitoring consisted of serial 24-hour Holter-recordings at discharge, 1, 3, 6, and 12 months post-CA, and every 6 months thereafter. Atrial arrhythmia recurrence was defined as any (symptomatic or asymptomatic) documented atrial arrhythmia post-CA, such as AF, atrial tachycardia (AT) or atrial flutter, sustaining >30 seconds.⁴ Early recurrence of atrial arrhythmia and late recurrence of atrial arrhythmia (LRAA) were defined as the atrial arrhythmia recurrence within the 3-month blanking period after CA and after the 3-month blanking period, respectively. Patients experiencing a LRAA were offered AAD therapy or repeat CA.

Twelve-Month Outcome Assessment

At 12 months after the index CA, structured follow-up outcome assessment was completed, including rhythm outcome evaluation, repeat SF-36 questionnaire and repeat

CPET in all patients, as well as repeat echocardiogram in patients with baseline systolic left ventricular (LV) dysfunction (LV ejection fraction [EF] <50%). Afterwards, the patients were followed by 24-hour Holter recording every 6 months and treated in line with the current guidelines.

Study Design

The study consisted of 2 periods (Figure 1). The first study period included the first 12 months after index CA (during this time all patients underwent the baseline CPET, index CA of AF, structured clinical follow-up, the 12-month CPET retesting, and QoL reassessment). The analysis of these data provided insight into the impact of CA of AF on exercise tolerance improvement. The second study period included clinical follow-up after 12 months from index CA. These data enabled the assessment of relationship between the 12-month post-CA exercise capacity improvement and the long-term rhythm outcome (ie, beyond 12 months post-CA).

Statistical Analysis

All continuous variables are presented as mean±SD or mean with 95% CI, while categorical variables were given as percentages. Comparison of continuous variables before and after CA was performed using the paired Student *t* test (normally distributed variables) or Wilcoxon signed-rank test (asymmetrical distribution). Significance of difference between the subgroups (PAF versus NPAF, and late recurrence of atrial arrhythmia [LRAA] versus no LRAA) was analyzed using the unpaired Student *t* test or Mann-Whitney *U* test, as appropriate. Bonferroni correction was applied to adjust significance threshold in order to mitigate type I error because of multiple testing. Proportions were compared using χ^2 or Fisher test. Risk factors for LRAA were evaluated using univariate and multivariate Cox regression that analyzed all variables listed in Table 1 (clinical variables) and Table 2 (CPET parameters). A 2-sided *P* value of <0.05 was considered significant. All analyses were conducted using SPSS software (version 20.0, IBM).

RESULTS

The study included 110 patients (the mean age was 57.5±10.6 years, 77.2% were males) who underwent their index CA of PAF (n=66) or NPAF (n=44) after a trial of mean 1.7±0.8 AADs. At baseline, systolic LV dysfunction (LV EF <50%) was recorded in 10 patients (PAF, n=2; NPAF, n=8). Baseline patients' characteristics are presented in Table 1. The patients with NPAF, compared with those with PAF, had a significantly larger LA, lower LV EF, and higher prevalence of heart failure and amiodarone use before the CA (Table 1).

Table 1. Clinical Characteristics of the Study Patients Before CA Procedure

	All Patients (n=110)	Patients With PAF (n=66)	Patients With NPAF* (n=44)	P Value
Age, y	57.5±10.6	58.2±10.2	56.5±11.3	0.552
Male patients	85 (77.2%)	49 (74.2%)	36 (81.8%)	0.353
BMI, kg/m ²	27.3±3.4	26.9±3.6	27.9±3.0	0.126
History of AF before CA, y	7.4±6.2	6.7±5.7	8.4±7.0	0.229
EHRA symptom score (I–IV)	2.6±0.5	2.7±0.5	2.6±0.5	0.519
NYHA functional class (I–IV)	1.3±0.5	1.2±0.4	1.5±0.6	<0.001
SF-36 score	54.5±21.5	52.2±20.2	58.1±23.2	0.227
Failed AADs, n	1.6±0.8	1.6±0.8	1.6±0.7	0.939
Amiodarone	70 (63.6%)	32 (48.5%)	38 (86.4%)	<0.001
Beta-blockers	73 (66.3%)	42 (63.6%)	31 (70.5%)	0.458
LA diameter, mm	41.2±5.2	39.6±4.5	43.7±5.2	<0.001
LV EDD, mm	52.2±4.1	51.7±3.8	53.0±4.5	0.123
LV EF, %	60±7.7	62.1±6.8	56.7±8.1	<0.001
LV systolic dysfunction (LV EF <50%)	10 (9.1%)	2 (3.0%)	8 (18.2%)	0.014
Comorbidities				
Hypertension	59 (53.6%)	40 (60.6%)	19 (43.2%)	0.073
Diabetes mellitus	15 (13.6%)	8 (12.1%)	7 (15.9%)	0.571
Congestive heart failure	13 (11.2%)	3 (4.5%)	10 (22.7%)	0.006
Stroke	10 (9.1%)	6 (9.1%)	4 (9.1%)	0.735
Coronary artery disease	6 (5.5%)	2 (3.0%)	4 (9.1%)	0.215
eGFR, mL/min per 1.73 m ²	94.6±24.1	94.6±23.4	94.7±25.3	0.775
CHA ₂ DS ₂ -VAsc score	1.6±1.4	1.6±1.3	1.6±1.5	0.821
Index CA procedure data				
PV isolation	110 (100%)	66 (100%)	44 (100%)	>0.999
LA linear ablation	41 (37.2%)	3 (4.5%)	38 (86.4%)	<0.001
CFAE ablation	27 (24.5%)	7 (10.6%)	20 (45.5%)	<0.001
CT-isthmus ablation	39 (35.5%)	24 (36.4%)	15 (34.1%)	0.875
Total radiofrequency delivery time, min	71.8±28.6	62.3±26.5	86.4±25.7	<0.001
Fluoroscopy time, min	31.3±12.6	28.4±12.3	36.1±11.7	0.002
Major complications†	6 (5.4%)	4 (6.1%)	2 (4.5%)	0.931
Repeat CA procedure	20 (18.2%)	13 (19.7%)	7 (15.9%)	0.614

Data are presented as mean±1 SD or as percentages. AADs indicates antiarrhythmic drugs; AF atrial fibrillation; BMI, body mass index; CA, catheter-ablation; CFAE, complex fragmented atrial electrograms; CT, cavo-tricuspid; EDD, end-diastolic diameter; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; LA, left atrium; LV, left ventricle; NPAF, nonparoxysmal atrial fibrillation; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; PV, pulmonary vein; and SF-36, 36-Item Short Form Health Survey.

*NPAF included patients with persistent AF (n=38) and patients with long-standing persistent AF (n=6).

†Major complication: cardiac tamponade (n=1), pericarditis (n=1), arteriovenous fistula (n=1), inguinal hematoma requiring transfusion (n=2), and systemic infection (n=1).

Rhythm Outcome Post-CA

The early recurrence of atrial arrhythmia within the 3-month blanking period was detected in 21 patients (19.2%). At 12 months after index CA, LRAA was recorded in 14 patients (12.7%). Of the latter, 6 patients only received an AAD, while 8 patients underwent repeat CA after an unsuccessful AAD trial (Figure 1). Overall, during the follow-up of 42.8±7.8 months from the index CA, a total of 29 patients (26.3%) experienced the LRAA (PAF, n=11; NPAF, n=1; paroxysmal AT, n=9; persistent AT, n=8) and CA was repeated in a total of 20 patients (18.2%), as presented in Figure 1.

There was no fatal outcome during the study period.

QoL at 12 Months Post-CA

The 12-month post-CA assessment of QoL revealed a significant improvement in the total SF-36 score, PCS, and MCS values compared with pre-ablation (54.5±21.5 versus 76.4±20.6, 53.9±23.7 versus 76.9±21.5, and 55.1±21.9 versus 75.9±21.1, respectively; all *P*<0.001).

In patients with pre-ablation systolic LV dysfunction (n=10), the 12-month echocardiographic re-evaluation demonstrated a significant recovery of LV EF (43.9±5.9% pre-CA versus 55.1±4.5% post-CA, *P*<0.001).

Table 2. Change of CPET Parameters at 12 Months Following CA AF Procedure in All Patients

CPET Parameter	Before CA	Post CA	Δ [Post CA—Before CA], n (95% CI)	P Value (Post CA vs Before CA)
Work time, s	612.7 \pm 149.6	615.9 \pm 156.0	3.2 (–22.6 to 29.1)	0.804
Maximal workload, W	124.7 \pm 37.4	131.8 \pm 37.2	7.1 (1.9 to 12.4)	0.008
Maximal SBP, mm Hg	171.6 \pm 29.8	174.8 \pm 29.5	3.3 (–3.2 to 9.8)	0.322
Maximal DBP, mm Hg	89.3 \pm 14.6	89.9 \pm 16.9	0.6 (–3.6 to 4.9)	0.418
$\Delta\text{VO}_2/\Delta\text{WR}$	7.4 \pm 4.4	8.9 \pm 2.4	1.5 (0.7 to 2.4)	0.026
VE/ VCO_2 slope	29.4 \pm 5.4	28.3 \pm 4.7	–1.2 (–2.2 to –0.1)	0.010
VO_2 at VAT, mL/kg per min	11.5 \pm 2.9	12.1 \pm 2.8	0.6 (0.0 to 1.1)	0.039
Peak VO_2 , mL/kg per min	18.4 \pm 4.6	19.5 \pm 4.8	1.2 (0.3 to 2.1)	0.009
RER at max. workload	0.971 \pm 0.081	1.034 \pm 0.207	0.063 (0.019 to 0.106)	<0.001
HR at rest, bpm	88.8 \pm 25.8	78.4 \pm 17.5	–10.4 (–16.5 to –4.3)	0.006
HR at VAT, bpm	113.5 \pm 24.1	99.8 \pm 15.7	–13.7 (–19.7 to –7.7)	<0.001
HR at max. workload, bpm	138.1 \pm 25.3	124.3 \pm 18.2	–13.8 (–19.9 to –7.6)	<0.001
O_2 pulse difference between max. workload—rest, mL/beat	7.3 \pm 3.0	8.6 \pm 3.2	1.3 (0.6 to 1.9)	<0.001
PET CO_2 difference between max. workload—rest, mm Hg	5.8 \pm 3.5	5.7 \pm 4.2	–0.1 (–1.0 to 0.8)	0.742

Data are presented as mean \pm 1 SD or as mean with 95% CI. Bonferroni correction was applied for multiple analysis: *P* value is considered significant if <0.0036 (0.05/14=0.0036). $\Delta\text{VO}_2/\Delta\text{WR}$ indicates relationship between oxygen uptake and the work rate; AF, atrial fibrillation; bpm, beats per minute; CA, catheter-ablation; CPET, cardiopulmonary exercise testing; DBP, diastolic blood pressure; HR, heart rate; O_2 pulse, oxygen pulse; PET CO_2 , end-tidal partial pressure of carbon dioxide; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAT, ventilatory anaerobic threshold; VE/ VCO_2 , ratio between ventilation efficiency and carbon dioxide output; and VO_2 , oxygen uptake.

Exercise Capacity Improvement 12 Months Post-CA

The baseline CPET was performed during sinus rhythm in 58 patients (52.7%) and during AF, AT, or atrial flutter in the remaining 52 patients (47.3%). During the baseline CPET, an AF/AT/atrial flutter was recorded significantly less commonly in patients with PAF than in those with NPAF (16/66 versus 36/44, *P*<0.001). However, the 12-month CPET was performed during sinus rhythm in all but 2 study participants.

Postablation Exercise Tolerance Improvement in All Patients

Overall, the 12-month CPET (compared with the baseline test) demonstrated a significant improvement in several parameters, as presented in Table 2, including the RER at maximum workload, HR at VAT, HR at maximum exercise, and O_2 pulse increase during the test (all *P*≤0.001).

Exercise Tolerance Change in Relation to the Rhythm Outcome Post-CA

In patients who maintained sinus rhythm at 12 months post-CA (*n*=96), but not among those with documented 12-month LRAA (*n*=14), the CPET re-testing revealed a significant improvement of the maximum workload, VO_2 uptake at maximum exercise, RER at maximum workload, and O_2 pulse increase during

the test (all *P*≤0.001), as presented in Table 3 and Figure 2A and 2B. In addition, 12 months after CA these patients had a significantly lower HR at VAT as well as HR at maximum exercise (all *P*≤0.001).

Post-CA Exercise Tolerance Change in Relation to the Type of AF

Only the patients with PAF significantly improved the RER at the maximum workload at 12 months postablation. However, a significant reduction in the HR during all stages of exercise (at rest, VAT, and maximum workload) and an increase in the O_2 pulse difference achieved during the test were exclusively recorded among patients with NPAF. In addition, the average improvement in these CPET parameters was significantly better in patients with NPAF than in those with PAF (all *P*≤0.001; Table 4 and Figure 2C and 2D).

Sensitivity Analysis

A sensitivity analysis excluding patients with systolic LV dysfunction at baseline (*n*=10) also showed a significant 12-month post-CA change in the following CPET parameters: the RER at maximum workload (Δ 0.061 [0.014–0.108], *P*<0.001), HRs at VAT and maximum exercise (Δ –12.2 [–18.5 to –5.8] beats per minute and Δ –12.3 [–18.5 to –6.1] beats per minute, respectively, all *P*≤0.001), and the O_2 pulse increase during the test (Δ 1.2 [0.5–1.8] mL/beat, *P*=0.002).

Table 3. Change of CPET Parameters at 12 Months Following CA AF According to the 1-Year Rhythm Outcome

CPET Parameter	The 12-mo Outcome	Before CA	Post CA	P Value (Post CA vs Before CA)	Δ [Post CA—Before CA], n (95% CI)	P Value (LRAA vs No LRAA)
Work time, s	LRAA	627.4±103.2	554.4±131.5	0.026	−73.0 (−136.0 to −10.0)	0.024
	No LRAA	610.5±155.6	625±157.9	0.304	14.5 (−13.3 to 42.3)	
Maximal workload, W	LRAA	124.3±28.9	113.9±36.9	0.172	−10.4 (−25.8 to 5.1)	0.011
	No LRAA	124.7±38.6	134.4±36.7	0.001	9.7 (4.2 to 15.2)	
Maximal SBP, mm Hg	LRAA	172.8±24.6	157.1±27.0	0.102	−15.6 (−34.6 to 3.3)	0.026
	No LRAA	171.4±30.6	177.5±29.1	0.084	6.1 (−0.8 to 12.9)	
Maximal DBP, mm Hg	LRAA	88.3±13.8	89.6±12.7	0.829	1.3 (−11.3 to 13.9)	0.677
	No LRAA	89.5±14.8	90.0±17.5	0.383	0.5 (−4.0 to 5.1)	
$\Delta\text{VO}_2/\Delta\text{WR}$	LRAA	6.5±3.8	7.5±3.0	0.278	1.0 (−1.0 to 3.0)	0.996
	No LRAA	7.6±4.5	9.2±2.3	0.042	1.6 (0.6 to 2.6)	
VE/ VCO_2 slope	LRAA	29.2±4.7	29.5±4.8	0.770	0.3 (−1.9 to 2.5)	0.189
	No LRAA	29.4±5.5	28.1±4.7	0.005	−1.3 (−2.5 to −0.1)	
VO_2 at VAT, mL/kg per min	LRAA	11.3±1.5	11.2±1.9	0.852	−0.1 (−1.1 to 1.0)	0.352
	No LRAA	11.6±3.0	12.2±3.0	0.022	0.7 (0.1 to 1.3)	
Peak VO_2 , mL/kg per min	LRAA	17.9±2.9	16.3±4.3	0.198	−1.6 (−3.7 to 0.6)	0.017
	No LRAA	18.4±4.9	20.0±4.7	0.001	1.6 (0.6 to 2.5)	
RER max. workload	LRAA	0.999±0.046	0.984±0.122	0.601	−0.015 (−0.075 to 0.045)	0.065
	No LRAA	0.967±0.085	1.041±0.216	<0.001	0.075 (0.026 to 0.124)	
HR at rest, bpm	LRAF	90.1±28.7	80.1±20.0	0.300	−10.0 (−25.1 to 5.1)	0.981
	No LRAF	88.5±25.4	78.1±17.2	0.011	−10.5 (−17.2 to −3.7)	
HR at VAT, bpm	LRAA	115.1±24.0	99.6±12.0	0.061	−15.5 (−31.8 to 0.8)	0.817
	No LRAA	113.2±24.2	99.8±16.3	<0.001	−13.4 (−20.0 to −6.9)	
HR at max. workload, bpm	LRAA	140.0±21.8	119.5±18.9	0.036	−20.5 (−37.2 to −3.8)	0.399
	No LRAA	137.8±25.9	125.0±18.1	0.001	−12.8 (−19.5 to −6.0)	
O_2 pulse difference between max. workload—rest, mL/beat	LRAA	6.9±2.3	7.3±2.8	0.469	0.4 (−0.8 to 1.7)	0.308
	No LRAA	7.4±3.1	8.8±3.2	<0.001	1.4 (0.7 to 2.1)	
PET CO_2 difference between max. workload—rest, mm Hg	LRAA	4.9±3.5	5.7±3.3	0.270	0.8 (−0.7 to 2.2)	0.254
	No LRAA	6.0±3.5	5.7±4.3	0.512	−0.2 (−1.2 to 0.7)	

Data are presented as mean±1 SD or as mean with 95% CI. Bonferroni correction was applied for multiple analysis: P value is considered significant if <0.0036 (0.05/14=0.0036). $\Delta\text{VO}_2/\Delta\text{WR}$ indicates relationship between oxygen uptake and the work rate; AF, atrial fibrillation; bpm, beats per minute; CA, catheter-ablation; CPET, cardiopulmonary exercise testing; DBP, diastolic blood pressure; HR, heart rate; LRAA, late recurrence of atrial arrhythmia; O_2 pulse, oxygen pulse; PET CO_2 , end-tidal partial pressure of carbon dioxide; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAT, ventilatory anaerobic threshold; VE/ VCO_2 , ratio between ventilation efficiency and carbon dioxide output; and VO_2 , oxygen uptake.

Correlation Between the QoL Score and CPET Parameters Improvements

There was no significant correlation between the 12-month change in SF-36 score ($\Delta 21.9$ [18.1–25.7]) and changes in the most important CPET parameters (Δ maximum workload, Δ ventilatory efficiency/ VECO_2 , Δ peak VO_2 , and Δ HR at maximum exercise; all $P>0.05$).

Risk Factors for Very Late Arrhythmia Recurrence Post-CA

A very late recurrence of atrial arrhythmias, occurring beyond 12 months from CA, was detected in 15 of 96 patients (15.6%) who initially were arrhythmia-free at

12 months post-CA. In these patients, the mean time from CA to very late recurrence of atrial arrhythmias was 25.4±7.0 months (from 15 to 39 months). Univariate analysis showed a significant association between the very late recurrence of atrial arrhythmias and the 12-month improvement in work time (Δ work time, $P=0.007$), Δ SF-36 score ($P=0.040$), Δ MCS ($P=0.034$), and pre-ablation amiodarone use ($P=0.050$). Multivariable Cox analysis identified that only Δ work time was independently associated with very late recurrence of atrial arrhythmias, with a crude hazard ratio of 0.936 (95% CI, 0.894–0.979) for each 10-second increase in the work time following ablation, $P=0.004$; the result remained unchanged after adjusting for patients' age,

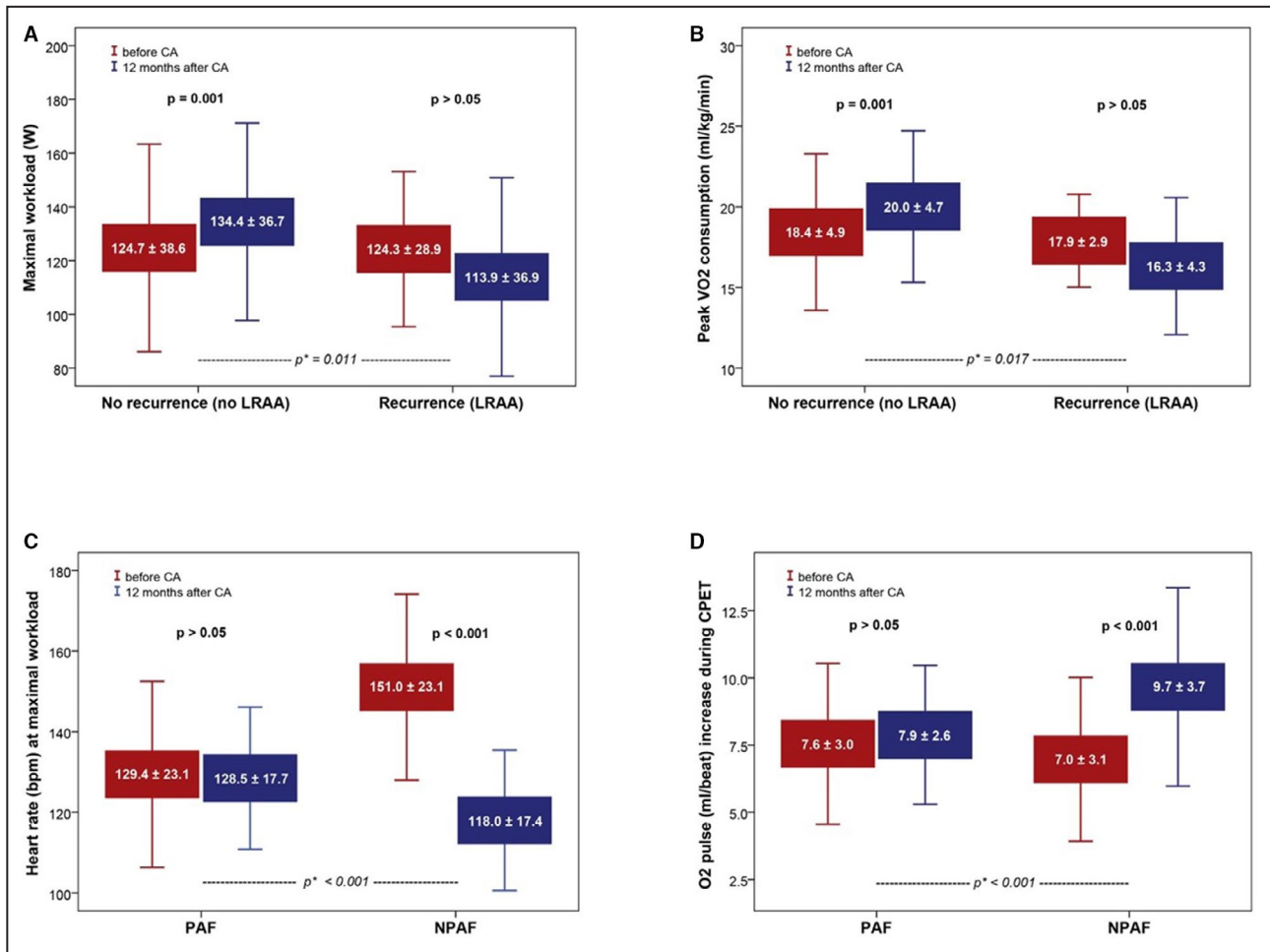


Figure 2. The arrhythmia-free patients, but not the patients with the recurrence, demonstrated a significant increase in (A) the maximal workload and (B) the peak VO₂ uptake 12 months after CA of AF; a better improvement of (C) the heart rate and (D) the O₂ pulse increase during exercise at the 12-month re-evaluation after the index CA of NPAF compared with PAF. AF indicates atrial fibrillation; CA, catheter-ablation; CPET, cardiopulmonary exercise test; LRAA, late recurrence of atrial arrhythmia; NPAF, nonparoxysmal atrial fibrillation; PAF, paroxysmal atrial fibrillation; and VO₂, oxygen consumption. *P significance for difference between the subgroups.

sex, baseline AF type, baseline CHA₂DS₂VASc score, and systolic LV dysfunction.

DISCUSSION

The main findings of our study are (1) successful CA of both PAF and NPAF, resulting in a significant improvement in exercise tolerance at 12 months after the procedure; (2) the physiological mechanisms of functional capacity recovery after CA differ between patients with PAF and NPAF; and (3) a greater increase in the CPET maximal work time 12 months post-CA predicted later sinus rhythm maintenance.

Functional Capacity After CA of AF

The occurrence of AF results in loss of LA systole, shortening of LV filling time, reduction in stroke volume/

cardiac output, and exercise intolerance.¹¹ One of the main treatment goals in patients with AF is the functional and symptomatic recovery as well as QoL improvement.¹² The successful cardioversion of AF was associated with a significant peak VO₂ increase, whereas the AF recurrence led to peak VO₂ decrease at 2-year follow-up exercise testing.³ Similarly, successful CA of NPAF was accompanied by significant improvement in the peak VO₂ at 6 months^{5,6} and was followed with further peak VO₂ increase at 12 months post-CA.⁶

Fast, prolonged, or repetitive episodes of AF may lead to (reversible) impairment of LV systolic function and its dilatation, whereas substantial reduction in AF burden after CA provides a resolution of the AF-related tachy-cardiomyopathy.^{4,10} Therefore, the improvement in exercise capacity after CA of AF in patients with baseline systolic LV dysfunction may be attributable to recovery of LV contractility and LV EF.^{4,6,10,12} In

Table 4. Change of CPET Parameters at 12 Months Following CA AF According to Type of AF

CPET Parameter	Type of AF	Before CA	Post CA	P Value (Post CA vs Before CA)	Δ [Post CA—Before CA], n (95% CI)	P Value (PAF vs NPAF)
Work time, s	PAF	604.2±134.9	603.3±151.9	0.963	−0.8 (−36.3 to 34.6)	0.706
	NPAF	625.2±169.9	634.5±161.8	0.629	9.3 (−29.0 to 47.5)	
Maximal workload, W	PAF	123.0±36.0	131.4±32.7	0.016	8.4 (1.6 to 15.3)	0.990
	NPAF	127.2±39.7	132.4±43.4	0.228	5.2 (−3.4 to 13.8)	
Maximal SBP, mm Hg	PAF	174.5±31.8	174.8±30.0	0.943	0.3 (−7.9 to 8.5)	0.366
	NPAF	167.3±26.2	175.0±29.0	0.164	7.7 (−3.3 to 18.6)	
Maximal DBP, mm Hg	PAF	87.9±14.6	90.7±19.1	0.748	2.9 (−3.2 to 9.0)	0.764
	NPAF	91.5±14.5	88.8±13.2	0.331	−2.7 (−8.1 to 2.8)	
ΔVO ₂ /ΔWR	PAF	7.7±4.2	9.0±2.3	0.207	1.3 (0.2 to 2.4)	0.442
	NPAF	7.0±4.7	8.9±2.6	0.055	1.9 (0.5 to 3.3)	
VE/VCO ₂ slope	PAF	29.5±4.9	27.9±4.9	0.041	−1.6 (−3.0 to −0.2)	0.588
	NPAF	29.3±6.1	29.0±4.2	0.123	−0.3 (−2.0 to 1.4)	
VO ₂ at VAT, mL/kg per min	PAF	11.6±2.8	12.3±3.0	0.065	0.7 (0.0 to 1.4)	0.704
	NPAF	11.4±3.0	11.8±2.6	0.291	0.5 (−0.5 to 1.4)	
Peak VO ₂ , mL/kg per min	PAF	18.5±4.4	19.7±4.8	0.032	1.2 (0.1 to 2.4)	0.873
	NPAF	18.2±5.0	19.3±4.8	0.122	1.1 (−0.4 to 2.6)	
RER at max. workload	PAF	0.972±0.069	1.012±0.065	0.001	0.040 (0.017 to 0.063)	0.753
	NPAF	0.970±0.098	1.066±0.316	0.011	0.096 (−0.009 to 0.201)	
HR at rest, bpm	PAF	82.5±26.9	80.6±16.7	0.371	−1.9 (−10.1 to 6.4)	<0.001
	NPAF	98.0±21.0	75.0±18.3	<0.001	−23.0 (−30.8 to −15.2)	
HR at VAT, bpm	PAF	105.9±22.7	103.3±14.6	0.883	−2.6 (−9.5 to 4.3)	<0.001
	NPAF	124.8±21.7	94.6±16.0	<0.001	−30.1 (−39.0 to −21.2)	
HR at max. workload, bpm	PAF	129.4±23.1	128.5±17.7	0.994	−1.0 (−7.6 to 5.7)	<0.001
	NPAF	151.0±23.1	118.0±17.4	<0.001	−33.1 (−42.3 to −23.8)	
O ₂ pulse difference between max. workload—rest, mL/beat	PAF	7.6±3.0	7.9±2.6	0.404	0.3 (−0.5 to 1.1)	<0.001
	NPAF	7.0±3.1	9.7±3.7	<0.001	2.7 (1.7 to 3.7)	
PET CO ₂ difference between max. workload—rest, mm Hg	PAF	6.0±3.5	5.5±4.3	0.341	−0.5 (−1.7 to 0.7)	0.311
	NPAF	5.5±3.6	6.0±4.1	0.542	0.5 (−0.9 to 1.8)	

Data are presented as mean±1 SD or as mean with 95% CI. Bonferroni correction was applied for multiple analysis: *P* value is considered significant if <0.0036 (0.05/14=0.0036). ΔVO₂/ΔWR indicates relationship between oxygen uptake and the work rate; AF, atrial fibrillation; bpm, beats per minute; CA, catheter-ablation; CPET, cardiopulmonary exercise testing; DBP, diastolic blood pressure; HR, heart rate; NPAF, nonparoxysmal atrial fibrillation; O₂ pulse, oxygen pulse; PAF, paroxysmal atrial fibrillation; PET CO₂, end-tidal partial pressure of carbon dioxide; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAT, ventilatory anaerobic threshold; VE/VCO₂, ratio between ventilation efficiency and carbon dioxide output; and VO₂, oxygen uptake.

our study, a significant improvement of the majority of CPET parameters after CA of AF is confirmed by sensitivity analysis even after removal of patients with pre-ablation systolic LV dysfunction.

Interestingly, our study found no correlation between QoL improvement and increase in exercise capacity after CA. Probably patients with AF during their daily activities rarely reach the (sub)maximal exercise tolerance threshold, and their QoL deterioration is not mediated predominantly by maximal exercise-related symptoms.¹

Functional Capacity Improvement After CA of PAF and NPAF

We showed for the first time a significant recovery from exercise intolerance not only after (successful)

CA of NPAF, but also after CA of PAF. Our study provides a comprehensive analysis of CPET parameter changes after CA of AF, and in contrast to previous studies it includes a full set of CPET parameters. This thorough evaluation of changes in CPET parameters following CA of AF provided further insight into specific physiological mechanisms of functional improvement after CA with respect to the type of AF. Although the present study demonstrates a significant increase in patients' level of maximal exercise after CA in both NPAF and PAF, it seems that the mechanisms of this improvement may differ according to the AF type.

Similar to previous studies,^{5,6} the functional recovery among patients with NPAF in our study was mediated mainly by significant reduction in ventricular rate at all stages of CPET, since three quarters of patients

performed a pre-ablation test during ongoing (fast) AF, whereas the majority of patients were in sinus rhythm at follow-up CPET. Moreover, the CPET parameters other than the HR remained mostly unaffected. A more advanced stage of atrial remodeling and more extensive LA substrate ablation (beyond PV isolation) could be responsible for irreversible impairment of LA transport in patients with NPAF, or in these patients a notable recovery of LA contractility simply requires more time after CA.^{10,13}

Although almost one quarter of patients with PAF (16 of 66, 24%) were in AF during pre-ablation CPET, and all of them were in sinus rhythm at follow-up re-testing, no significant change in the HR at 12 months post-CA was registered in these patients. Nevertheless, in patients with PAF, the increase of exercise capacity post-CA was clearly demonstrated, with a significant improvement of the RER at maximal workload. Imaging studies already reported an association between PAF and the loss of effective LA mechanical function.^{14,15} The “elimination” of PAF (but not NPAF) by CA and successful sinus rhythm maintenance promote the improvement of LA booster pump, atrioventricular synchrony, as well as the reduction of LA size and volume, reflecting a better LA reservoir function.¹⁶ In addition, reduction of AF burden after CA because of absence of asymptomatic AF recurrences may contribute to improvement of LA contraction. This may result in stroke volume and cardiac output increase, and exercise tolerance recovery.¹⁷

Functional Capacity Recovery Post-CA and Long-Term Rhythm Outcome

The assessment of maximal functional capacity by CPET is an important diagnostic and prognostic tool for various patients with cardiovascular diseases, such as those with heart failure, valvular disease, hypertrophic cardiomyopathy, or pulmonary hypertension.¹⁸ In addition, the CPET enables estimation of the efficacy of specific treatment/rehabilitation programs.^{7,8,18} Moreover, the degree of improvement in cardiopulmonary exercise capacity following the therapeutic intervention in these patients predicts major adverse cardiovascular events and mortality.^{2,7,8,18}

In the present study, the extent of improvement in the work time at the 12-month CPET after CA was independently associated with long-term rhythm outcome. Thus, patients who exhibit a greater prolongation of work time during the first 12 months post-CA have a lower probability for very late arrhythmia relapse.

Clinical Implications

We speculate that patients who achieved a greater improvement in cardiovascular endurance during the

first year after CA of AF initially presented at CA in an earlier stage of LA remodeling and therefore had “a better reserve” for functional improvement. During the early stage of LA disease, the PV triggers play a predominant role in AF initiation and perpetuation and, therefore, the CA early in the course of AF may provide a better long-term rhythm outcome.^{4,10,12} In addition, wider use of CPET may facilitate a more optimal selection of patients for CA and long-term rhythm monitoring strategy, which may influence a treatment decision about the AADs and oral anticoagulant use late after the procedure.^{4,10,12}

Study Limitations

The study group is relatively small and there is no control group, but our results convincingly demonstrate a significant improvement in a majority of CPET parameters following CA of AF.

The post-CA monitoring by Holter recordings most likely underestimated the “true” AF recurrence rate because of underdetection of silent/short AF episodes, but this post-CA strategy was in line with the current guidelines.^{4,10} Obviously, the long-term continuous rhythm monitoring with implantable loop-recording post-CA would provide better insight into the correlation between AF burden reduction and exercise tolerance recovery after the procedure.

The functional improvement post-CA could be attributed to a more aggressive management of cardiometabolic risk factors (eg, hypertension, obesity, etc) in the period between 2 CPET examinations.¹⁹ However, none of the patients was included in a structured and goal-directed therapeutic/rehabilitation program post-CA and they were only advised on general lifestyle modifications.

The assessment of baseline LA tissue damage pre-CA by magnetic resonance imaging or voltage LA mapping was not performed, because these work-ups would considerably increase the cost of treatment and duration of CA.

CONCLUSIONS

Successful CA of PAF or NPAF is followed by significant improvement in maximal exercise capacity at 12 months. The postablation functional recovery among patients with NPAF is mainly driven by reduction in HR, whereas in those with PAF the functional improvement after CA is reflected by improvement of the RER at maximal workload. There is no significant relation between QoL and degree of maximal exercise capacity after CA, but a greater extent of exercise capacity improvement within the first year post-CA is independently associated with the long-term maintenance of sinus rhythm. Our findings suggest that CPET

could be used as a risk assessment tool in patients undergoing CA of AF.

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