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Predictors of atrial fibrillation recurrence after atrial fibrillation ablation with cryoballoon

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Abstract

Background: *Catheter ablation of atrial fibrillation is recommended for patients with symptomatic paroxysmal atrial fibrillation (PAF) despite anti-arrhythmic drugs (AADs). Radiofrequency ablation is widely accepted as an effective treatment for PAF. Cryoenergy by cryoballoon technique is an alternative to radiofrequency (RF) ablation. Cryoballoon ablation is safe, and has a similar success rate in comparison to RF ablation. AF recurrence with cryoballoon ablation is roughly 30%. The aim of this study is to determine the predictors of AF recurrence after cryoballoon ablation.*

Methods and Results: *Sixty one patients with symptomatic PAF despite AADs without structural heart disease were included. Cryoballoon ablation was performed in 60 patients (36 males, mean age: 54.6 ± 10.7, mean left atrium size: 3.74 ± 0.39 mm). Transthoracic echocardiography including tissue Doppler imaging was performed in all subjects during sinus rhythm at baseline and after the ablation. Intra-atrial and inter-atrial electromechanical delays, and PA-lateral were measured. All patients were scheduled for 24 h Holter recording at baseline and at 3, 6, 9 months follow-up. Venous samples were collected to measure CK-MB, Troponin-T (TnT), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels at baseline and 24 h after ablation. Median follow up was 10 (8–12) months. Forty eight (80%) patients were in sinus rhythm during the follow up. In receiver operating curve (ROC) analysis, intraleft atrial electromechanical delay and PA-lateral achieve an area under the curve (AUC) 0.97 ($p < 0.001$) and 0.69 ($p < 0.001$) for the ability to predict AF recurrence. A cut-off value for baseline intraleft atrial electromechanical delay of 29.5 ms predicted AF recurrence with sensitivity of 85% and specifity of 98%. A cut-off value for PA-lateral of 125 ms predicted AF recurrence with sensitivity of 80% and specifity of 90%. In ROC analysis, age achieves an AUC 0.822 ($p = 0.006$) for the ability to predict AF recurrence. A cut-off value for age of 64 predicted AF recurrence with sensitivity of 71% and specifity of 90%. Early recurrence of AF (HR = 60, 95% CI 18.61–417.86, $p < 0.001$) predicted also late recurrence of AF.*

Conclusions: *The increase in AF recurrence by increased intraleft atrial electromechanical delay, PA-lateral and older age show the importance of substrate in AF mechanism. Early recurrence was the strongest predictor of late recurrence of AF; therefore, existence of blanking period for cryoballoon ablation should be questioned.* (Cardiol J 2013; 20, 3: 294–303)

Key words: cryoballoon ablation, intraleft AEMD, early atrial fibrillation recurrence

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. The treatment approach for AF includes either restoration and mainteinance of sinus rhythm or ensuring adequate ventricular rate control. Maintainance of sinus rhythm may be provided by anti-arrhythmic drugs (AADs) or catheter ablation. Catheter ablation of AF is recommended for patients with symptomatic paroxysmal atrial fibrillation (PAF) despite AADs [1]. Pulmonary vein isolation (PVI) has become a major curative measure of AF in drug resistant patients [2, 3]. Radiofrequency (RF) ablation is widely accepted as an effective treatment for PAF. Performing point-by-point ablation using RF energy is challenging. Cryoenergy by cryoballoon technique is an alternative to RF ablation. Balloon-based cryoenergy for PVI simplifies the reliable creation of a complete circumferential lesion around the pulmonary veins (PV) with only a limited number of applications. Cryoballoon ablation is safe, and has a similar success rate, when compared to RF ablation with comparable procedure and fluoroscopy times in patients suffering from PAF [4]. However, reported 1 year success rates are limited to 60–74% [5–8]. Therefore, the aim of this study is to identify the predictors of success specifically in patients undergoing cryoballoon ablation for PAF.

Methods

Patients

Sixty one consecutive patients without structural heart disease with symptomatic PAF resistant to one or more AADs, who were referred for catheter ablation to Hacettepe University Hospital, were enrolled in this study. During transseptal puncture cardiac tamponade occurred in one patient and he was treated by percutaneous pericardiosynthesis. The process was terminated and that patient was not included in the analysis. Residual 60 patients (36 males, mean age 54.6 ± 10.7) were followed and analyzed. European Heart Rhythm Association (EHRA) symptom scores of all patients were recorded. Alcohol consumption of patients was inquired; patients were classified as nondrinkers, moderate drinkers (having up to 1 drink per day for women and up to 2 drinks per day for men) and heavy drinkers (more than moderate drinking) [9]. Before and 24 h after the ablation cardiac enzymes (CK-MB, troponin-T [TnT]) and inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) were measured.

Patients were followed with routine and symptom-driven ambulatory monitoring at hospital. Follow-up was scheduled at 3, 6, 9, and 12 months following ablation. Patients resumed their oral anticoagulation and AAD, except amiodarone, following ablation for at least 3 months. If they had remained in sinus rhythm, their AADs would have been discontinued at the 3-month follow-up visit. Anticoagulation decision after 3 months was made according to CHA_2DS_2-VASc stroke risk score.

Transesophageal echocardiography was performed on all candidates to exclude the presence of thrombi.

Recurrence was defined as any documented atrial tachyarrhythmia (AF or an organized atrial tachyarrhythmia) lasting at least for 30 s. Recurrences that occurred at any time during the 3-month blanking period following ablation were classified as early, recurrences beyond the 3-month blanking period following the procedure were classified as late [3].

The exclusion criteria were as follows: (1) patients who had structural heart disease, moderate-severe valvuler disease, (2) ejection fraction (EF) < 55% (measured by transthoracic echocardiogram), (3) left atrial diameter > 50 mm, (4) patients who had hyperthyroidism, (5) contraindication to anticoagulation.

All patients gave their written informed consent prior to inclusion in the study. The study was approved by the local institutional ethics committee.

Electrocardiographic evaluation

Standard ECG were taken from all patients with sweeping rate of 25 mm/s and amplitude of 1 mV/cm. P-wave dispersion (PWD), defined as the difference between Pmax and Pmin, was manually measured from 12-lead ECG during sinus rhythm by 2 independent and experienced investigators using magnifying lens and calipers [10, 11].

Transthorasic echocardiography

Transthorasic echocardiographic examination was performed on all subjects using a SystemFive (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound scanner with 2.5–3.5 MHz transducers. Left atrial diameter and left ventricular end diastolic diameter were measured in anatomical M-mode in a parasternal long axis view. Left ventricular (LV) EF was measured according to the modified Simpson's method using apical 4- and 2-chamber views. Pericardial effusion was determined before the ablation and in the first day after the ablation.

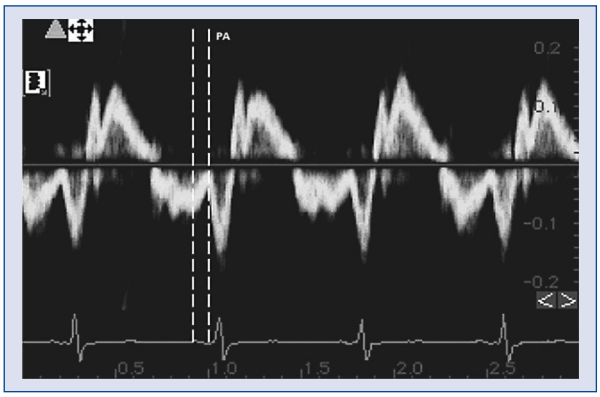

Figure 1. Time interval from the onset of P wave on surface ECG to the beginning of A wave (PA).

Lead II electrocardiogram was recorded continuously. Pulsed wave tissue Doppler echocardiography was performed by transducer frequencies of 3.5–4.0 MHz, adjusting the spectral pulsed Doppler signal filters up to a Nyquist limit of 15–20 cm/s, and using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. In apical 4-chamber view, the pulsed Doppler sample volume was subsequently placed at the level of LV lateral mitral annulus, septal mitral annulus and right ventricular (RV) tricuspid annulus. Tissue Doppler pattern was characterized by a positive myocardial systolic wave (S) and 2 negative diastolic waves; early (E) and atrial (A). Time intervals from the onset of P wave on the surface ECG to the beginning of A wave (PA) representing atrial electromechanical delay (AEMD) were obtained from lateral mitral annulus, septal mitral annulus and RV tricuspid annulus, and named as lateral PA, septal PA and RV PA respectively (Fig. 1). The timing of mechanical activation of each reference point, namely lateral mitral, septal mitral and RV tricuspid annuli, depends on the distances of these points to sinus node.The RV tricuspid annulus is the earliest, and lateral mitral annulus are the latest points to be activated by the impulse arising from the sinus node. Therefore, it is hypothesized that the difference between any 2 reference points reflects the mechanical delay between these 2 points. The difference between septal PA and RV PA was defined as intra-right AEMD (septal PA–RV PA), the difference between lateral PA and septal PA was defined as intraleft AEMD (lateral PA–septal PA), and the difference between lateral PA and RV PA (lateral PA–RV PA) was defined as inter-AEMD [12, 13]. Echocardiographic analysis was performed by the same echocardiographer in order to eliminate inter-observer variability. All patients were examined before the ablation.

Computerized tomography

All patients (61) were evaluated with contrast enhanced cardiac computed tomography (CT) angiography before the ablation. Multidetector row CT technology was used (Definition, Siemens Medical Solutions, Erlangen, Germany). ECG-referenced scans were performed after intravenous administration of contrast material. Because pulmonary vein assessment was the primary clinical goal, 1.5-mm-thick images were reconstructed. Standard clinical workstation (Leonardo, Siemens) was used and advanced 3D off-line postprocessing was performed. The 3D CT dataset was reconstructed to obtain standard cardiac views as used in echocardiography. We first reconstructed standard 2- and 4-chamber views. Left atrium (LA) size was determined by manually tracing the LA borders in the 4-chamber view and using computer software that calculates the outlined area. The short-axis view was reconstructed as a plane perpendicular to the long axis of these 2 views at the level of the mid LA. In this short-axis view, the periatrial epicardial fat thickness was measured (in cm) as the shortest distance between the mid LA wall and 3 anatomic landmarks: esophagus (E–LA), main pulmonary artery (LA–PA), and descending thoracic aorta (Ao–LA) (Fig. 2). These measurements were prospectively determined, based on preliminary reviews of representative CT scans before starting the study, which showed that the esophagus, PA, and thoracic aorta were readily identifiable anatomic structures that could be used to measure LA epicardial fat [14].

Measurements were made using digital calipers by a single investigator with an intraobserver reproducibility of 0.961 (95% confidence interval [CI] 0.912–0.986; intraclass correlation, same below) on measurements of LA area and 0.972 (95% CI 0.932–0.998) on measurements of epicardial fat. In a sample of 40 randomly selected patients, the interobserver reliability was 0.952 (95% CI 0.920–0.971) on measurements of LA area and 0.975 (95% CI 0.948–0.992) on measurements of epicardial fat.

Ablation procedure

PVI using the cryoballoon technique (ArcticFrontTM, Cryocath, Quebec, Canada) was performed as described before [7, 8, 15]. The 28 mm balloon was used. With the deflated balloon

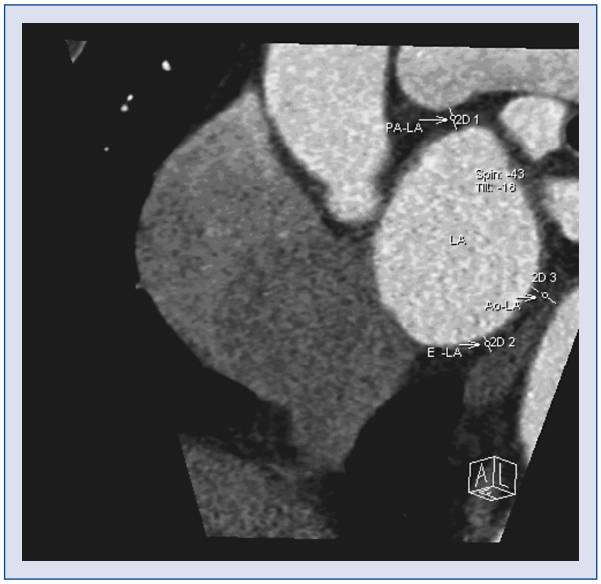

Figure 2. In this view, the thickness of the epicardial fat can be demonstrated between the LA and 3 anatomic landmarks: esophagus, main pulmonary artery, and descending thoracic aorta; PA — main pulmonary artery; LA — left atrium; Ao — descending aorta; E — esophagus; PA-LA — peri-atrial epicardial fat located between mid left atrium and pulmonary artery; E-LA — periatrial epicardial fat located between mid left atrium and esophagus; Ao-LA — periatrial epicardial fat located between mid left atrium and descending aorta. Orientation cube: A — anterior; F — feet; L — left.

catheter inside the sheath, a guidewire was placed in one of the pulmonary vein (PV) branches. The balloon was then advanced towards the PV ostium and inflated. We aimed for at least 2 cryoballoon ablations on every targeted PV. Additional delivery of cryoenergy was applied after the guidewire was placed in different branches of the PV with early branching, which usually allowed for better contact of the balloon at different sites of the PV antrum. Application time was 240 to 400 s per freeze. If PV occlusion was not achieved by simply pushing the balloon against the PV ostium, additional techniques, previously described as "hockey stick technique" and "pull-down technique", were performed [6]. A 6-F decapolar catheter was advanced to the coronary sinus for anatomical guidance and pacing, it was also used to measure the intra-left atrial conduction time (ILCT). ILCT was measured as the difference between atrial electrograms in proximal and distal CS electrodes [16].

A multipolar catheter was placed in the superior vena cava for phrenic nerve stimulation during ablation of the right-sided PVs. The PVs were checked for isolation 20 min after the last application in the same order as they had been frozen with a circular mapping catheter (LASSO, Biosense Webster, USA).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (version 20.0, SPSS, Inc., Chicago, U.S.). Continuous variables are reported as mean ± standard deviation (SD) or median, interquartile range (IQR). Categorical variables are presented as number (percentage) and were compared by means of the χ^2 test. Continuous variables were analyzed for a normal distribution using the Kolmogorov-Smirnov test and Shapiro-Wilk test. Comparison of continuous variables was performed using the Student's t-test. For comparing nonparametric variables Mann-Whitney U test and Wilcoxon Rank Tests were used. Univariable and multivariable Cox proportional hazard analyses were performed to investigate predictors of AF recurrence after cryoballoon ablation. Age, gender, hypertension, coronary artery disease, alcohol consumption, AF duration, LA diameter, LA volume, EF, EHRA symptom score, pericardial effusion, biomarkers, p wave dispersion, ILCT, PA septal, PA lateral, PA tricuspit, intra-right AEMD, intra-left AEMD, inter AEMD, epicardial fat thickness, and early recurrence of AF were included in the univariable analyses. Variables with a p value < 0.05 in the univariate analysis were included into the multivariate analysis. Multivariate analysis was performed using a backward stepwise conditional approach. Event-free survival was calculated by Kaplan-Meier analysis as the time from initial pulmonary vein isolation to the first documented AF episode. Receiver operating characteristics (ROC) curve analysis was performed to establish the parameters that can best predict the arial fibrillation recurrence and the best cut-off points for those parameters. Correlation was tested with Pearson correlation coefficient. P value less than 0.05 was considered statistically significant.

Results

We analyzed 60 patients (36 males) with mean age of 54.6 ± 10.7 and LA size of 3.74 ± 0.39 mm; EF of 66.00 ± 5.09; unsuccessful AAD number of 1.36 ± 0.6; median EHRA score of 3. All patients had used at least 1 AAD and 16 (26%) of patients used amiodarone. Other AADs were propafenon,

Table 1. Baseline clinical characteristics of patients.

Age (mean)	54.6 ± 10.7
Male	36 (60%)
Coronary artery disease	5 (8.3%)
Hypertension	23 (38.3%)
Alcohol consumption	13 (21.6%)
Previous AF ablation	7 (11.6%)
AF duration (months, median, IQR)	36 (24–96)
Amiodarone	16 (26.6%)
Antiarrhythmic drug	1.36 ± 0.6
EHRA symptom score (median)	3
P wave dispersion [ms]	46.40 ± 8.2
Intra-left atrial conduction time [ms]	26 ± 8

AF — atrial fibrillation; EHRA — European Heart Rhythm Association

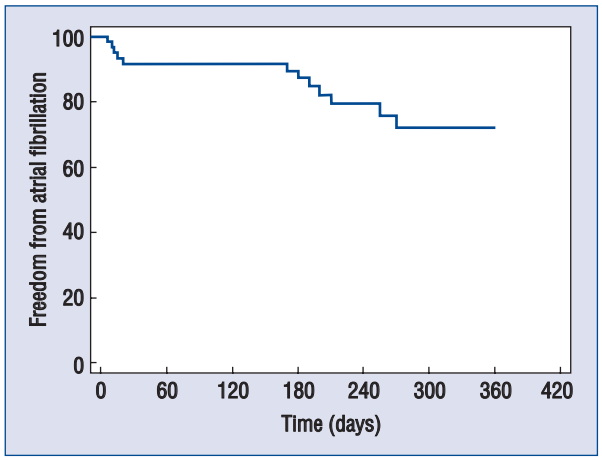

Figure 3. Kaplan-Meier plot on event free survival to first ECG documented atrial fibrillation period postablation.

Table 2. Baseline echocardiographic parameters of patients.

Left atrium diameter [cm]	3.74 ± 0.39
Left atrium volume [mL]	48 ± 3
Ejection fraction [%]	66.00 ± 5.09
PA septal [ms]	106.28 ± 15.96
PA lateral [ms]	126.57 ± 26.6
PA tricuspit [ms]	88.64 ± 17.57
Intra-right AEMD [ms]	16.9 ± 9.2
Intra-left AEMD [ms]	24.43 ± 6.96

AEMD — atrial electromechanical delay

sotalal and dronaderone. Five (8.3%) patients had coronary artery disease and 23 (38.3%) patients had hypertension. Thirteen (21.6%) patients were moderate alcohol drinkers, others were nondrinkers, there were no heavy alcohol drinkers. Seven (11.6%) patients had previous radiofequency (RF) ablation procedure. Baseline clinical characteristics and echocardiographic parameters are shown in Tables 1 and 2. The procedural end-point of PV isolation was reached in all patients.

All biomarkes were in the normal range before the procedure and all of the biomarkers increased after the procedure (Table 3).

Follow up

Patients were followed for a median of 10 (8–12) months. Eighty percent of patients reached to 1 year follow up. Patients had an ECG recorded at each follow-up visit along with Holter monitoring (24 h) 3, 6, and 12 months following the ablation. AF recurred in the first 3 months in 10 patients (17%) and in 8 patients of those (80%) AF recurred after first 3 months. RF ablation was performed for 2 patients and reconnection was seen in the left lower PV. Six patients were followed with AAD. Three of these patients experienced typical atrial flutter, 1 patient experienced LA tachycardia and other 6 had AF. Forty eight (80%) patients were in sinus rhytm during the follow up (Fig. 3).

Factors related to late recurrence of AF

Univariate and multivariate Cox proportional hazard analyses were performed for predictors of late recurrence of AF. The clinical features of patients with and without late recurrence of AF are shown in Table 4. Significant univariate predictors of AF recurrence following ablation were: age (HR = 1.18, 95% CI 1.05–1.33, p = 0.006), EHRA symptom score (HR = 13.43, 95% CI 2.21–81.71, p = 0.005), intra-left AEMD (HR = 1.57, 95% CI 1.16–2.12, p = 0.003), PA-lateral (HR = 1.12, 95%

Table 3. Post-procedure biomarkers' values.

Biomarker	Post-prosedure	Normal limits
C-reactive protein median (min, max)	0.82 (0.01–4.07) mg/dL	0–0.8 mg/dL
Troponin-T median (min, max)	0.41 (0.01–1.16) ng/mL	< 0.014 ng/mL
CK-MB median (min, max)	18.4 (2.69–56.88) ng/mL	0–4.94 ng/mL

Table 4. Characteristics of patients with and without late recurrence of AF.

Variable	Late recurrence of AF	No recurrence	P
Age	61.75 ± 9.91	52.80 ± 10.25	0.002
Gender (M/F)	29/19	7/5	0.98
Hypertension	6	17	0.41
Coronary artery disease	3	2	0.52
EHRA symptom score	4	3	0.001
Alcohol consumption	5/12 (41.66%)	8/48 (16.6%)	0.07
Intra-left AEMD [ms]	34.14 ± 9.45	23.09 ± 5.43	< 0.001
PA septal [ms]	107.32 ± 16.82	106 ± 14. 72	0.73
PA lateral [ms]	134.57 ± 16.66	120 ± 13.72	< 0.001
PA tricuspit [ms]	90.62 ± 16.62	86.72 ± 12.54	0.62
Intra-right AEMD [ms]	18.8 ± 4.72	14.92 ± 5.64	0.72
Inter AEMD [ms]	42.38 ± 14.04	38.64 ± 10.44	0.46
Early recurrence of AF	8/12 (66.7%)	2/46 (4.2%)	< 0.001
PAF duration (median) [month]	60	36	0.35
LA diameter [cm]	3.75 ± 0.39	3.68 ± 0.39	0.55
LA volume [mL]	49 ± 3	46 ± 2	0.72
Ejection fraction [%]	65.50 ± 3.52	66.15 ± 5.45	0.63
E-LA [cm]	0.48 ± 0.07	0.46 ± 0.09	0.56
PA-LA [cm]	0.62 ± 0.16	0.68 ± 0.2	0.42
Ao-LA [cm]	0.39 ± 0.11	0.50±0.14	0.053
P wave dispersion [ms]	51.22 ± 6.12	42 ± 4.82	< 0.001
Intra-left atrial conduction time [ms]	36.22 ± 8.42	22.22 ± 5.23	< 0.001

AF — atrial fibrillation; LA — left atrium; EHRA — European Heart Rhythm Association; AEMD — atrial electromechanical delay, PA-LA — peri-atrial epicardial fat located between mid left atrium and pulmonary artery; E-LA — periatrial epicardial fat located between mid left atrium and esophagus; Ao-LA — periatrial epicardial fat located between mid left atrium and descending aorta

CI 1.01–2.02 p = 0.006), PWD (HR = 1.36, 95% CI 1.10–1.96, p < 0.003), ILCT (HR = 1.40, 95% CI 1.18–2.02, p < 0.001) and early recurrence of AF (HR = 60, 95% CI 18.61–417.86, p < 0.001). We also looked at data and determined if a correlation existed between intra-left AEMD and ILCT and p wave dispersion. Intra-left AEMD and ILCT showed a moderate positive correlation (r = 0.694, p < 0.001), intra-left AEMD and p wave dispersion showed weak positive correlation (r = 0.482, p < 0.001) (Fig. 4).

AF duration prior to ablation, gender, coronary artery disease, hypertension, alcohol usage, LA diameter, LA volume, EF, biomarkers, epicardial fat, pericardial effusion were not related to late recurrence of AF.

Following multivariate analysis, significant predictors of AF recurrence were the same as the univariate analysis.

ROC curve analysis of intra-left AEMD, PA lateral and age showed that they had AUC of 0.973; 0.694 and 0.821 (ROC curves analysis, p < 0.001) (Fig. 5). The sensitivity of intra-left AEMD ≥ 29.5 ms for predicting AF recurrence was 85% with a specificity of 98%. The sensitivity of PA lateral ≥ 125 ms for predicting AF recurrence was 80% with a specificity of 90%. The sensitivity of 64 years age for predicting AF recurrence was 71% with a specificity of 90%.

Discussion

In this study, we investigated the predictors of recurrence in patients undergoing cryoballoon ablation for paroxysmal AF. The main findings were as follows: clinical success in regard to the freedom from recurrent AF was 80%, early recurrence of AF was the most important predictor of late recurrence of AF, intra-left AEMD, PA lateral, EHRA symptom score and age predicted late recurrence of AF. Atrial fibrillation duration prior to ablation, gender, coronary artery disease, hypertension, alcohol consumption, LA diameter, LA volume, EF, biomarkers, epicardial fat, pericardial effusion did not predict late recurrence of AF.

One year success of AF ablation in other studies was 60–70% [17, 18]. Eighty percent success of our study may be the result of normal LA dimen-

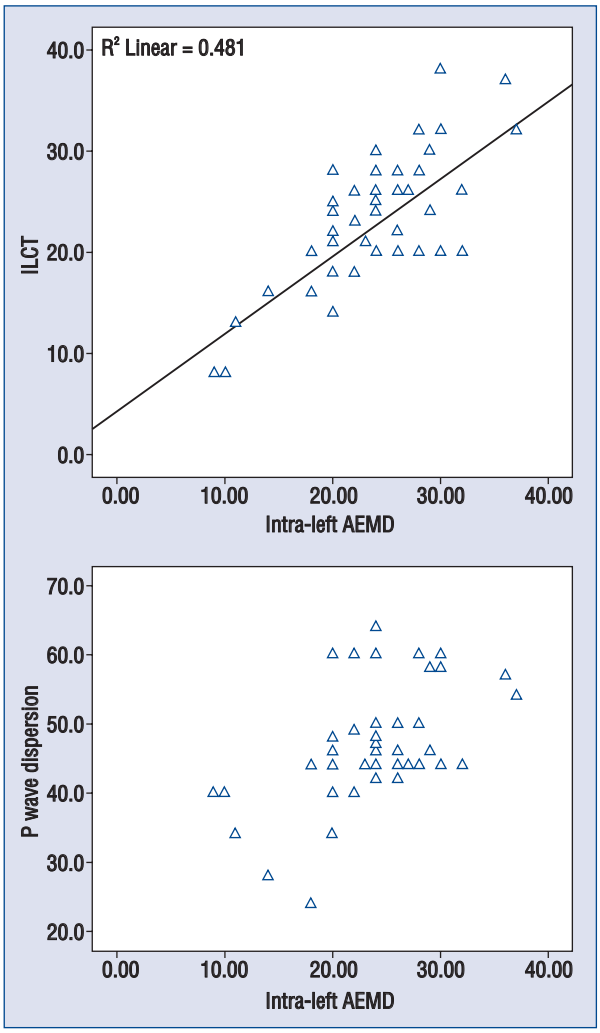

Figure 4. Scatter plot graphs showing the correlations between intra-left atrial electromechanical delay (AEMD) and intra-left atrial conduction time (ILCT) and p wave dispersion.

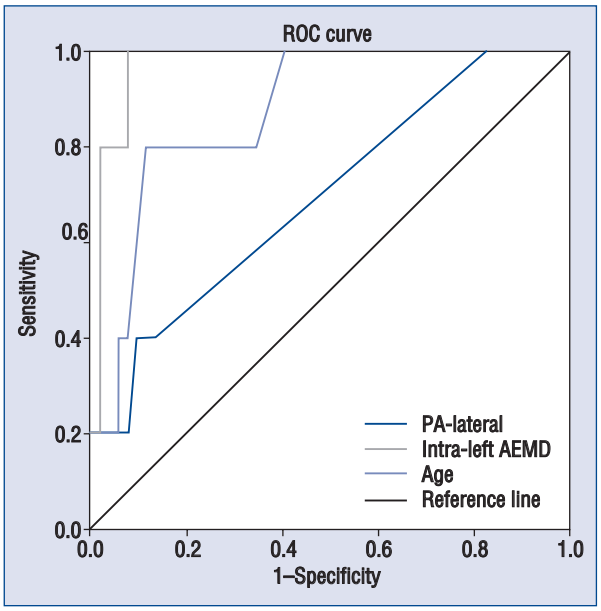

Figure 5. Receiver operating characteristic curves for intra-left atrial electromechanical delay (AEMD) (AUC: 0.97, 95% CI 0.93–1.00, $p < 0.001$), PA-lateral (AUC: 0.69, 95% CI 0.45–0.93, $p < 0.001$) and age (0.87, 95% CI 0.74–1.00, $p < 0.006$).

sions, inclusion of only PAF patients, no structural heart disease, and single center study.

Previous studies showed that postablation inflammation around PVs caused increase in inflammatory markers and cardiac enzymes [19, 20]. When cryoballoon ablation is performed, lesion formation occurs at the entire circumference of the balloon and that results in a long circumferential lesion. The higher rise of biomarkers indicates more myocardial injury. However, this did not translate into late ablation success in our study. These markers represent overall inflammation and injury, they don't represent each PV separately. Therefore, higher rise may represent the sum of one transmural lesion and one superficial lesion.

AF ablation creates large lesions and this may play a role in effusion formation. Ten percent of our patients had pericardial effusion. Pericardial effusion may be a sign of lesion thickness. Pericardial effusion and late recurrence of AF were not related ($p > 0.05$) in our study, it may be due to the fact that it is a nonspesific sign of injury as biomarkers.

Batal et al. [14] demonstrated that increased posterior LA fat thickness was associated with AF burden independent of age, body mass index, or LA area. They tought that local inflammatory mediators produced by the periatrial epicardial fat in the LA posterior wall promoted the activation of ectopic foci in the PV ostia. In our study we could not find any relationship between periatrial adiposity and late recurrence of AF.

Ethanol and its metabolite acetaldehyde have been shown to increase levels of circulating catecholamines. Ethanol may also induce oxidative stress and release of plasma free fatty acids. These indirect effects of ethanol may be arrhythmogenic, particularly in individuals prone to AF such as patients with focal AF. A meta-analysis supported these pathophysiologic expression and showed that habitual heavy alcohol drinking was associated with an increased risk of AF [21].

In our study there was no relationship between alcohol intake and late recurrence of AF. It may be related to our patient population, because all of our patients were moderate alcohol drinkers and nondrinkers.

In our study we could not find any stastical significant relationship between late recurrence of AF and LA diameter, LA volume and EF, it may be related to their normal values. Perhaps LA anatomical remodelling was less in our group. There was no relationship with AF duration also, it may be because it doesn't demonstrate the AF frequency and AF episode duration, so it doesn't reflect atrial remodeling.

High EHRA symptom score was related to late recurrence of AF, perhaps it is because these patients have more symptomatic PAF episodes than the others.

Age

It was shown that age was a strong predictor of AF recurrence in patients with maze procedure and RF AF ablation [22–25]. Ageing leads to interstitial fibrosis and more extensive LA remodeling; therefore it increases the likelihood of additional AF triggers, which may predispose to recurrent AF after limited ablation. By ageing scar in the LA increases, the presence of LA scar is more important than enlargement in predicting AF recurrence [26]. In our study, as in the previous studies, age was predictor of late recurrence of AF and when the cut-off point of age is 64 the sensitivity for predicting AF recurrence was 71% with a specifity of 90%. This result reminds about the importance of the substrate in spite of normal LA dimensions.

Intra-left AEMD, P wave dispersion, ILCT, PA lateral

Development of AF requires a "trigger" and an anatomic or functional substrate capable of both initiation and perpetuation of AF. Atrial remodeling constitutes for substrate. Atrial remodeling develops in 3 levels; electrical, cellular and anatomical. The electrical remodeling process contributes to the increasing stability of AF during the first days after its onset. Electrical remodeling in AF is described as shortening of atrial effective refractory period, discordance of atrial effective refractory period with heart rate and increase in intra-atrial conduction time. Short refractory period and delayed conduction may increase the number of daughter wavelets. Relation between Inter-atrial and intra-atrial conduction block and AF was shown in previous studies [27, 28].

In our study intra-left AEMD, P wave dispersion, ILCT and PA lateral were shown as predictors of late recurrence of AF ($p < 0.001$). There was moderate correlation between intra-left AEMD and ILCT, and weak correlation between intra-left AEMD and p wave dispersion. These results are similar to the results of Deniz et al. [29] study. Therefore, intra-left AEMD can be used as indictor of atrial conduction time for prediction of sinus rhythm maintenance.

Deniz et al. [30] demonstrated an increase in intra-left atrial mechanical delay in PAF patients and this delay was an independent risk factor for PAF. den Uijl et al. [31] demonstrated relationship between PA lateral and late recurrence of AF. In our study the area under the ROC curve (index of discrimination) for PA lateral was 0.69 ($p < 0.001$), indicating a low discriminative power. The intra-left AEMD demonstrated a higher degree of discrimination than PA lateral with an area under the ROC curve of 0.97 ($p < 0.001$).

All of these show importance of LA remodeling in AF recurrence with normal LA dimensions.

Early recurrence of AF (ERAF)

In previous RF ablation studies early recurrence was observed in 33.8–54% of patients [32–35], so early recurrence was traditionally seen as a benign process not affecting long term results. Then, a lot of studies showed that ERAF was an important risk factor for late recurrence of AF [33, 35–40]. The possible causes of ERAF are: (1) transient stimulatory effect of acute inflammatory response following the histopathologic tissue damage that resulted from RF energy; (2) reconnection of electrical conduction between the LA and PVs and/or resumption of electrical activity in pre-ablation lines; (3) non-PV foci triggering AF, and (4) transient imbalance of autonomic nervous system [35].

In our study, ERAF (HR = 60, 95% CI 18.61–417.86, $p < 0.001$) was the most important predictor of late recurrence of AF. ERAF was seen in 10 patients (17%). ERAF percent was lower in our study, it may be due to the choice of using cryoenergy in our study. Therefore, there was a smaller inflammation reaction, smaller triggering effect and all of our patients were PAF patients with normal LA dimensions, so that is why there were less triggers out of PVs. Usually, in RF ablation studies, 50% of patients with ERAF get better [32, 33, 39, 41], but in our study there had been no improvement in 8 (80%) patients with ERAF and in these patients late recurrence was seen. This may be because of

the fact that we used cryoenergy and others used RF energy. RF energy causes larger inflammation and this may trigger early AF but cryoenergy causes less inflammation so it has less triggering effect. When there is an early recurrence with cryoenergy it is probably because of reconnection. There is a blanking period description for RF ablation but we advise to revise the existence of blanking period for cryoballoon ablation.

Limitations of the study

A relatively small number of patients is the main limitation of our study. The follow up period is not long enough (1 year). Some asymptomatic recurrence may be undetected without the use of long-term recording. Substrate, as a predictor of recurrence, could have been visualized better by magnetic resonance imaging.

Conclusions

Our study is the first study showing the relation between intra-left AEMD and late recurrence of AF. It is a better predictor than PA lateral. Age is an important factor for late recurrence of AF. These three parameters indicate the importance of atrial remodeling and atrial substrate. Extended ablation techniques may be used for such patients. Early recurrence of AF is the most important predictor of late recurrence of AF in cryoballoon ablation patients. Existence of blanking period should be reevaluated for cryoballoon ablation.

Conflict of interest: none declared

References

1. Calkins H, Kuck KH, Cappato R et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace, 2012; 14: 528–606.
2. Fuster V, Ryden LE, Cannom DS et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J, 2006; 27: 1979–2030.
3. Calkins H, Brugada J, Packer DL et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: Recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm, 2007; 4: 816–861.
4. Linhart M, Bellmann B, Mittmann-Braun E et al. Comparison of cryoballoon and radiofrequency ablation of pulmonary veins in 40 patients with paroxysmal atrial fibrillation: a case-control study. J Cardiovasc Electrophysiol, 2009; 20: 1343–1348.
5. Van Belle Y, Janse P, Theuns D, Szili-Torok T, Jordaens L. One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace, 2008; 10: 1271–1276.
6. Chun KR, Schmidt B, Metzner A et al. The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. Eur Heart J, 2009; 30: 699–709.
7. Neumann T, Vogt J, Schumacher B et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol, 2008; 52: 273–278.
8. Van Belle Y, Janse P, Rivero-Ayerza MJ et al. Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: Feasibility, complications, and short-term outcome. Eur Heart J, 2007; 28: 2231–2237.
9. Alcohol and Public Health Available from: http://www.cdc.gov/alcohol/faqs.htm.
10. Andrikopoulos GK, Dilaveris PE, Richter DJ, Gialafos EJ, Synetos AG, Gialafos JE. Increased variance of P wave duration on the electrocardiogram distinguishes patients with idiopathic paroxysmal atrial fibrillation. Pacing Clin Electrophysiol, 2000; 23: 1127–1132.
11. Ozdemir O, Soylu M, Demir AD et al. Does p-wave dispersion predict the atrial fibrillation occurrence after direct-current shock therapy? Angiology, 2006; 57: 93–98.
12. Ozer N, Yavuz B, Can I et al. Doppler tissue evaluation of intra-atrial and interatrial electromechanical delay and comparison with P-wave dispersion in patients with mitral stenosis. J Am Soc Echocardiogr, 2005; 18: 945–948.
13. Valzania C, Rocchi G, Biffi M et al. Left ventricular versus biventricular pacing: a randomized comparative study evaluating mid-term electromechanical and clinical effects. Echocardiography, 2008; 25: 141–148.
14. Batal O, Schoenhagen P, Shao M et al. Left atrial epicardial adiposity and atrial fibrillation. Circ Arrhythm Electrophysiol, 2010; 3: 230–236.
15. Nolker G, Heintze J, Gutleben KJ et al. Cryoballoon pulmonary vein isolation supported by intracardiac echocardiography: Integration of a nonfluoroscopic imaging technique in atrial fibrillation ablation. J Cardiovasc Electrophysiol, 2010; 21: 1325–1330.
16. Josephson ME. Electrophysiologic investigation. In: Josephson ME ed. Clinical cardiac electrophysiology: Techniques and interpretation. 4th Ed. Wolters Kluwer/Lippincott Williams and Wilkins, Philadelphia 2008: 20–68.
17. Andrade JG, Khairy P, Guerra PG et al. Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies. Heart Rhythm, 2011; 8: 1444–1451.
18. Packer DL, Irwin JM, Champagne J et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: First results of the North American Arctic Front STOP-AF pivotal trial. J Am Coll Cardiol, 2010; 55: E3015–E3016.
19. Schmidt M, Marschang H, Clifford S et al. Trends in inflammatory biomarkers during atrial fibrillation ablation across different catheter ablation strategies. Int J Cardiol, 2012; 158: 33–38.
20. Kuhne M, Suter Y, Altmann D et al. Cryoballoon versus radiofrequency catheter ablation of paroxysmal atrial fibrillation: Biomarkers of myocardial injury, recurrence rates, and pulmonary vein reconnection patterns. Heart Rhythm, 2010; 7: 1770–1776.

21. Kodama S, Saito K, Tanaka S et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. J Am Coll Cardiol, 2011; 57: 427–436.
22. Lee SH, Kim JB, Cho WC et al. The influence of age on atrial fibrillation recurrence after the maze procedure in patients with giant left atrium. J Thorac Cardiovasc Surg, 2011; 141: 1015–1019.
23. Tzou WS, Marchlinski FE, Zado ES et al. Long-term outcome after successful catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol, 2010; 3: 237–242.
24. Winkle RA, Mead RH, Engel G, Patrawala RA. Long-term results of atrial fibrillation ablation: the importance of all initial ablation failures undergoing a repeat ablation. Am Heart J, 2011; 162: 193–200.
25. Gerstenfeld EP, Sauer W, Callans DJ et al. Predictors of success after selective pulmonary vein isolation of arrhythmogenic pulmonary veins for treatment of atrial fibrillation. Heart Rhythm, 2006; 3: 165–170.
26. Cummings JE, Schweikert R, Saliba W et al. Left atrial flutter following pulmonary vein antrum isolation with radiofrequency energy: Linear lesions or repeat isolation. J Cardiovasc Electrophysiol, 2005; 16: 293–297.
27. Simpson RJ, Jr., Amara I, Foster JR, Woelfel A, Gettes LS. Thresholds, refractory periods, and conduction times of the normal and diseased human atrium. Am Heart J, 1988; 116: 1080–1090.
28. Platonov PG, Yuan S, Hertervig E et al. Further evidence of localized posterior interatrial conduction delay in lone paroxysmal atrial fibrillation. Europace, 2001; 3: 100–107.
29. Deniz A, Sahiner L, Aytemir K et al. Tissue Doppler echocardiography can be a useful technique to evaluate atrial conduction time. Cardiol J, 2012; 19: 487–493.
30. Deniz A, Yavuz B, Aytemir K et al. Intra-left atrial mechanical delay detected by tissue Doppler echocardiography can be a useful marker for paroxysmal atrial fibrillation. Echocardiography, 2009; 26: 779–784.
31. den Uijl DW, Gawrysiak M, Tops LF et al. Prognostic value of total atrial conduction time estimated with tissue Doppler imaging to predict the recurrence of atrial fibrillation after radiofrequency catheter ablation. Europace, 2011; 13: 1533–1540.
32. Joshi S, Choi AD, Kamath GS et al. Prevalence, predictors, and prognosis of atrial fibrillation early after pulmonary vein isolation: findings from 3 months of continuous automatic ECG loop recordings. J Cardiovasc Electrophysiol, 2009; 20: 1089–1094.
33. Richter B, Gwechenberger M, Socas A, Marx M, Gossinger HD. Frequency of recurrence of atrial fibrillation within 48 hours after ablation and its impact on long-term outcome. Am J Cardiol, 2008; 101: 843–847.
34. Jiang H, Lu Z, Lei H, Zhao D, Yang B, Huang C. Predictors of early recurrence and delayed cure after segmental pulmonary vein isolation for paroxysmal atrial fibrillation without structural heart disease. J Interv Card Electrophysiol, 2006; 15: 157–163.
35. Cai L, Yin Y, Ling Z et al. Predictors of late recurrence of atrial fibrillation after catheter ablation. Int J Cardiol, 2013; 164: 82–87.
36. Arya A, Hindricks G, Sommer P et al. Long-term results and the predictors of outcome of catheter ablation of atrial fibrillation using steerable sheath catheter navigation after single procedure in 674 patients. Europace, 2010; 12: 173–180.
37. Lee SH, Tai CT, Hsieh MH et al. Predictors of early and late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. J Interv Card Electrophysiol, 2004; 10: 221–226.
38. Khaykin Y, Oosthuizen R, Zarnett L et al. Clinical predictors of arrhythmia recurrences following pulmonary vein antrum isolation for atrial fibrillation: predicting arrhythmia recurrence post-PVAI. J Cardiovasc Electrophysiol, 2011; 22: 1206–1214.
39. Tao H, Liu X, Dong J et al. Predictors of very late recurrence of atrial fibrillation after circumferential pulmonary vein ablation. Clin Cardiol, 2008; 31: 463–468.
40. D'Ascenzo F, Corleto A, Biondi-Zoccai G et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation? A meta-analysis. Int J Cardiol, 2012 [Epub ahead of print].
41. Bertaglia E, Stabile G, Senatore G et al. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. Pacing Clin Electrophysiol, 2005; 28: 366–371.