Exercise-based Predictors of Late Recurrence of Atrial Fibrillation After Catheter Ablation

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Abstract

Freedom from atrial fibrillation at 1 year is estimated to be between 55–80 % of patients undergoing catheter ablation. A significant number of them would require repeat procedures due to recurrent AF. Patients at higher risk for developing recurrent AF could benefit from different ablation strategies and post-ablation rhythm control therapy. We aim to identify the exercise-based risk factors associated with the first recurrence of AF between 3 and 36 months following the ablation. Patients (n=98, 69.4 % men) referred for catheter ablation of paroxysmal AF underwent simultaneous arm ergometry, exercise echocardiography and invasive left atrial pressure measurements. After the index ablation procedure, follow-up visits were scheduled. The observed freedom from AF recurrence during the follow-up was 81 %. Multivariable-adjusted Cox regression revealed the peak VO_2 as the most significant predictor of late AF reccurence (hazard ratio 0.53, $p<0.005$). Among analyzed parameters, the lowest prediction error was achieved by including left atrial volume index, left atrial pressure and peak VO_2 into age and sex adjusted Cox model (AIC=132.02, C-statistics=0.83). Presence of either decreased exercise capacity or elevated left atrial pressure is able to identify patients with potentially impaired left atrial function and different clinical outcome after conventional pulmonary vein isolation.

1. Introduction

Catheter ablation has become a standard therapy for atrial fibrillation (AF). In paroxysmal AF patients, high acute success rates are achievable by only pulmonary vein isolation (PVI). But the procedural strategy must reflect patient-specific left atrial (LA) pathology to reach durable efficacy in recurrent AF. Identification of patients at higher risk for developing recurrent AF is primarily based on LA voltage mapping, AF duration, LA enlargement, age, presence of structural heart diseas or cardiac imaging [1]. The cardiopulmonary function has been shown to correlate well with the disease severity in connection with prognosis of patients [2]. Exertional dyspnea is a frequently observed complaint in patients with AF [3], and is hypothesized to be associated with AF recurrence after AF ablation [4].

The aim of this study was to identify clinical, echocardiography (EchoCG), and the exercise-based risk factors that could facilitate patients‘ selection for different and more favourable ablation strategy. We hypothesized that the presence of either elevated LA pressure (LAP) or deteriorated peak VO_{VO2} is associated with the time to first recurrence of AF between 3 and 36 months following the ablation. Several similar studies [4–6] has been conducted in the past, yet to our knowledge, this is the largest clinical study evaluating exercise-based AF risk factors during sinus rhythm and before first ablation therapy.

2. Material and Methods

2.1. Patients

We studied 98 patients (68 men, 30 women, median age 62 years) who where referred for catheter ablation of paroxysmal AF to St. Anne's University Hospital between October 2013 and May 2017. Inclusion criteria for this study were as described in previous papers [7]: a) sinus rhythm on electrocardiography on the day of ablation; b) normal resting heart rate in the range of 50–90 beats/min; c) no history of myocardial infarction or angina pectoris; d) normal LVEF ($\geq$ 50%), no wall motion abnormality, and non-dilated left ventricle. The exclusion criterie were: a) presence of valvular or congenital heart disease, hypertrophic cardiomyopathy, mitral regurgitation, liver or re-

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nal disease, b) coronary artery disease, c) previously performed catheter ablation for AF. The study was approved by the ethics committee of St. Anne's Hospital. All the patients provided written consent to the investigations.

2.2. Study protocol

Study protocol was as previously described in Meluzin et al. [7]. Briefly: The day before procedure patients underwent conventional EchoCG and baseline laboratory test to determine whether they fullfilled inclusion criteria.

The next day, all the patients underwent heart catheterization. Following transseptal puncture, a 7-F fluid-filled pigtail catheter (Pro-Flo Standard Straight Pigtail 7F, Medtronic Inc., Minneapolis, MN, USA) was positioned at the middle of left atrium and its correct position verified by fluoroscopy. Subsequently, graded supine resting and exercise arm ergometry simultaneous with LAP monitoring were performed.

Exercise tests were performed on a MOTOmed letto2 arm ergometer (type 280, RECK-Technik GmbH & Co. KG, Betzenweiler, Germany). The excercise load started at 10 W for first 2 minutes and was then increased by 10 W after every other 2 minutes until the occurrence of dyspnea or fatigue.

Measurement of LAP was performed using a pigtail catheter and calibrated blood pressure transducer (DTX-Plus DT-XX, Argon Medical Devices, Singapore) positioned at the mid-axillary line of the patient. The entire measurement system was zero-referenced against the ambient air pressure. Resting and exercise LAP values were continuously recorded using the Bard electrophysiological recording system (Bard LabSystem Pro EP Recording System 2.6a.0.5, Clearsign, CR Bard Inc., USA).

Patients then underwent pulmonary vein isolation with radiofrequency catheter ablation. Follow-ups were scheduled at 1, 3, 6, 12, 24 and 36 months after the index ablation procedure. AF symptoms and adverse events were reviewed through a physical examination and and either a 72-h Holter monitor recording or 1-week transtelephonic ECG recording. Patients with AF recurrence where referred for repeated ablation procedure.

2.3. Parameter measurement

LAP (LAP_{rest}) was analyzed at the time of the preexercise resting, and exercise LAP (LAP_{ex}) was evaluated within 12 seconds after the termination of exercise. Both LAP_{rest} and LAP_{ex} were averaged over the pressure waveform data obtained during 12 seconds and were expressed as the means. $LAP_{rest} \geq 15$ mmHg was defined as abnormal [5].

Maximal oxygen consuption VO_{2max} for arm threadmill excercise was estimated by applying the metabolic equation for arm cycling to the maximum workload [8]:

$$\mathrm{VO_{2max}} = \mathrm{O_{2cost}} + \frac{\mathrm{W_c VO_{2rest}}}{\mathrm{M_d}}, \qquad (1)$$

where W_c is peak exercise workload (W), M_d is a body weight (kg), O_{2cost}=$18\,\mathrm{mlkg^{-1}W^{-1}}$ is O_2 cost of cycling against external load, and VO_{2rest}=$3.5\,\mathrm{mlkg^{-1}min^{-1}}$ is resting VO_2.

Lef atrial volume index (LAVI) was calculated by dividing LA volume by body surface area of subjects. LA volume was obtained using modified Simpson's methods by the means of three to six consecutive heart cycles. Measurement was performed by one experienced observer, who was blinded to the LAP values.

Weeks to event (WtE) were estimated in patients with AF recurrence as number of weeks elapsed between index procedure and first ocurrence of AF symptoms. Blanking period of 3 month were used according to HRS/EHRA/ECAS concensus statement [9]. WtE in repeated procedures were not considered in the study in patients with AF recurrence out of blanking period.

2.4. Statistical analysis

Results are reported as relative or absolute frequencies or mean±SD if they follow a normal distribution, and as median and interquartile range otherwise. Student t-test or Mann-Whitney U test were used for mutual comparisons of the groups, when appropriate. Between-group differences were compared by Chi-Square test. Pearson's parametric and biserial coefficient of correlation was used to quantify mutual relationships among continuous parameters and categorical parameters, respectively.

Candidate variables for the regression models were selected based on the absence of crosscorrelation. Multivariate-adjusted Cox regression analysis approache were used to asses predictive value of VO_{2max}, LAP_{rest} and other significant univariable predictors. The analyses were conducted in Python 3.6.

3. Results

The study comprised 98 patients with paroxysmal AF and preserved LV ejection fraction, most of them being overweight hypertensive men. Median follow-up time 104 weeks (87-133). Median time to AF recurrence was 54 (35–106) weeks when relapsing (Table 1). The median (LAP_{rest}) at rest was 11 mmHg. 21 and 47 patients has LAP elevated above 15 mmHg before and after excercise, respectively. Significant median deteoriation in VO_{2max} in patients with AF recurrence was $2.5\,\mathrm{mlkg^{-1}min^{-1}}$.

Figure 1 shows the strenght of relationship between analyzed parameters. Strong correlation was found primarily

Table 1: Baseline data of the study cohort divided in patients with and w/o AF recurrence after ablation procedure.

Parameters	AF-free	AF rec.	p
Counts	79 (81 %)	19 (19 %)	
Sex (female)	23 (29 %)	7 (37 %)	0.705
Age	62 (54—66)	62 (52-–63)	0.305
BMI	28 (25-–30)	30 (26-–34)	0.091
Hypertension	47 (59 %)	12 (63 %)	0.975
HLP	37 (47 %)	11 (58 %)	0.542
Diabetes	7 (9 %)	3 (16 %)	0.636
Obesity	20 (25 %)	9 (47 %)	0.107
LV function			
EF (%)	63.5±6.2	63.1±5.6	0.752
NYHA	2 (1—2)	2 (1—2)	0.227
LA params.			
LAVI	38±8	41±7	0.082
LAP_{rest}	10 (8–13)	12 (9–18)	0.074
LAP_{ex}	13 (9-–19)	20 (13-–26)	0.029
Excercise			
$Time_{ex}$	9.0 (6.3-–11.0)	6.5 (5—8.5)	0.001
$VO2_{max}$	13.0±2.4	10.5±2.0	0.001

between LAP before and after excercise (r=0.78), excercise time and peak VO_2 (r=0.80), and excercise time and sex (r_{pb}=0.68).

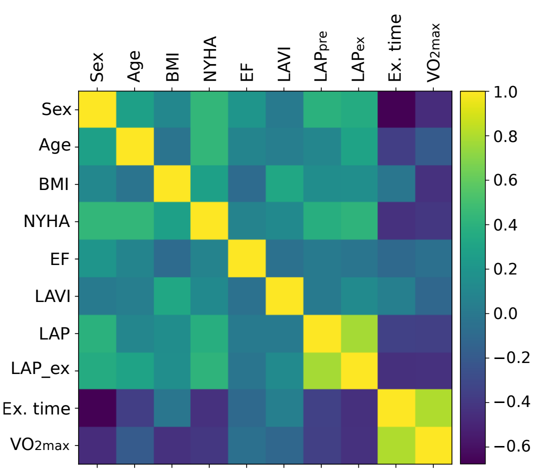

Figure 1: Correlation matrix of mutual relationships between clinical parameters.

In Table 2, the multivariate Cox regression model (best AIC=132.02 and C-statistics=0.83) adjusted for age, sex and left atrial volume revealed decreased excercise tolerance represented by decreased VO_{2max} as a strong predictor (significant OR 0.53; CI 0.39-–0.71) of early AF recurrence during 36 month follow-up. Elevated level of preexcercise LAP was also identified as significant predictor of AF recurrence, however, with lower OR 1.17 CI 1.02–1.33 compared to VO_{2max}.

The following variables were also tested stepwise but neither of them improved model performance nor reached statistical significance: a) comorbidities such as arterial hypertension, diabetes, HLP or obesity; b) ejection fraction; c) NYHA; and d) BMI.

Replacing LAP_{rest} by LAP_{ex} showed worsening of prediction error, and suprisingly insignificant contribution of LAP_{ex} with OR 1.04 CI 0.96–1.12 (p=0.35). As expected, including excercise time OR 0.99 CI 0.98–0.99 instead of peak VO_2 led to enhanced effect of age to OR 5.5.

Table 2: Multivariate analysis of post-ablation AF recurrence based on clinical, left atrial function and excercise-based predictors.

	Odds ratio	95% CI	p
Age (yrs)	0.93	0.88–0.98	**0.01**
Sex (Female)	2.97	0.88–10.05	0.08
LAVI	1.05	0.99–1.10	0.09
LAP_{rest}	1.17	1.02–1.33	**0.02**
VO_{2max}	0.53	0.39–0.71	$<$**0.005**

4. Discussion

As a main finding the multivariate analysis of baseline data identified female sex, elevated left atrial pressure and deterotiated cardiopulmonary function as independent predictor of AF recurrence.

Sufficient evidence has been provided on the excercise impairment and lowered peak VO_2 adjusted to body weight in patients with AF compared to a group of healthy heart rate standardized controls [10, 11]. However, the association between AF recurrence and cardiopulmonary function was firstly reported by Yamashita et al. [4] in 31 patients undergoing excercise 1 month after ablation. Their results indicated that the peak VO_2 could be clinically useful for the prediction of AF recurrences after AF ablation with AUC over 0.75, and a sensitivity and specificity of about 70 %. Our study provides consistent results and complementary information about preoperative cardiopulmonary reserve in AF patients with up to 36 months follow-up after ablation. Reduced cardiopulmonary function is thought to be in association with pathological conditions such as hypertension, diabetes mellitus, congestive heart failure, or valvular disease. Together with advanced age and female sex those are known AF risk factors. One can thus hypothesise it could partly account for the relationships between peak VO_2 and AF recurrence.

The evidence of relationship between left atrial hypertension and AF recurrence after ablation procedure has been previously reported by Sramko et al. [5]. The study showed the presence of either resting or exercise-induced abnormal elevation of LAP predicted the outcome of ablation independently from other known risk factors. The cohort includes both patients with paroxysmal and persistant AF, suggesting some of the LAP measurements could be carried out during an ongoing AF. In our study we find only small and insignificant association between abnormal post-excercise LAP and AF recurrence measured in patients with paroxysmal AF and sustained sinus rhythm. On the other hand the differences in resting LAP between patients with succesfull ablation and AF recurrence imply that the assessment of the LA hemodynamics could be used clinically to test of the overall LA condition.

The study did not find any significant link between common comorbidities and AF recurrence which is in contradiction to data from German ablation registry [6].

4.1. Limitations

There are several limitations in the study, which includes a small study population without healthy controls. Yet, it is still the largest study to this date to seek the relationship between peak VO_2 and other parameters with long term efficacy of AF ablation. Due to echocardiography feasibility the study analyzed group of patients with normal LVEF and those who were referred to catheter ablation for paroxysmal form of AF. Eventhough the study followed common stress testing recommendations, the estimation of peak VO_2 might be biased by using linear body weight corrected model instead of direct measurement. Moreover, obtained values of VO_2 are significantly lower than one should expected in the population of patients with AF. It can be partially explained by non-standard testing environment, where excercise test was performed on EP lab patient table under sterile conditions.

5. Conclusion

Presence of either decreased exercise capacity or elevated left atrial pressure is able to identify patients with potentially impaired left atrial function and different clinical outcome after conventional pulmonary vein isolation.

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