ORIGINAL ARTICLE

Arrhythmia Termination During Radiofrequency Delivery Improves Outcomes after Catheter Ablation for Persistent and Long Standing Persistent Atrial Fibrillation

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ABSTRACT

Background: Achieving long-term successful outcomes with catheter ablation (CA) of persistent atrial fibrillation (PsAF) remains a challenge. Multiple attempts to determine effective ablation strategies besides the pulmonary veins (PV) were made but, so far, there is no agreed standard approach and no clear consensus as to which is the best one. Among the most frequently used techniques was ablation of complex atrial fractionated electrograms (CFAE) but studies showed contradictory results. The optimal procedural endpoint also needs further refinement.

Objectives: We sought to evaluate outcomes in regard to patient characteristics and procedural termination. We also aimed to assess whether continuation of antiarrythmic therapy in the blanking period (1 to 3 months after the procedure) influences long term results.

Methods: We enrolled consecutive patients with persistent and long-standing PsAF (LS-PsAF) who underwent one or more radiofrequency catheter ablations (RF CA) - pulmonary vein antral isolation (PVAI), followed by CFAE or resultant atrial tachycardia/flutter elimination, were retrospectively analyzed. Procedural objective was tachyarrhythmia (AF or resultant atrial flutters/tachycardias) termination (TT) to sinus rhythm (SR) during RF delivery. If after extensive substrate based or activation guided ablation sinus rhyhtm was not restored, conversion was performed with antiarrhythmic drugs (AAD), overdrive pacing or electrical shock. Screening for arrhythmia recurrence was performed via clinical interview and 48 hours Holter monitoring at 1,3 and 6 months and then every 6 months.

Results: The cohort included 94 patients (age 54.5±11.4, 67 (71%) males, CHADSVASc 2.3±2, 11 (12%) LS-PsAF) Acute restoration of sinus rhythm (SR) was achieved in 93.4% of the cases, 43% by ablation of CFAE or resultant atrial tachycardia/flutter(AT/AFL), 36.2% by electric cardioversion, 7.4% by chemical conversion, 3.1 % overdrive pacing, 3.7 % spontaneuous/mechanical. The long term success rate after a mean of 1.7±0.8 procedures was 59% at a mean follow-up period of 80±28 months. Freedom from AF was significantly higher when arrhythmia termination was obtained during RF delivery (p – 0.003). Short-term use of AAD in the blanking period did not lead to improved long term outcomes.

Conclusions: In patients with PsAF and LS-PsAF restoration of sinus rhyhtm during RF delivery for pulmonary vein isolation, ablation of CFAE or resultant atrial tachyarrhythmia predicts long term procedural success. Further research to determine the best strategy to achieve this outcome is necessary.

Keywords: arrhythmia, radiofrequency, catheter ablation, atrial fibrillation.

REZUMAT

Introducere: Obținerea de rezultate favorabile pe termen lung prin ablație transcateter (CA) pentru fibrilația atrială persistentă (FiA Ps) rămâne o provocare. Au fost facute multiple tentative de stabilire a strategiei optime de ablație în afara venelor pulmonare, însă până în prezent nu există o abordare standard sau un consens general acceptat. Printre cele mai folosite tehnici utilizate, a fost ablația electrogramelor atriale complexe fracționate (CFAE) dar studiile au arătat rezultate contradictorii. Obiectivul procedural optim necesită de asemenea cercetări suplimentare.

Obiective: Ne-am propus evaluarea rezultatelor post-ablație în funcție de caracteristicile pacienților și modalitatea de terminare a procedurii. Analizarea impactului medicației antiaritmice administrate în primele 1-3 luni postprocedural asupra rezultatelor pe termen lung a constituit un obiectiv secundar.

Material și metode: Au fost analizați restrospective pacienți cu FiA Ps și persistentă pe termen lung care au efectuat ablație transcateter într-o manieră graduală (CARTO3, izolare antrală a venelor pulmonare (PVAI), ablație CFAE sau a tahicardiilor/flutterelor atriale rezultante. Endpoint-ul procedural a fost oprirea FiA (sau a tahiaritmiilor organizate

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rezultante) în timpul tirului de ablație. Dacă acest lucru nu a fost posibil în urma ablației extensive, conversia la ritm sinusal a fost efectuată prin administrarea de antiaritmic, soc electric extern sau stimulare antitahicardică. Urmărirea pentru recidive aritmice a fost efectuată prin interviu clinic și monitorizări holter 48 ore la 1, 3, 6 luni apoi din 6 în 6 luni.

Rezultate: Au fost în total 94 de pacienți (vârsta medie 54,5 ±11,4, 71% bărbați, cu un scor CHADSVasc mediu de 2,3 ±2 și 12% cu FiA persistentă pe termen lung). Conversia la ritm sinusal a fost posibilă în 93,4% din cazuri, 43% în timpul tirului de ablație cu radiofrecvență (RF), 36,2% conversie electrică, 7,4% chimic, 3,1% pacing antitahicardic, 3,7% spontan/mecanic. Rata de succes după un număr mediu de proceduri de 1,7±0,8 și o perioadă medie de urmărire de 80±28 de luni a fost de 59%. Analiza Kaplan Meier a arătat că pentru cei la care a fost posibilă conversia la ritm sinusal în timpul tirului de ablație, supraviețuirea fără recidivă a fost semnificativ statistic mai mare (p=0,003). Utilizarea de antiaritmice pentru o perioadă scurtă de timp postablație nu a fost asociată cu rezultate mai favorabile.

Concluzie: Rezultate optime pot fi obținute și pentru FiA Ps si persistentă pe termen lung prin ablație cu radiofrecvență (izolare de vene pulmonare urmată de ablația CFAE sau a eventualelor tahiaritmii organizate rezultante). Oprirea FiA (sau a tahiaritmiei rezultate post modificare de substrat) în timpului tirului de ablație este predictivă pentru rezulate superioare pe termen lung, însă pentru a determina cea mai bună strategie ablativă în astfel de cazuri, studii suplimentare sunt necesare.

Cuvinte cheie: aritmie, radiofrecvență, ablație de caterer, fibrilație atrială.

BACKGROUND

Radiofrequency cathter ablation (RF CA) has proven its superiority vs antiarrhythmic drugs (AAD) for maintaining sinus rhythm (SR) in patients with atrial fibrillation (AF). It was also reported that it has reduced mortality in patients with heart failure by about 40%[1], along with the incidence of ischemic stroke[2] and dementia[3]. However, long-term successful outcome for persistent atrial fibrillation (PsAF) is lower than for paroxysmal AF. Although additional ablation beyond the pulmonary veins (PVs) is considered to maximize success rates, a randomized clinical trial has proven no benefit from additional ablation[4].

There are also contradictory results concerning the same type of additional ablation (besides pulmonary vein isolation), with some authors finding that linear ablation or CFAEs do not add on efficacy[4] while others show that they are essential for long term succes[5]. These conflicting results might be explained by inhomogenous ablation techniques and procedural end-points. If there is a difference in overall success rate between patients with acute termination of AF during ablation and those without is still under debate[5,6].

OBJECTIVES

We sought to determine the long term clinical outcome in persistent AF patients who underwent one or more RF CA in a stepwise approach and to identify the prognostic factors for the clinical success after all procedures, in regard to patient characteristics and procedural end-point (tachyarrhythmia termination (TT) by RF delivery). We also aimed to assess whether continuation of antiarrythmic therapy in the blanking period (1 to 3 months after the procedure) influences long term results.

METHODS

Study population

A total of 94 consecutive patients with Ps and LS-PsAF who underwent catheter ablation in our center were retrospectively analyzed. Preprocedural characteristics (significant comorbidities, cardiovascular risk factors, AF history, prior medication), ECGs (before and after the procedure), routine laboratory tests and echocardiographic data were collected. All patients had previously tried at least one antiarrhythmic medication without success.

Ablation procedure

A stepwise CA (pulmonary vein antral isolation (PVAI) followed by CFAE or resultant atrial tahcycardia/flutter elimination) under Carto 3 (Biosense Webster, Irvine, CA) was performed, on uninterrupted antioagulation (NOAC/VKA), with femoral approach and acces to the left atrium via single transseptal puncture with a Lasso Nav catheter and a Thermocool Smart Touch (Biosense Webster, Irvine, CA) ablation catheter. After the transseptal puncture, unfractionated heparin was administered in order to maintain an ACT ≥350sec, ACT was monitored every 30 minutes.

The technique used for pulmonary vein isolation was circumferential antral ablation, each vein separately or encircling two ispilateral veins. Pulmonary vein entrance and exit block was demonstrated for all the veins.

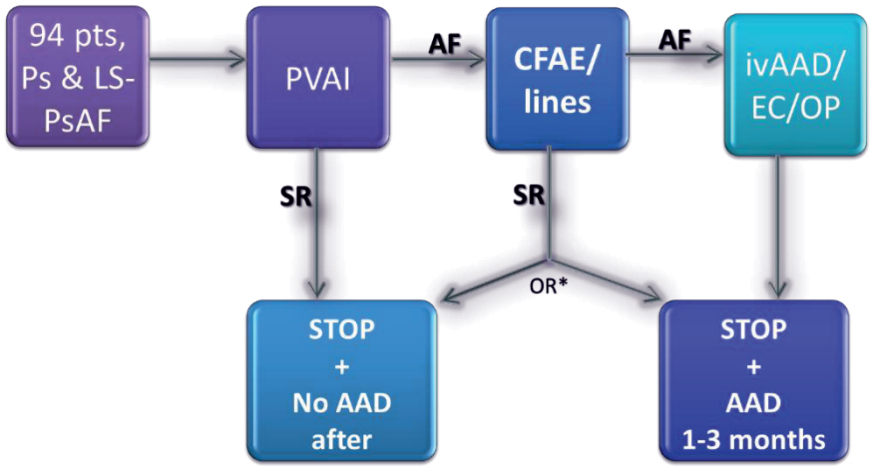


Figure 1. Procedural protocol. PVAI=pulmonary vein antral isolation, CFAE=complex fractionated atrial electrograms, AAD=antiarrhythmic drugs, E=electrical cardioversion, OP=overdrive pacing, AF=atrial fibrillation, SR=sinus rhythm.

When sinus rhythm was obtained during RF delivery for PVAI/or the patient was in sinus rhythm from the beginning, the procedure was continued until all the pulmonary veins were isolated and no further left atrial substrate ablation was performed. If the patient was still in AF/AT/AFL after PVAI, CFAE/lines/activation guided ablation was performed until SR was obtained. Regions with a mean cycle length of less than 120 ms and low amplitude (often <0.5 mV) with a repetitive pattern of local activation were defined as „CFAE" based on previously published data[7,8].

If AF or resultant tachyarrhythmia continued after all possible substrate was eliminated, overdrive pacing or chemical/electrical conversion to SR was performed, as ilustrated in Figure 1. If AF was converted to an AT/AFL, it was mapped and ablated using 3D-activation mapping and entrainment maneuvers. When a critical isthmus of a macroreentrant circuit was identified, the lesions were deployed to achieve complete bidirectional conduction block. Arrhythmia induction after ablation was not attempted.

After restoration of sinus rhythm, a cavotricuspid isthmus (CTI) line was created in all patients, with an endpoint of bidirectional isthmus block.

During the repeat procedure, persistence of pulmonary vein isolation was evaluated first. In the presence of conduction recovery, re-isolation of the PVs was performed, then the strategy was similar with the initial procedure

Follow-up protocol

Screening for arrhythmia recurrence was performed via clinical interview and 48 hours Holter monitoring at 1, 3 and 6 months and then every 6 months. A 3 months blanking period was used for definition of recurrence status. Recurrence was defined as documented AF/ATs/AFL on the ECG or 48-h Holter monitoring, lasting >30 seconds.

Statistical analysis

IBM SPSS Statistics 22 and Analyse-It software for Microsoft Excel were used to analyse the data. Continuous variables are presented as mean±standard deviation or median (IQR), categorical variables by frequencies. For comparison of the subgroups, Wilcoxon-Mann-Whitney and Fisher's exact tests were employed, as well as Kaplan Meier plots to compare the cumulative probability of survival without arrhythmia relapse, Cox multivariate regression to evaluate the predictors of arrhythmia recurrence.

RESULTS

The cohort included 94 patients, predominantly males (71%) with a mean age of 54.5 ±11.4 years and a mean time from first AF diagnostic of 5.5±3.7 years. At the initial procedure 18.4% (14 patients) were in SR. More than half of the patients (53.1%) underwent a single procedure, 35.1% two procedures, 10.6% three and 1.2% had 4 procedures.

There were no significant differences between the group in which TT was obtained during RF delivery and the one in which the sinus rhyhtm was obtained via other methods, in regard to comorbidities and risk factors (Table 1).

Acute intraprocedural restoration of sinus rhythm was achieved in 93.4% of the cases, 43% by ablation of

Table 1. Preprocedural characteritics of the studied patients

	Group in which TT was obtained during RF delivery	Group in which TT was not obtained by RF delivery	p value
General characteristics & comorbidities			
Age (years)	55.4±11.7	60±11.5	0.11
BMI (kg/m^2)	28.63±3.5	28.61±3.7	0.85
AF history (years)	5.14±3.05	4.96±4.39)	0.5
AF type LS-Ps	7.4%	24.2%	0.16
Male sex (%)	70.4%	78.1%	0.55
Hypertension	54%	75.9%	0.14
Ischemic heart disease	21.7%	20.7%	1
Heart failure	50%	34.8%	0.5
Structural heart disease	19.2%	8.3%	0.26
Dyslipidemia	50%	75%	0.08
Type II diabetes	34.8%	20.7%	0.34
Obstructive sleep apnea	28.6%	33.3%	0.76
Smoking	16.7%	20%	0.8
Atrial flutter	77.3%	55.6%	0.14
PSVT associated	5%	7.1%	0.79
CHA_2DS_2VASC score	2.6±2	1.7±2.1	0.13
Laboratory tests			
Cholesterol	171.11±39.01	165.98±39.36	0.69
Triglycerides	131.7±90.21	129.80±64.7	0.81
Serum creatinine level	0.99±0.2	0.83±0.2	0.09
NTproBNP	355.5±152.03	861.43±852.67	0.42
Serum hemoglobin	12.13±2.6	14.19±0.9	0.11
EKG measurements			
P wave duration(ms)	117.7±16.9	111±22.7	0.22
PR interval (ms)	190.8±26.8	194.5±45.7	1
QRS duration (ms)	95.5±17.5	93.8±20.9	0.53
cQT interval (ms)	462.5±32.7	441.9±34.8	0.13
Echocardiography			
LA(ap diam, mm)	45.7±4.5	42.7±7.8	0.04
LA area (cm^2)	24.11±4.01	23.09±4.16	0.66
LA (volume, ml/m^2)	44.69±11.9	47.27±6.88	0.88
RA (diam, mm)	43.2±6.8	43±8.2	0.8
LVEF (%)	54.87±6.14	49.96±10.59	0.09

TT=tachyarrhythmia termination; PSVT=paroxysmal supraventricular tachycardia, LA=left atrium, RA=right atrium, LVEF=left ventricular ejection fraction.

CFAE or resultant atrial tachycardia/flutter, 36.2% by electric cardioversion, 7.4% by chemical conversion, 3.1% overdrive pacing, 3.7% spontaneously/mechanical.

In the subgroup in which tachyarrythmia termination (TT) was obtained by ablation, in 73% of the cases SR conversion happened during RF delivery for CFAE/other substrate ablation and 23% of the case during PVAI (the regions targeted for substrate elimination are shown in below in Figure 3).

After a mean of 1.7±0.8 procedures at a mean follow up of 80±28 months, arrhythmia recurrence rate was 41% (39 patients).

A Kaplan-Meier analysis (Figure 4) showed that survival without arrhythmic recurrence was significantly greater for the patients in which sinus rhythm was obtained during RF delivery (log rank p =0.003).

Univariate analysis indicated that intraprocedural organization (meaning that after RF applications atrial fibrillation was converted into atypical atrial flutter/

Table 2. Procedural aspects and success rates

Procedural characteristics	Freq %
Acute SR restoration	93.4%
CFAE ablation	60%
Lines/PWBI	23%
Atypical atrial flutter ablation	20.5%
Recurrence rate after first procedure	65.2%
Recurrence rate after all procedures	41%

CFAE=complex fractioneted atrial electrograms; PWBI=posterior wall box isolation; SR=sinus rhythm.

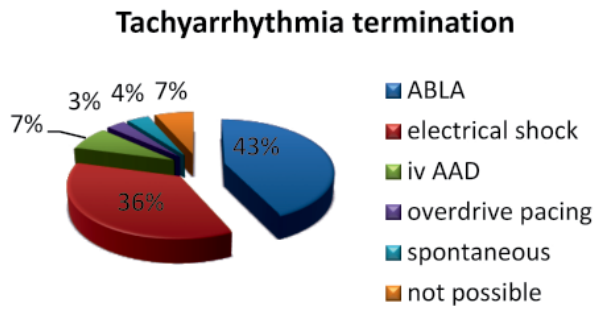


Figure 2. Frequencies of different methods used for conversion to sinus rhythm; AAD=antiarrhythmic drugs.

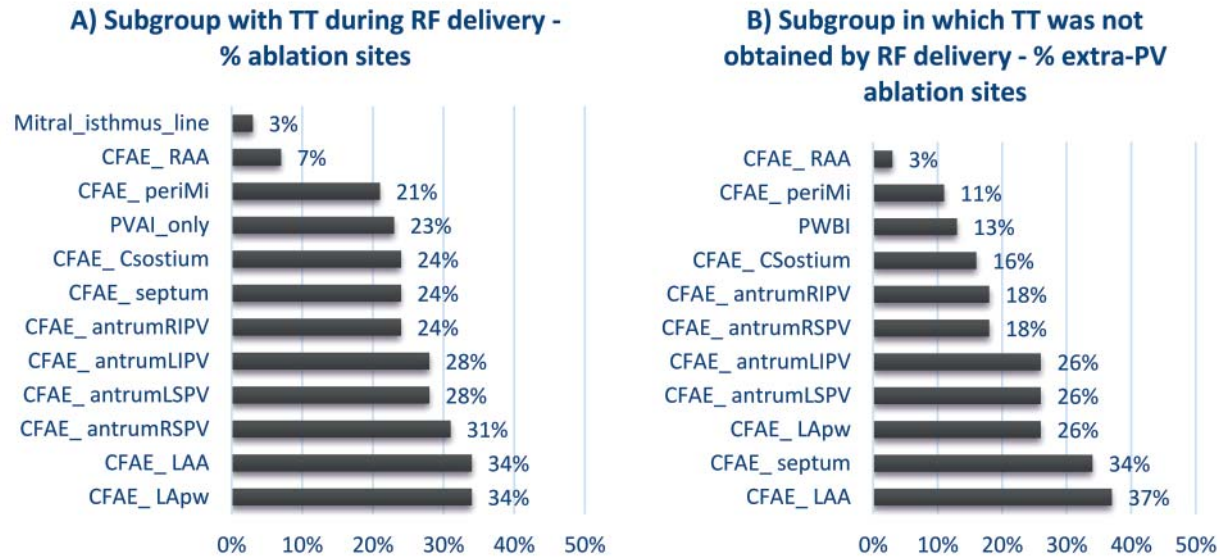


Figure 3. A)- Frequencies of ablation sites in the subgroup with TT, note in ~ 23% of the cases SR conversion took place during isolation of the pulmonary veins, cases in which no further substrate ablation was performed, only completion of the PVAI ; B) Frequencies of regions targeted for substrate elimination in the lot without TT; TT=tachyarhythmia termination; CFAE=complex fractionated atrial electrograms; LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein; RSPV=right superior pulmonary vein, RIPV right inferior pulmonary vein, PWBI=posterior wall box isolation; CS= coronary sinus; LAA=left atrial appendage; RAA=right atrial appendage; LApw=posterior wall of the left atrium.

atrial tachycardia) was associated with a lower risk of arrhythmia relapse (p=0.002). Also the mean CHA-2DS2VASC score (2.5±1.7 vs 1.2±2.2, p=0.04), and TT during RF (p – 0.02) were predictors for lower arrhyhtmia recurrence. Smaller left atrial volumes (79.5±23 ml vs 92.5±26 ml) and lower LDL levels (89.51±22.4 vs 122.6±26.4) were found in the group with lower arrhyhtmia recurrence but did not reach statistical significance (p=0.07).

A total of 19 patiens (~20%) patients received AAD post ablation in the blanking period (mean duration 1.9±1months). Amiodarone and propafenone were most frequently used, followed by flecainide and sotalol.

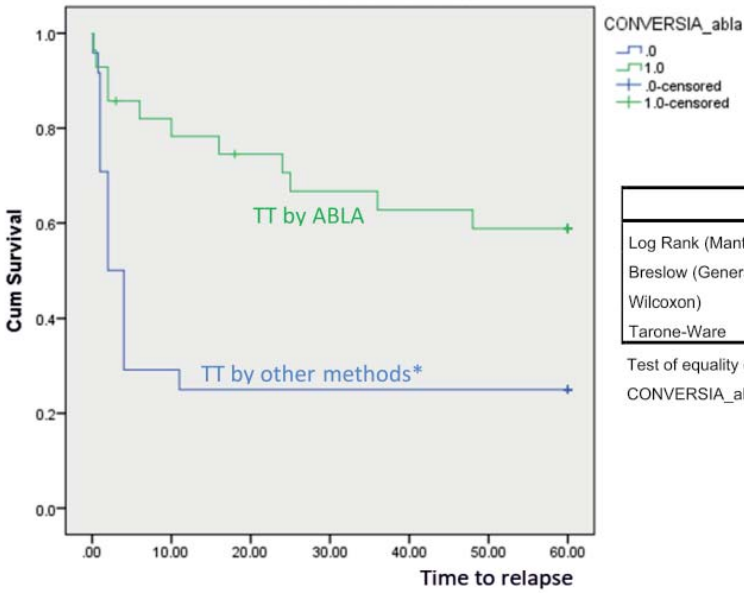
Short-term use of AAD in the blanking period did not lead to improved clinical outcomes at the later phase (p=0.8) as seen in the Kaplan Meier (Figure 5).

Univariate characteristics with a *p* value < 0.1 were considered for multivariate analysis but the only multivariate predictor of success was was tachyarrhythmia termination during RF delivery (p – 0.006).

DISCUSSION

The main finding of our study is that in patients with PsAF and LS-PsAF tachyarrhyhtmia termination during RF ablation portends a higher success rate.

The rationale for using termination as an endpoint of catheter ablation has been considered by analogy



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	9.100	1	.003
Breslow (Generalized Wilcoxon)	10.597	1	.001
Tarone-Ware	10.122	1	.001

Test of equality of survival distributions for the different levels of CONVERSIA_abla.

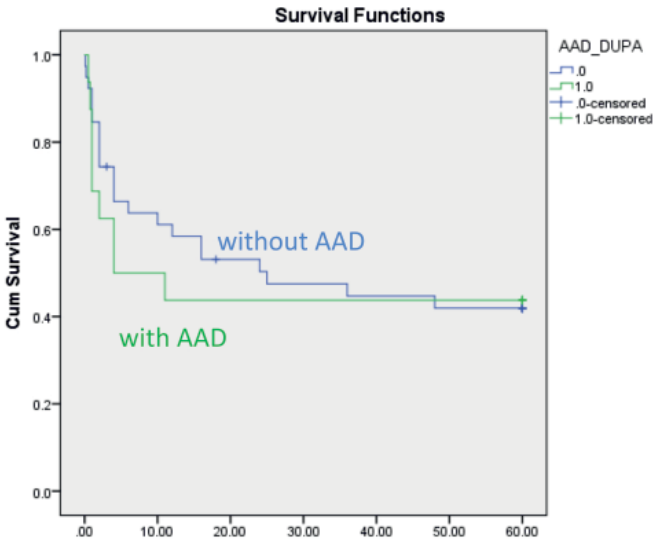
Figure 4. Kaplan Meier plot showing time to arrhythmic relapse in the group with tachyarrhythmia termination during RF delivery (green line) vs group in which that was not possible (blue line).

Table 3. Univariate predictors of arrhythmia recurrence

	Recurrence group	Arrhythmia free group	P value
Age (years)	56.5±12.6	55.6±11	0.5
Weight (kg)	89±16.6	84.8±15.1	0.66
BMI	29.06±4.1	27.29±3.7	0.12
AF history (years)	5.95±3.86	5.6±3.63	0.69
LS-Ps AF type (%)	12.8%	7.4%	0.69
Males (%)	73.7%	85.2%	0.36
Hypertension	66.7%	48%	0.18
Ischemic heart disease	24.3%	12.5%	0.33
Heart failure	25.9%	44.4%	0.21
Dyslipidemia	52.8%	56%	1
LDL cholesterol	89.51±22.4	122.6±26.4	0.07
Type II diabetes	22.2%	19.2%	1
GFR(MDRD)	84.88±9.9	90.66±33	0.54
CHA2DS2Vasc	2.5±1.7	1.2±2.2	0.04
Pw duration	113.4±21.5	118±13.6	0.28
PR interval	188.1±40.2	194.7±22	0.37
cQTi	449.4±34.5	451.4±38	0.61
LA ap mm	42.1±5.1	43.9±5.8	0.26
LA diam1	52.1±10.1	50±9	0.54
LA area (cm^2)	22.93±6.27	24.5±5.24	0.31
LA volume	92.5±26.7	79.5±23.5	0.07
E/A	2.03±0.65	1.75±0.7	0.4
TAPSE	20.7±8.7	25.8±4.8	0.43
Intraprocedural oganization	30.3%	71.4%	0.002
TT during RF delivery	22.2%	65.5%	0.02
CFAE ablation	71.9%	69.2%	1

Table 4. Comparison of the subgroups with and without short term antiarrhythmic drugs (AAD) postablation

Patient characteristics	with AAD	without AAD	P value
Age	54 ±11.6	55 ±11.5	0.9
BMI	29.3 ±3.9	29 ±3.8	1
Pwave (ms)	120 ±20	145 ±10	0.7
AF duration	5.6 ±2.3	5.7 ±4.5	0.9
LA-d	61 ±2.1	60.2 ±11.2	0.9
LA-area (cm^2)	31 ±2.8	24 ±2.9	0.07
LAAfw (m/s)	0.5 ±0.57	0.36 ±0.13	0.2
AF term by ABLA	37.5%	45%	1



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.075	1	.784
Breslow (Generalized Wilcoxon)	.407	1	.524
Tarone-Ware	.227	1	.634

Test of equality of survival distributions for the different levels of AAD DUPA.

Figure 5. Kaplan Meier plot- arrhythmia free survival time was not significantly influenced by the administration of antiarrhythmic drugs after the procedure; AAD = antiarrhythmic drugs.

with other tachyarrhythmias, termination of a long-standing arrhythmia during radiofrequency delivery that can be attributed to the functional elimination of a critical driving mechanism.

Our findings, that AF termination during RF delivery improves outcomes after catheter ablation of persistent AF have been previously reported in several studies[9,10,11]. Other trials , including the STAR AF II randomized trial, where PVI alone was compared to CFAE and linear ablations, showed no significant difference in 18-month AF-free survival between patients with and without acute arrhyhtmia termination (52.7% versus 42.4%; p=0.09), or among the three ablation strategies regardless of termination (59% of patients were AF-free at 18 months in the PVI group compared with 49% in the PVI + CFAE group and 46% in the PVI + linear ablation group; p=0.15). However, termination during the PVI step was predictive of AF-free survival (49.3% versus 35.7% in termination versus no termination, respectively; p=0.01)[4]. Nonetheless, a major criticism of STAR-AF II is that in 26% of the patients block was no present in the lines created.

Our overall success rate (59% after all multiple procedures) it is similar to those reported in most of the studies and it should be noted that, because of symptom improvement in a number of cases, some patients with recurrence did not undergo a repeat ablation. A higher rate of re-ablation may have resulted in improved outcomes (mean procedure number 1.7±0.8 is somewhat lower than usual values reported for catheter ablation for persistent AF)[5,12]. AAD use during blanking period after AF ablation did not influence outcomes in our study.

The mode of AF termination (directly to sinus rhythm versus via transformation into a more organized form of atrial arrhythmia tachycardia/atrial flutter)

was not predictive of recurrence in some studies[13], in our case intraprocedural organization seemed to be associated with fewer relapses but only in the univariate analysis. Some reaserchers find that AF termination at index ablation is associated with a greater proportion of recurrences in the form of AT/AFL relative to AF[10]. These, and perhaps other contradictory results, could be explained by the lack of standardization of the additional lesion sets and the fact that even apparently similar techniques (lines/CFAE) are defined and performed in various manners and with different endpoints in different centres.

Therefore, more focused mapping and ablation of non-PV triggers might be the solution for better rhythm outcome of PeAF ablation rather than an empirical extra-PV LA ablations. It might be essential to also consider patient factors before procedure, including clinical characteristics, biomarkers or genetic factors[9] when choosing an ablation strategy for PsAF.

Our study shows that arrhythmia termination during ablation, regardless of the method by which it is obtained, (CFAE/lines/etc) seems to indicate a more favourable prognosis but alternatively may indicate a subgroup of patients with a limited and ablation-sensitive set of driver mechanisms and more research is necessary in order to properly select the cases that warrant additional ablation beyond the PVAI.

STUDY LIMITATIONS

This is a single center, observational study, with a relatively small cohort and there was no randomization between groups with AAD vs without AAD.

Although the follow-up method was according to the guidelines, it is possible that the time to AF for some patients might not have been accurately captured due to intermittent monitoring.

CONCLUSION

We have found that in patients with PsAF and LS-PsAF restoration of sinus rhyhtm during pulmonary vein isolation, ablation of CFAE or resultant atrial tachycardia predicts long term procedural success. Further research to determine the best strategy to achieve this outcome is necessary. Postprocedural AAD do not influence long term results.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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