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ORIGINAL ARTICLE

Predictors of early and late left atrial tachycardia and left atrial flutter after catheter ablation of atrial fibrillation: Long-term follow-up

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Abstract

Background: *The aim of the study was identification of the predictors of left atrial tachycardia and left atrial flutter (LATAFL) after radiofrequency catheter ablation of atrial fibrillation (CAAF).*

Methods: *We followed 598 patients (71% male, 41% paroxysmal AF; median follow-up: 36 months) after a single step-wise CAAF procedure. The time to first documented LATAFL lasting longer than 30 s, documented in any kind of electrocardiography (ECG), was defined as an end-point.*

Results: *A single CAAF procedure resulted in LATAF in 58 (10%) patients. Additional lesions were performed in 275 (46%) patients. Early LATAFL recurrence (≤ 3 months since the index procedure) was observed in 11 (2%) patients. Late LATAFL (> 3 months) was noted in 47 (8%) patients. The univariate predictors of LATAFL recurrence were: type of AF (p = 0.003), the size of LA (p = 0.002) and the type of procedure (p = 0.0001). The identified single independent predictors of LATAFL recurrence were enlarged LA (p = 0.001) and multiple (≥ 2) additional lesions performed during the index procedure (p < 0.0001).*

Conclusions: *Higher rate of LATAFL recurrence was observed in patients with non-paroxysmal AF, enlarged LA and any additional lesions performed. Two independent predictors of LATAFL recurrence after CAAF were: the enlarged LA and multiple (≥ 2) additional lesions performed during the index procedure.* (Cardiol J 2015; 22, 5: 557–566)

Key words: atrial fibrillation, catheter ablation, left atrial tachycardia, left atrial flutter

Introduction

Catheter ablation of atrial fibrillation (AF) is a more effective therapeutic option for patients with AF, as compared to antiarrhythmic drugs (AADs) [1]. Multiple approaches for catheter ablation of AF (CAAF) have been developed. The current techniques focus on the elimination of mechanisms involved in the initiation (triggers) and maintenance (substrate) of AF [2, 3]. While ablation strategies that target pulmonary veins (PVs) are the cornerstone for most AF ablation procedures,

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more extensive ablation based on linear lesions or complex fractionated electrograms (CFAE) are approached in patients with long-standing persistent AF [3, 4]. Organized left atrial tachycardia and left atrial flutter (LATAFL) are common after CAAF with a reported incidence of 1.2–40% and the variability in the frequency of occurrence and the mechanism of LATAFL appears to be clearly dependent on the type of ablation procedure used and the extent of the underlying atrial disease [2]. Nevertheless, the predictors of LATAFL after CAAF are under debate [4].

The aim of the study was identification of the predictors of LATAFL after CAAF.

Methods

Patient characteristics

We followed 598 patients who had CAAF performed. The inclusion criteria, at the date of the procedure, were as follows: age 18–80 years, symptomatic and drug refractory non-valvular AF, AF documented in at least 2 electrocardiograms (ECGs) in a 3-month period preceding the ablation procedure and a signed informed consent obtained from the patient. The exclusion criteria included: acute reversible causes for AF, valvular AF, LATAFL documented in at least 1 ECG, known bleeding diathesis, intolerance of heparin or oral anticoagulation, left atrial (LA) thrombus, pregnancy or breastfeeding, abuse of drugs or alcohol, New York Heart Association (NYHA) class IV and other severe co-morbidities.

Pre-ablation preparation

Medical history was obtained during a visit to an outpatient-clinic with a review of the medical records including ECGs and Holter-ECG recordings of AF. The risk of procedure was discussed in detail, and all patients gave their written informed consent. AADs were discontinued at least 3 days before the ablation. Beta-blockers were allowed according to the protocol.

Assessment of the left atrial size

All patients underwent transthoracic echocardiography to determine LA diameter. The LA size was assessed by measurement of short and long axis in apical 4-chamber view. The normalized left atrial area (NLA), previously shown to be a stronger predictor of outcome than both LA short and long axis diameters, as well as LA area was calculated in each case [5].

NPAF and LATAFL definition

Non-paroxysmal AF (NPAF) was defined as persistent, long-lasting persistent, or paroxysmal AF (PAF) in patients with more than 500 h in symptomatic AF within 3 months prior to admission [5]. Left atrial tachycardia and left atrial flutter were defined as: (1) early LATAFL (occurring within the first 3 months) and (2) late LATAFL (occurring after the first 3 months).

Catheter ablation procedure

All procedures were performed under conscious sedation and analgesia. In all cases we used bi-plane fluoroscopy set in 60° LAO and 30° RAO views, respectively. After local anesthesia, a 10- or 20-polar steerable catheter was placed in the coronary sinus. Two transseptal sheets were introduced into the LA. The ablation procedures were performed with a support of a 3-dimensional (3D) electro-anatomical mapping system (Carto/EnSite) or with the previously described [6] high-density mapping catheter, HD Mesh Mapper™ (HDMM; Bard Electrophysiology, Lowell, MA, USA), placed in an antrum of the PV. A 7 F ThermoCool catheter (Biosense Webster) with a 3.5-mm irrigated tip was used for the ablation with radiofrequency energy settings chosen between 15 and 35 W and a cutoff temperature of 42°C. Ablation of each PV was carried out at the atrial side of the PV. A circumferential ablation line was performed around each PV, overlapping ipsilateral ablation lines.

The first step was the control of PV antrum isolation. In patients with sinus rhythm, the procedure was seized after confirming isolation of all veins, at least 30 min after last energy application. In patients with AF, when arrhythmia stopped spontaneously during PV isolation (PVI) at the antrum, the procedure was also aborted after confirming PVI. If AF continues, a stepwise approach including mitral isthmus line (MIL), roof line (RL), ablation of complex fragmented signals (CFAE) and endocardial lesion along coronary sinus (CSL) was implemented at the same procedure. When sinus rhythm could not be obtained during the procedure, cardioversion and re-mapping at sinus rhythm was planned at the end of procedure. The tightness of all linear lesions, respectively to the performed lesions in certain patient, and isolation of PVs and superior vena cava were controlled.

The acute endpoint for the procedure was elimination of PV antrum potentials and proving electrical isolation (bi-directional block) of PVs, superior vena cava and linear lesions, if performed.

Post-ablation management

Intravenous flow of heparin was continued to achieve a partial thromboplastin time of 60–80 s. All patients underwent trans-thoracic echocardiography to exclude pericardial effusion. Oral anticoagulation with coumadin was started 1 day after CAAF, targeting an international normalized ratio of 2.0 to 3.0.

Follow-up

After discharge from the hospital, the patients were scheduled for quarterly follow-up (FU) visits. One year after the intervention, FU visits were performed once a year. Seven-day Holter ECG recordings and a 12-channel ECG were obtained during each FU visit. Patients were asked to obtain an ECG, in our institution or outside, when feeling palpitations at times out of Holter-ECG monitoring periods.

Statistical methods

Study end-point. Time to first documented episode of LATAFL lasting longer than 30 s, documented in any kind of ECG was defined as an index parameter for a failure. Endpoint for analysis was the LATAFL-free survival within a FU time of 60 months.

Statistical analysis. The effect of discrete variables was studied using the Kaplan-Meier survival analysis with log-rank test. The parameters were dichotomized of derived from receiving operator characteristics (ROC)-curve optimal cut-off value, i.e. at the point, where the sum of sensitivity and specificity reached the maximum values. The impact of discrete variables on the outcome was described with positive and negative prediction accuracy and hazard ratio. The continuous data were presented as median and inter-quartile range, and categorical variables as numbers and percentages.

To avoid a potential model over-fitting, only the parameters revealed to be significantly associated with the outcome in univariate analysis were included in the multivariate Cox regression model performed using a step-down procedure. Two-tailed p values < 0.05 were considered statistically significant.

Results

Baseline and procedural characteristics

In this single-center study we included 598 patients (median FU of 36 months) who underwent a single CAAF procedure. The support of 3D

Table 1. Baseline characteristics (n = 598).

Parameter	N (%) or median (IQR)	
Male	425	(71%)
Age [years]	59	(52; 65)
History of AF [years]	4.4	(2.0; 8.2)
Paroxysmal AF	243	(41%)
Non-paroxysmal AF	355	(59%)
Body mass index	27.4	(25.2; 30.5)
Hypertension	435	(73%)
Coronary artery disease	49	(8%)
Dilated/hypertrophic cardiomyopathy	26	(4%)
Diabetes mellitus	55	(9%)
GFR	86.9	(74.7; 101.9)
Metabolic syndrome	243	(41%)
LVEF	60	(57; 62)
LA — short axis	40	(37; 43)
LA — long axis	55	(51; 59)
LA area	21.8	(19.1; 25.2)
Normalized LA area	10.6	(9.3; 12.0)

IQR — inter-quartile range; AF — atrial fibrillation; GFR — glomerular filtration rate; LVEF — left ventricular ejection fraction; LA — left atrium

electro-anatomical mapping system was used in 191 (32%) cases. Patients' baseline characteristics are summarized in Table 1.

Additional lesions were performed in 275 (46%) patients, including: RL in 220 (37%), MIL in 198 (33%), CSL in 92 (15%) and CFAE eliminated in 78 (13%) patients. In case of sustained arrhythmia, after having performed all steps of our protocol, the restoration of sinus rhythm with peri-procedural direct current electricial cardioversion was finally executed in 169 (28%) patients.

The median of cumulative time of procedure and fluoroscopy was 4.5 (4.0; 5.4) h and 61 (41; 90) min, respectively.

LATAFL-free survival and predictors of outcome after a CAAF procedure

A single CAAF procedure resulted in LATAF in 58 (10%) patients (Fig. 1). Early (≤ 3 months since the index procedure) LATAFL recurrence was observed in 11 (2%) patients. Late (> 3 months) LATAFL was noted in 47 (8%) patients. The characteristics of both groups are presented in Table 2.

The cut-off value of 11.5 for NLA was calculated from ROC-curve analysis. The univariate
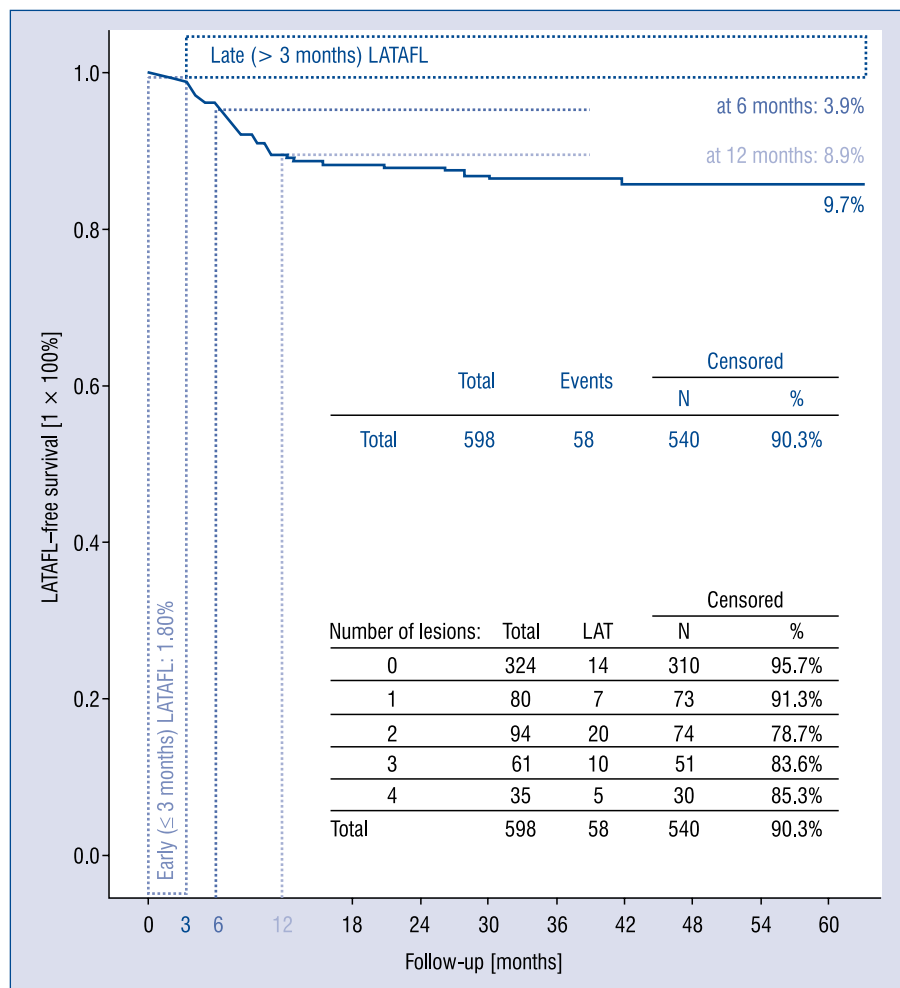
Figure 1. Late left atrial tachycardia and left atrial flutter (LATAFL) and a 5-year outcome. Kaplan-Meier event-free survival curve after a single catheter ablation. We observed recurrences of any arrhythmia (atrial fibrillation/LATAFL) in total of 250 (41.8%) patients during the follow-up period. LATAFL was diagnosed in electrocardiogram in 58 of these 250 patients.

predictors of LATAFL recurrence (Table 3) were: type of AF (p = 0.003), the size of LA (best defined with NLA, p = 0.002) and the type of procedure (p = 0.0001).

We found that the single independent predictors of LATAFL recurrence were (Table 3) enlarged LA, defined with NLA > 11.5 (Fig. 2A; p = 0.019) and multiple (≥ 2) additional lesions performed during the index procedure (Fig. 2B; p < 0.0001).

Complications

Cardiac tamponades, which occurred in 8 (1%) patients, were managed by pericardial puncture without further sequels. Pericardial effusion was found in 13 (2%) patients (2.17%).

Discussion

Main findings

We describe the independent predictors of LATAFL recurrence after CAAF: enlarged LA and multiple (≥ 2) additional lesions performed during the index procedure.

Outcome

The present study shows a 10% LATAFL recurrence rate in 598 patients with non-valvular AF after a single CAAF procedure. We observed most LATAFL recurrence in the first 12 months after CAAF (Fig. 1). The analysis of previous reports [6–29] revealed that total LATAFL recurrence in 5,273 patients after CAAF was 12%. Early and late

Table 2. The comparison of patients with early and late left atrial tachycardia and left atrial flutter (LATAFL) recurrence in follow-up (FU) (n = 58).

	LAT/LAFL recurrence in FU — n (%) or median (IQR)				P
	Early (≤ 3 months)		Late (> 3 months)		
Baseline data					
Number of patients	11		47		
Male	9	(82%)	33	70%	0.710
History of AF [years]	1.38	(0.42; 2.06)	4.35	(1.9; 6.84)	0.003
Non-paroxysmal AF	11	100%	34	72%	0.055
Age [years]	62	(57; 69)	61	(56.5; 68.0)	0.548
Body mass index	25.73	(24.3; 28.7)	27.28	(25; 31)	0.475
Hypertension	10	(91%)	39	(83%)	
Coronary artery disease	1	(9%)	1	(2%)	0.346
Dilated/hypertrophic cardiomyopathy	2	(18%)	2	(4%)	0.159
Diabetes mellitus	2	(18%)	1	(2%)	0.089
GFR	81.68	(74.3; 111.7)	82.54	(71.2; 94.0)	0.422
LVEF	52	(47; 57)	60	(56; 62)	0.008
LA — short axis	59	(58.0; 61.5)	56	(51.5; 61.5)	0.095
LA — long axis	43	(40.5; 45.5)	41	(38; 45)	0.232
LA area	24.94	(23.8; 27.1)	22.96	(20.5; 26.7)	0.036
Normalized LA area	12.49	(11.8; 14.1)	11.12	(10.0; 12.6)	0.017
Procedural data					
PVI + at least one additional lesion	8	(73%)	36	(77%)	0.999
Roof line	7	(64%)	32	(68%)	0.999
Mitral isthmus line	7	(64%)	29	(62%)	0.999
Coronary sinus	4	(36%)	12	(26%)	0.475
CFAE	2	(18%)	11	(23%)	0.999
PVI + 1 lesion	0		7	(15%)	X
PVI + ≥ 2 lesions	8	(73%)	29	(62%)	0.206
AAD in follow-up					
AAD: class I	1	(9%)	8	(17%)	0.671
AAD: class II	9	(82%)	38	(81%)	0.999
AAD: class III	3	(27%)	11	(23%)	0.999
Amiodarone	2	(18%)		8 (17%)	0.999
Dronedarone	1	(9%)		2 (4%)	0.444
Sotalol	0			1 (2.1%)	0.999

IQR — inter-quartile range; AF — atrial fibrillation; GFR — glomerular filtration rate; LVEF — left ventricular ejection fraction; LA — left atrium; PVI — pulmonary veins isolation; CFAE — complex fractionated electrograms; AAD — antiarrhythmic drugs

secondary LATAFL were observed in 14% and 9% of patients, respectively. Higher LATAFL recurrence rate was found only in patients with rheumatic heart disease [30]. Our data are comparable with reported total and late LATAFL recurrence (10% and 8%, respectively). Lower number of early LATAFL recurrence in our group is the result of our step-wise approach, focused on elimination of all peri-procedural arrhythmias, which was not applied by any of the previous authors describing early LATAFL recurrence.

Types of LATAFL
Nagamoto et al. [19] described primary (pre-procedural) and secondary (procedural-related) LATAFL. Both types were further defined as early (which appeared during a procedure) and late (after a procedure) arrhythmias. He concluded that

Table 3. Predictors of outcome after a single catheter ablation of atrial fibrillation ablation procedure.

A. Continuous variables (ROC analysis)	AUC	95% confidence interval		P
		Lower	Upper	
History of atrial fibrillation	0.441	0.357	0.525	0.192
Age	0.564	0.474	0.654	0.156
Body mass index	0.488	0.391	0.584	0.782
LA — long axis diameter in 4-chamber view	0.651	0.572	0.730	0.001
LA — short axis diameter in 4-chamber view	0.613	0.525	0.702	0.012
LA area	0.646	0.569	0.723	0.001
Normalized LA area	0.680	0.607	0.753	0.000
Left ventricular ejection fraction	0.555	0.473	0.637	0.165
Renal function, GFR	0.555	0.476	0.634	0.168
B. Discrete variables	**Hazard ratio**	**95% confidence interval**		**P**
		Lower	Upper	
Non paroxysmal atrial fibrillation	2.568	1.354	4.872	0.003
Normalized LA > 11.5	2.435	1.410	4.206	0.002
Any additional lesion	4.236	2.267	7.915	0.0001
Number of lesions* ≥ 2	4.410	2.609	7.491	0.0001
C. Multivariate Cox regression model	**Hazard ratio**	**95% confidence interval**		**p**
		Lower	Upper	
Number of lesions* ≥ 2	2.22	1.21	4.99	0.000
Enlarged LA, normalized LA > 11.5	1.88	1.11	3.19	0.019

*Any performed additional lesions are included; GFR — glomerular filtration rate; LA — left atrium
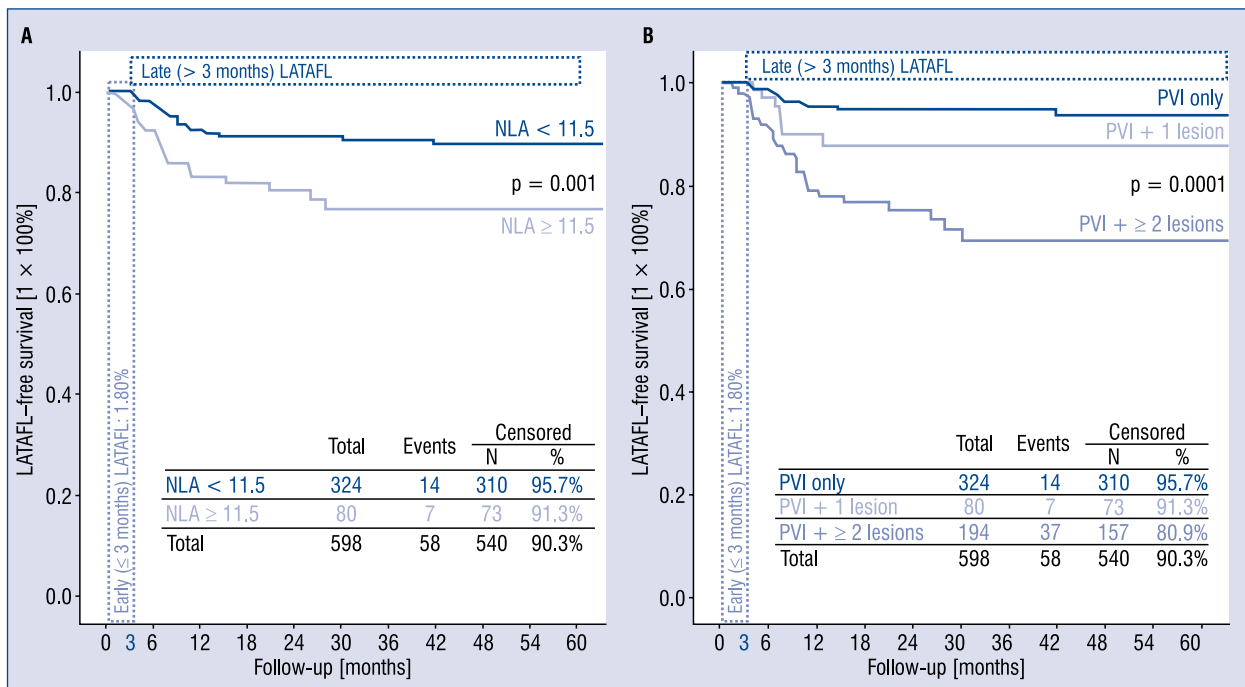

Figure 2. The size of left atrium (**A**), number of additional lesions (**B**) and a 5-year outcome. Kaplan-Meier event-free survival curve after a single catheter ablation; LATAFL — left atrial tachycardia and left atrial flutter; NLA — normalized left atrial area; PVI — pulmonary vein isolation.

early secondary LATAFL should be ablated when it presented as a pre-ablation arrhythmia or a peri-procedurally ongoing LATAFL resulting from a focal or gap-related macro-reentrant mechanism [19]. However, the ongoing LATAFL resulting from non-gap-related macro-reentry (except for typical isthmus-dependent atrial flutter) could be monitored [19].

Our definition of LATAFL follows recent consensus [4] and clearly demarcates peri-procedural (i.e. very early) from post-procedural (early, i.e. 3-month blanking period related, and late, i.e. > 3 months since a procedure) LATAFL. Any peri-procedural arrhythmia was approached according to our step-wise protocol. However, we cannot exclude that some of the observed LATAFLs, especially in patients after PVI only, were of the primary type (early or late), not identified before the procedure. Still, we performed a thorough selection of patients at inclusion, and no record of documented pre-procedural LATAFL was identified. Consequently, we focused on both early (≤ 3 months) and late (> 3 months) LATAFLs only.

Early secondary LATAFL

We observed early secondary LATAFL only in patients with NPAF, lower left ventricular ejection fraction and enlarged LA. All these factors are related to structural remodeling of LA which results in local substrate prone to supra-ventricular arrhythmias (SVA) [31]. In all these cases we performed PVI and multiple additional lesions. We assume that such substrate modifications were enough for acute peri-procedural success, as we aimed for (following our protocol) total elimination of all ongoing SVA during the index procedure.

In an animal model, complete replacement of necrotic muscle with collagen was observed 4 weeks after radiofrequency ablation [32]. At 10 to 12 weeks, the replaced myocardium was less cellular and the collagen more dense. The necrotic atrial myocardium was replaced by a collagenous matrix containing small islands of surviving myocardium [32]. The anatomically remodeled atrium requires more time after ablation to reverse its vulnerability to triggers [33], and is more susceptible to early arrhythmia relapses [31]. Such a deep and wide injury within LA tissue needs time for local healing, i.e. the slow process of scarring which itself can be pro-arrhythmic. The delay in time between tissue injury to secondary LATAFL appearance could also be supported by the previous observation which showed that peri-CAAF inducibility of LATAFL does not predict its clinical recurrence

in FU [18, 34]. Still, we cannot exclude the co-existence of unknown pre-procedural or unmasked peri-procedural SVA. Interestingly, patients with early recurrence had shorter history of AF which further supported the idea of "healing-tissue"-related early LATAFL.

Late secondary LATAFL

Late secondary LATAFL recurrence was mainly observed in patients with a long history of AF, i.e. one of the mechanisms could be the continuous process of substrate remodeling within LA, which we hoped to slow down with CAAF, as curing could not be suspected in such a case. Subsequent explanation is the iatrogenic effect of any of the lesions produced, as well as gaps within linear lesions. Moreover, the interaction between the lesions and preexisting regions with abnormal electrical properties cannot be excluded. As all above are present in LA after CAAF, the final mechanism of secondary LATAFL is complex in its nature and difficult to be simply defined.

Predictors of recurrence after CAAF

While many predictors of AF recurrence following CAAF have been proposed [3, 4, 35], predictors of LATAFL are under debate. We show that independent predictors of LATAFL recurrence after CAAF are: the enlarged LA and multiple (≥ 2) additional lesions performed during the index procedure.

Atrial enlargement, a result of atrial remodeling, is an important clinical predictor of AF maintenance [36]. The electrical remodeling in the atria, which results in shortening of the effective refractory period, is involved in the occurrence and maintenance of atrial fibrosis [37]. Contractile remodeling is evidenced by a decrease in atrial contractility which leads to dilation of the atria [38]. Structural remodeling within atria is evidenced by interstitial fibrosis and atrial dilatation [39]. This expanded the space between cardiomyocytes, likely due to the loss of cells and fibrotic replacement and expansion of the extracellular matrix, may also cause conduction delays between cardiomyocytes themselves and allow for alternate pathways of conduction [39]. These changes are electrically apparent as ectopic foci and anisotropic conduction, which create non-uniform wave fronts that allow abnormal re-entrant arrhythmias [40]. Atrial dilation increases the amount of atrial tissue that can accommodate reentry circuits [41]. Atrial dimensions are a particularly important determinant of the occurrence of multiple-circuit reentry [42].

Within larger atrial size more circuits can be accommodated and long-wavelength circuits that are too large for a normal-sized atrium can be supported [41]. Consequently, AF in the remodeled LA is not only trigger- but also substrate-dependent.

The iatrogenic effect of additional lesions is known [6–29]. Linear lesions result in linear scars which limit areas of LA activation. Nevertheless, performing linear lesions in dilated LA can be challenging due to the fact thatthey have to be longer than in not-dilated LA. The vast majority of arrhythmias that occur after CAAF are re-entrant (83%) [1–6, 8–25] and use gaps in prior ablation lines. Elimination of the dominant arrhythmia may uncover, suppressed so far, ectopic foci. Additionally, electrogram-guided ablation and elimination of CFAE, aimed at ectopic foci, also result in many scattered areas of block, which in combination with existed regions of anisotropic conduction, promote substrate for re-entry. Consequently, the combination of LA enlargement and multiple lesions results in changed electrophysiological environment and development of secondary arrhythmias. Our step-wise approach showed that avoidance of multiple ablation lesions cannot be avoided in many patients. Nevertheless, the collected data show that limiting additional lesions (with step-wise approach), demonstration of conduction block within the lines and PV disconnection are likely to decrease the prevalence of post-CAAF LATAFL [21].

Clinical implications

Clinical implications of our results are substantial for patients planned for CAAF. Firstly, the outcome data should be presented. A procedure in patients with enlarged LA and premeditated for additional lesions might result in LATAFL. Consequently, subsequent CAAF can be needed. Secondly, thorough monitoring after CAAF is crucial. Incidence of late arrhythmia recurrence may be related to the extent of ECG monitoring and earlier recurrence may be missed in selected patients with no or minimal symptoms [4]. Clinical evaluation should be performed on regular basis and any complaint of "heart palpitations" [43] should be addressed. Finally, attention in control of patient-related risk factors remains an integral part of management after the CAAF procedure [4].

Limitations of the study

Our study has a few limitations: (1) This is a single-center, non-randomized report. However, there was no selection bias for study inclusion since all consecutive patients undergoing radiofrequency catheter ablation for AF at our institution were included for analysis. (2) A potential variability of operator experiences with the stepwise ablation approach might further limit our results. (3) We did not use any protocol of LATAFL induction after CAAF procedure. Nevertheless, it was previously shown that arrhythmia inducibility was not predictive of atrial arrhythmia recurrence in FU [18, 34]. (4) According to the latest Consensus Report [4], the FU results are presented without consideration of recurrences during the blanking period. (5) The latest data [44], unknown at the time of selection of our study cohort, show that continuous monitoring with implanted devices is significantly superior to intermittent monitoring. Our FU was based on clinical evaluation and 7-day Holter-ECG recordings.

Conclusions

Our data show that a step-wise CAAF procedure results in relatively low LATAFL recurrence rate in a very long-term FU. Most LATAFL recurrences occurred in the first 12 months if only PVI was performed. In patients in whom any additional lesions were performed, most recurrences occurred in the first 30 months. A plateau in LATAFL-free survival was noted in both groups thereafter.

Higher rate of LATAFL recurrence was observed in patients with NPAF, enlarged LA and any additional lesions performed. We defined 2 independent predictors of LATAFL recurrence after CAAF: the enlarged LA and multiple (≥ 2) additional lesions performed during the index procedure.

The presented data follow the latest indications for CAAF [4]. Performing CAAF at earlier stage of AF, in not-dilated LA, may allow limiting the need for additional lesions. Such an approach is likely to decrease the prevalence of LATAFL after CAAF.

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