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Antoine Da Costa *

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Research Article

Spontaneous Sinus Rhythm Restoration Within the Blanking Period as a Predictor of Late Recurrence After Catheter Ablation of Persistent Atrial Fibrillation

Jean-Baptiste Guichard [1,2,3], Karim Benali [1, 2], Pauline Mahinc [1], Maurine Guirao [1], Cécile Romeyer [1], Cedric Yvorel [1], Roger Borràs [3], Jean Michel Vovor [1], Antoine Da Costa [1,2]*

[1]Department of Cardiology, University Hospital of Saint-Étienne, Saint-Étienne, France.

[2]Sainbiose, DVH, Inserm U1059, University Hospital of Saint-Étienne, Saint-Étienne, France.

[3]Arrhythmia Unit, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Carrer Villarroel 170, 08036 Barcelona, Spain.

***Corresponding Author:** Antoine Da Costa, Service de Cardiologie, Hôpital Nord Centre Hospitalier Universitaire de Saint-Etienne F-42055 Saint-Etienne Cedex 2.

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Abstract

Aim - Various ablation strategies have been developed for persistent atrial fibrillation (AF), but there is no standardized management for early and late post-procedural management periods. The clinical benefits of spontaneous restoration of sinus rhythm (SR) during the blanking period, without electrical cardioversion at the end of the procedure, remain unknown.

Objectives - The primary goal of our prospective observational cohort study was to determine the proportion of patients who achieve SR spontaneous restoration during the 3-month blanking period. The secondary goal was to assess predictors of long-term AF-free survival following ablation for persistent AF, with a particular focus on the role of spontaneous SR restoration during the procedure and after the 3-month blanking period.

Materials and Methods – This was an observational, prospective, monocentric, cohort trial designed to assess arrhythmia-free survival during a median 17.8-month follow-up after catheter ablation (CA) for persistent AF without electrical cardioversion at the end of the procedure. The study recorded spontaneous SR restoration at the end of the 3-month blanking period and reported supraventricular arrhythmia recurrence and/or continuation during the follow-up.

Results. Out of 213 patients included in the prospective cohort, 60 patients (28.2%) achieved SR restoration during the CA procedure. Among patients with arrhythmia continuation at the end of the procedure, spontaneous SR restoration was observed in 68 patients (44.4%) at the end of the 3-month blanking period. Lack of spontaneous SR restoration during the blanking period (OR=2.25, 95%CI:1.12-3.84) and ablation of complex fractionated atrial electrograms (OR=2.25, 95%CI:1.09-4.65) were found to be independent predictors of arrhythmia recurrence or continuation during the median 17.8-month follow-up. SR restoration during the CA procedure was not associated with arrhythmia-free survival during the long-term follow-up. Conclusions. This study evaluated a novel approach of tolerating arrhythmia continuation after CA for persistent AF and avoiding electrical cardioversion. Spontaneous SR restoration at the end of the 3-month blanking period is frequent and an independent predictor of arrhythmia-free survival during the long-term follow-up.

Conclusion

This study evaluated a novel approach of tolerating arrhythmia continuation after CA for persistent AF and avoiding initial electrical cardioversion. Spontaneous SR restoration at the end of the 3-month blanking period is frequent and an independent predictor of arrhythmia-free survival during the long-term follow-up.

Keywords: persistent atrial fibrillation; catheter ablation; blanking period; early recurrence; sinus rhythm restoration

Abbreviations

AAD: anti-arrhythmic drug

AF: atrial fibrillation

AFL: atrial flutter

CA: catheter ablation

CFAE: complex fractionated atrial electrogram

CTI: cavo-tricuspid isthmus

EAM: electroanatomical mapping

ECG: electrocardiogram

LA: left atrium

PVI: pulmonary vein isolation

SR: sinus rhythm

Introduction

Half of patients with atrial fibrillation (AF) experience a persistent form of the condition (1), which is associated with a more unfavorable prognosis compared to paroxysmal AF in terms of thromboembolic risk, heart failure and health care utilization (2,3). In addition, the therapeutic management of persistent AF is suboptimal, and rhythm control has limited long-term success in treating this condition, though AF catheter ablation (CA) is more favorable than anti-arrhythmic drug (AAD) therapies (4). Nonetheless, CA for persistent AF is not well standardized due to the various lesion set options and periprocedural management. As a result, the AF-free survival during a 12-month follow-up after CA for persistent AF ranges between 51% and 69% in different randomized controlled trials (4–7). While pulmonary vein isolation (PVI) seems to be the preferred treatment for paroxysmal AF, the optimal ablation strategy for persistent AF remains unclear excepted for patients with heart failure (8,9). As highlighted in the STAR-AF-II study and various meta-analyses, the benefits of atrial substrate ablation, including the creation of additional lines or the ablation of complex fractionated atrial electrograms (CFAE), is not demonstrated (5). While current recommendations suggest ablation for symptomatic persistent AF following antiarrhythmic treatment failure or as a first-line option (10), procedural and peri-procedural modalities are not standardized. More recently, several studies have been published in favor of CA approach for persistent AF particularly in heart failure populations (11-13). In patients with heart failure and AF, CA has been shown to reduce arrhythmia burden, reverse left ventricular remodeling, and reduce mortality as well as in end-stage heart failure (13). Other strategies than CFAE have been evaluated with apparent better long-term success but strategies are still of debate (14, 15). The improvements in ablation technique and peri-procedural patient management could enhance the long-term prognosis of AF-free survival (14, 15). Although restoration of sinus rhythm (SR) during the ablation procedure appears to predict better long-term outcomes (7), the prognostic value of this strategy is unclear due to conflicting results (16). However, SR restoration through atrial substrate ablation has several limitations, including the need for extensive and/or multiple ablations, which can increase procedural complications. In persistent AF, the significance of the commonly accepted 3-month blanking period following PVI is not well understood, particularly in cases of atrial substrate ablation and frequent use of electrical cardioversion at the end of the procedure (17–20). The yield of SR spontaneous restoration during the 3-month blanking period in the absence of cardioversion at the end of the procedure is not known.

The primary goal of our prospective observational cohort study was to determine the proportion of patients who achieve SR spontaneous restoration during the 3-month blanking period. The secondary goal was to assess predictors of long-term AF-free survival following ablation for persistent AF, with a particular focus on the role of spontaneous SR restoration during the procedure and after the 3-month blanking period.

Materials and methods

Study population

Consecutive patients diagnosed with persistent AF and scheduled for radiofrequency CA were systematically enrolled at the University Hospital of Saint-Étienne, France from May 2017 to December 2020. Patients with symptomatic and AAD refractory persistent AF were screened for eligibility in this prospective cohort study. Persistent AF was defined as continuously sustained AF lasting beyond 7 days, including episodes terminated by pharmacological or electrical cardioversion after 7 days (10). Only patients in AFib for the CA procedure were included in the study. Patients with a contraindication for CA, such as intracardiac thrombus diagnosed by pre-procedural transesophageal echocardiogram, and patients without a minimum 3-month clinical follow-up after CA (n=10), were excluded from the cohort. Every included patient provided informed and written consent, and the research protocol was approved by the local ethics committee of the University Hospital of Saint-Étienne, France.

Electrophysiological study and catheter ablation

All patients undergoing CA for persistent AF were required to continue taking oral anticoagulants including new oral anticoagulants or vitamin K antagonists, without any discontinuation for at least 3 weeks before the procedure until the day of the procedure (10). AADs were resumed four hours after the end of the procedure. The electrophysiological procedure was performed with patients under conscious sedation or general anesthesia. Transvenous access to the left atrium (LA) was achieved by transseptal puncture under fluoroscopic and/or echocardiographic guidance. A steerable decapolar catheter was placed into the coronary sinus for pacing and recording purposes. The non-steerable sheaths, diagnostic and mapping catheters were continuously perfused with heparinized saline serum. After the transseptal puncture, a weight-based bolus dose of unfractionated heparin was administered, and additional boluses were given based on an activated clotting time greater than 300 seconds.

Electroanatomical mapping (EAM) was performed using a high-density diagnostic catheter (PENTARAY or LASSO catheters) and a 3D-mapping system (CARTO 3 system). Radiofrequency CA was performed using an additional transseptal puncture and a 3.5mm open irrigated-tip magnetic ablation catheter (Navistar RMT ThermoCool or Smarttouch catheters).

The CA procedure involved circumferential PVI as the primary step and achieved by eliminating or dissociating pulmonary vein potentials using the HD diagnostic catheter. Subsequently, the operator at their discretion performed an additional ablation based on EAM assessment of the atrial substrate. Various tool set options were used to ablate the atrial substrate, either individually or in combination, including ablation of complex fractionated atrial electrograms (CFAE), coronary sinus defragmentation, additional atrial lines such as roof and posterior mitral lines, Marshall vein ethanol infusion, and ablation of the cavo-tricuspid isthmus (CTI). SR restoration during the ablation procedure was systematically recorded, and no electrical or pharmacological cardioversion was performed during or at the end of the CA procedure.

Definition of the explanatory covariates

The clinical covariates used in this study were collected at baseline when patients were included. Medication use, including AADs and betablockers, as well as the CHA2DS2-VASc score, which includes congestive heart failure, hypertension, age≥75, diabetes mellitus, and prior stroke or transient ischemic attack, were also collected. The HAS BLED score was calculated based on different clinical features, including hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, age over 65, and drugs/alcohol use. Hypertension was defined as an average blood pressure among three measures of >140mmHg systolic, or >90mmHg diastolic, or use of blood pressure medication at inclusion. Diabetes mellitus and dyslipidemia were defined as the use of antidiabetic medication and medication for lipid disorders, respectively. Obstructive sleep apnea was reported if the patient had a history of severe obstructive sleep apnea and/or chronic treatment with continuous positive airway pressure machine. Long-standing persistent AF was defined as continuous AF lasting more than 12 months10. A preprocedural transthoracic echocardiography was performed to assess left ventricular ejection fraction, the presence of dilated LA, defined as a LA area greater than 24 cm2, and aortic and mitral valve disease based on the presence of moderate or severe mitral and aortic regurgitation and/or stenosis.

Post-ablation management and follow-up

Oral anticoagulation was continued for 2 months after CA and thereafter depending on the physician's discretion (10). The same AAD regimen was continued after the CA procedure until the first 3-month clinical follow-up (10). Before patient discharge, which occurred 24 hours after CA, rhythm assessment was conducted based on a 12-lead surface electrocardiogram (ECG). Clinical visits were conducted at 3, 6, and 12 months, during which, patient symptoms were evaluated, a 12-lead ECG, and a 72-hour Holter ECG was recorded. Any changes in medication were also reported. No patients were cardioverted during the 3 months blanking period. Therapeutic management at 3 months after CA, which corresponded to the end of the blanking period following CA, was thoroughly documented, including AAD initiation and/or change, management of electrical cardioversion, and redo CA procedure. In cases where arrhythmia persisted after the 3-month blanking period, the patient was scheduled for an electrical cardioversion and/or redo CA procedure. The therapeutic management during the follow-up period was determined at the discretion of the physician. The presence of supraventricular arrhythmia was defined as the detection of AF, typical or atypical atrial flutter (AFL).

Statistical analysis

Continuous variables were presented as mean ± standard deviation, while median and interquartile range were used as appropriate. Categorical variables were expressed as absolute numbers and percentages. Logistic regression analysis was used to investigate the impact of baseline characteristics on arrhythmia recurrence, with a significance level set at $P<0.05$. Backward stepwise selection algorithms were employed to construct the multivariate logistic regression model, where covariates with a P-value<0.10 in the univariate analysis were retained in the final model. The odds ratio and 95% confidence interval were also calculated. All statistical tests used a two-sided type I error of 5%. The R software for Windows version 4.2.1 (R Project for Statistical Computing, Vienna, Austria) was used for the statistical analysis.

Results

Baseline characteristics

A total of patients with persistent AF underwent CA and were included in this prospective cohort study. The baseline characteristics of the patients are summarized in Table 1. The mean age of the patients was 66 years, with 80.8% of them being male, and a median CHA2DS2 VASc score of 2. The median AF duration was 6 months, with 17.8% of the cohort having long-standing persistent AF. Most patients were receiving AAD and betablockers at inclusion. Two-thirds of the patients had LA dilation. In addition to circumferential PVI, CFAE ablation (61.5%) was mainly performed, followed additional lines (31.0%), CTI ablation (9.9%), and ethanol infusion of the vein of Marshall (8.9%).

		All (n=213)	
Clinical features			
Age (years)		66	60 - 71
Age>65		114	53.5%
Male gender		172	80.8%
Body mass index (kg/m2)		28.5	+/- 4.9
Hypertension		94	44.1%
Diabetes mellitus		25	11.7%
Obstructuve sleep apnea		34	16.0%
History of vascular diseases		54	25.4%
History of stroke		9	4.2%
Long-standing persistent atrial fibrillation		38	17.8%
AF duration (months)		6	3 - 12
History of catheter ablation		27	12.7%
CHA2DS2 VASc score		2	1 -3
HAS BLED score		1	0 - 2
Ecocardiographic features			
Left ventricular ejection fraction (%)		54.5	+/- 10.4

Dilated left atrium			123	57.7%
Mitral valve disease			14	6.6%
Aortic valve disease			7	3.3%
Catheter ablation features				
Ablation of extra-PVI sites			168	78.9%
	Ablation of CFAE		131	61.5%
	Management of additional lines		66	31.0%
	Alcoolization of the vein of Marshall		19	8.9%
	ICT ablation		21	9.9%
Sinus rhythm during catheter ablation			60	28.3%
Medical management after the catheter ablation				
Periprocedural management				
	Use of betablockers		125	58.7%
	Use of AAD		184	86.4%
Management at 3 mont post procedure				
	Supraventricular arrhythmia		99	46.5%
	Electrical cardioversion		62	29.1%
	Left catheter ablation		24	11.3%
	Use of AAD		106	49.8
Long-term follow-up				
Follow-up duration (months)			17.8	7.0 - 26.0
Reccurence			71	33.3%
	AF		51	27.7%
	Atypical AFL		18	8.5%
	Typical AFL		2	0.9%

Table 1: Baseline and follow-up characteristics.

AAD: antiarrhythmic drug; AF: atrial fibrillation; AFL: atrial flutter; CTI: cavo-tricuspid isthmus; PVI: pulmonary vein isolation.

Continuous variables were presented as mean ± standard deviation, while median-interquartile range was used as appropriate. Categorical variables were expressed as total numbers and percentages.

Sinus rhythm restoration along the follow-up

Among the baseline 213 patients, 60 patients (28.2%) obtained SR restoration during the CA procedure. The detailed distribution of SR restoration at the end of the blanking period and during long-term follow-up according to rhythm status at the end of the ablation procedure is provided in Figure 1. Briefly, SR restoration was observed in 114 patients (53.5%) at the end of the 3-month blanking period after the CA procedure. Notably, SR was observed at the end of the blanking period in 68 patients (44.4%) who did not achieve SR restoration during the ablation procedure. During a median follow-up of 17.8 months, SR restoration was evaluated in 66.7% (142 patients) of the entire cohort.

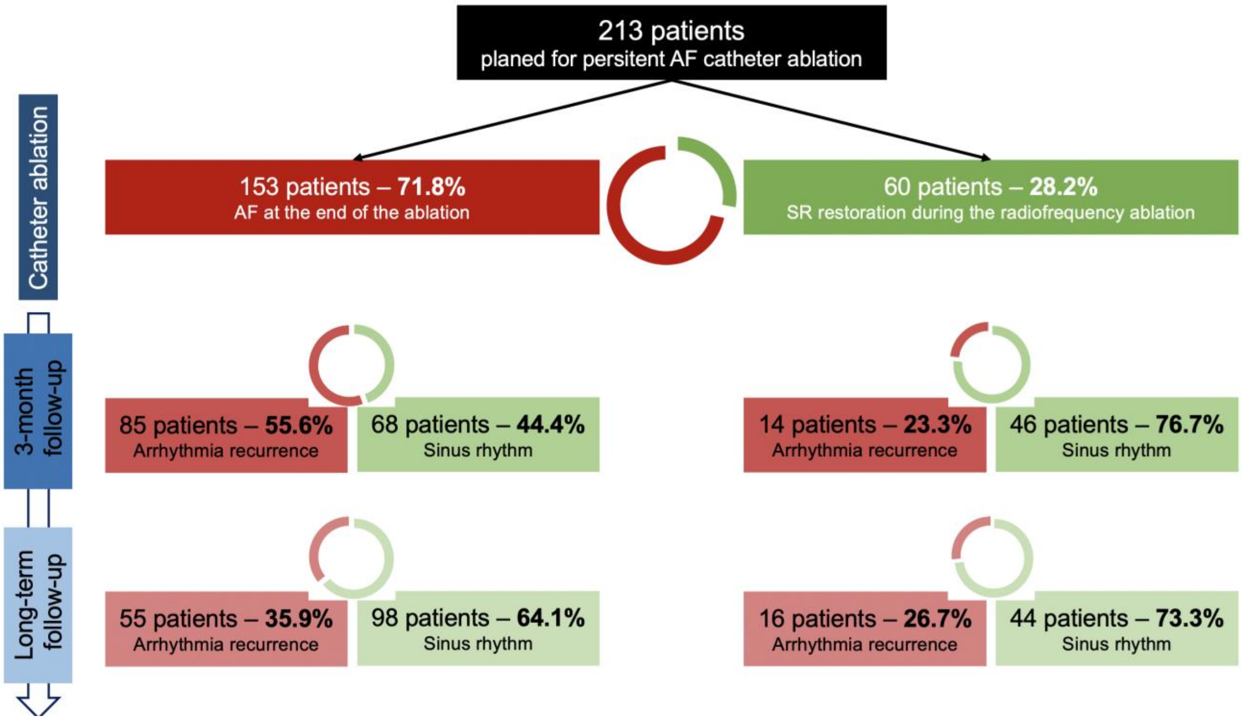

Figure 1: Distribution of rhythm features at the end of the index ablation and during the 17.8-month follow-up.

A detailed distribution of SR restoration and persistent arrhythmia at 3-month and long-term follow-up is detailed according to the rhythm status at the end of the index ablation.

AF: atrial fibrillation; SR: sinus rhythm

Predictors of AF-free survival during the follow-up

This cohort study identified several factors associated with AF-free survival during the 17.8-month follow-up, as shown in Table 2. Univariate analysis revealed that the assessment of supraventricular arrhythmia at the end of the blanking period (OR=3.09, 95%CI:1.71-5.60), the management of electrical cardioversion at 3 months (OR=2.08, 95%CI:1.12-3.84), and ablation of CFAE during the index procedure (OR=2.07, 95%CI:1.13-3.79) were linked to persistent arrhythmia. There was a trend towards an association between long-standing persistent AF and persistent arrhythmia during follow-up, although statistical significance was not reached. In contrast, the use of AAD before and after the blanking period was associated with SR restoration. Multivariate analyses identified two independent predictors of persistent arrhythmia during follow-up: the assessment of supraventricular arrhythmia at the end of the blanking period (OR=2.25, 95%CI:1.12-3.84), and ablation of CFAE (OR=2.25, 95%CI:1.09-4.65).

Given that the lack of SR restoration at the end of the blanking period is a major predictor of poor prognosis during the follow-up, Table 3 provides further analysis of baseline predictors of persistent AF at 3 months. While SR restoration during the ablation procedure is independently associated with the assessment of SR 3 months thereafter (OR=4.17, 95%CI: 2.08-8.33), ablation of CFAE and additional lines were found to be independently associated with persistent arrhythmia at the end of the blanking period (OR=2.00, 95%CI: 1.03-3.89 and OR=3.07, 95%CI: 1.51-6.23, respectively). The ablation of CFAE (OR=10.77, 95%CI: 1.32-87.66) was the only independent predictor of arrhythmia recurrence in form of atypical AFL compared with AF recurrence (Table 4).

		Persistent Arrhythmia	Sinus rhythm	Unadjusted			Adjusted		
		(n=71)	(n=142)	OR	95% CI	P	OR	95% CI	P
Clinical features									
Age		67 (61 - 71)	66 (60 - 72)	1.02	(0.98-1.06)	0.28			
Male gender	52 (75.4%)	117 (81.3%)	0.81	(0.40-1.66)	0.57				
Body mass index (kg/m2)	28.0 +/- 5.1	28.8 +/- 4.8	0.96	(0.90-1.02)	0.21				
Hypertension	22 (31.9%)	72 (50.0%)	**0.54**	**(0.30-0.98)**	**0.04**	**0.43**	**(0.21-0.87)**	**0.02**	
Diabetes mellitus	6 (8.7%)	19 (13.2%)	0.61	(0.23-1.61)	0.32				
Obstructive sleep apnea	13 (18.8%)	21 (14.6%)	1.31	(0.62-2.81)	0.48				
History of vascular diseases	17 (24.6%)	37 (25.7%)	0.92	(0.47-1.79)	0.92				
Long-standing persistent atrial fibrillation	17 (24.6%)	21 (14.6%)	**1.86**	**(0.90-3.86)**	**0.10**	-	-	-	

History of catheter ablation		10 (14.5%)	17 (11.8%)	1.21	(0.52-2.79)	0.66			
CHA2DS2 VASc score		2 (1 - 3)	2 (1- 3)	0.91	(0.73-1.12)	0.35			
Echocardiographic features									
Left ventricular ejection fraction (%)		54 +/- 10	55 +/- 11	0.99	(0.96-1.02)	0.41			
Dilated left atrium		40 (74.1%)	83 (68.0%)	1.44	(0.71-2.95)	0.31			
Mitral valve disease		3 (4.3%)	11 (7.6%)	0.53	(0.14-1.95)	0.34			
Catheter ablation features									
Ablation of extra-PVI sites									
	Ablation of CFAE	48 (69.6%)	78 (54.2%)	**2.07**	**(1.13-3.79)**	**0.02**	**2.25**	**(1.09-4.65)**	**0.03**
	Management of additional lines	18 (26.1%)	48 (33.3%)	0.67	(0.35-1.26)	0.21			
	Ethanol infusion of the vein of Marshall	5 (7.2%)	14 (9.7%)	0.69	(0.24-2.00)	0.50			
	CTI ablation	7 (10.1%)	14 (9.7%)	1.00	(0.39-2.60)	1.00			
Sinus rhythm during catheter ablation		16 (23.2%)	44 (30.6%)	0.65	(0.34-1.25)	0.20			
Catheter ablation features									
Periprocedural management									
	Use of betablockers	37 (53.6%)	88 (61.1%)	0.70	(0.39-1.25)	0.23			
	Use of AAD when catheter ablation	56 (81.2%)	129 (89.6%)	**0.37**	**(0.15-0.95)**	**0.04**	**-**	**-**	**-**
Management at 3-month post procedure									
	Supraventricular arrhythmia	44 (62.0%)	55 (38.2%)	**3.09**	**(1.71-5.60)**	**<0.01**	**2.25**	**(1.12 - 4.42)**	**0.02**
	Electrical cardioversion	27 (39.1%)	35 (24.3%)	**2.08**	**(1.12-3.84)**	**0.02**	**-**	**-**	**-**
	Left catheter ablation	9 (13.0%)	15 (10.4%)	1.23	(0.51-2.96)	0.65			
	Use of AAD	55 (79.7%)	129 (89.6%)	**0.34**	**(0.13-0.84)**	**0.02**	**-**	**-**	**-**

Table 2: Univariate and Multivariate logistic regression models to predict persistent arrhythmia during a median 17.8-month follow-up.

AAD: antiarrhythmic drug; AF: atrial fibrillation; AFL: atrial flutter; CTI: cavo-tricuspid isthmus; PVI: pulmonary vein isolation.

Backward stepwise selection algorithms were used for building up the multivariate logistic regression model.

	Arrhythmia	Sinus rhythm	Unadjusted			Adjusted		
	(n=99)	(n=114)	OR	95% CI	P	OR	95% CI	P
Clinical features								
Age	66 (61 - 71)	67 (60 - 71)	1.02	(0.98 - 1.05)	0.37			
Male gender	81 (81.8%)	88 (77.2%)	1.44	(0.72 - 2.88)	0.31			
Body mass index (kg/m2)	28.9 +/- 5.5	28.2 +/- 4.3	1.03	(0.97 - 1.09)	0.34			
Hypertension	45 (45.5%)	49 (43.0%)	1.13	(0.66 - 1.95)	0.66			
Diabetes mellitus	12 (12.1%)	13 (11.4%)	1.09	(0.47 - 2.51)	0.85			
Obstructuve sleep apnea	17 (17.2%)	17 (14.9%)	1.20	(0.58 - 2.50)	0.63			
History of vascular diseases	26 (26.3%)	28 (24.6%)	1.11	(0.60 - 2.07)	0.74			
Long-standing persistent atrial fibrillation	21 (21.2%)	17 (14.9%)	1.36	(0.66 - 2.79)	0.40			
History of catheter ablation	11 (11.1%)	16 (14.0%)	0.77	(0.34 - 1.74)	0.77			
CHA2DS2 VASc score	2 (1 - 3)	2 (1 - 3)	1.01	(0.83 - 1.23)	0.92			

Echocardiographic features								
Left ventricular ejection fraction (%)	55 +/- 10%	55 +/- 10%	1.00	(0.97 - 1.03)	0.99			
Dilated left atrium	60 (60.6%)	63 (55.3%)	1.24	(0.65 - 2.38)	0.51			
Mitral valve disease	5 (5.1%)	9 (7.9%)	0.62	(0.20 - 1.92)	0.41			
Catheter ablation features								
Ablation of extra-PVI sites								
Ablation of CFAE	67 (67.7%)	59 (51.8%)	**1.95**	**(1.12 - 3.41)**	**0.02**	**2.00**	**(1.03-3.89)**	**0.04**
Management of additional lines	38 (38.4%)	28 (24.6%)	**1.91**	**(1.06 - 3.46)**	**0.03**	**3.07**	**(1.51-6.23)**	**<0.01**
Alcoolization of the vein of Marshall	11 (11.1%)	8 (7.0%)	1.66	(0.64 - 4.30)	0.30			
ICT ablation	4 (4.0%)	17 (14.9%)	**0.24**	**(0.08 - 0.74)**	**0.01**	-	-	-
Sinus rhythm during catheter ablation	13 (13.1%)	46 (40.4%)	**0.24**	**(0.12 - 0.48)**	**<0.01**	**0.27**	**(0.13 - 0.56)**	**<0.01**
Catheter ablation features								
Use of betablockers	53 (53.5%)	72 (63.2%)	0.67	(0.39 - 1.17)	0.16			
Use of AAD	82 (82.8%)	103 (90.4%)	**0.27**	**(0.09 - 0.76)**	**0.01**	0.37	(0.12-1.13)	0.08

Table 3: Univariate and Multivariate logistic regression models to predict persistent arrhythmia at the end of the blanking period following the index catheter ablation.

AAD: antiarrhythmic drug; AF: atrial fibrillation; AFL: atrial flutter; CTI: cavo-tricuspid isthmus; PVI: pulmonary vein isolation.

Backward stepwise selection algorithms were used for building up the multivariate logistic regression model.

	aAFL	AF	Unadjusted			Adjusted		
	(n=18)	(n=51)	OR	95% CI	P	OR	95% CI	P
Clinical features								
Age	67 (61 - 70)	68 (61 - 71)	0.97	(0.89-1.05)	0.44			
Male gender	4 (23.5%)	11 (22.0%)	1.09	(0.30-4.02)	0.90			
Body mass index (kg/m2)	29.5 +/- 4.5	27.5 +/- 5.2	1.08	(0.97-1.20)	0.17			
Hypertension	6 (35.3%)	16 (32.0%)	1.16	(0.36-3.69)	0.80			
Diabetes mellitus	2 (11.8%)	4 (8.0%)	1.53	(0.26-9.23)	0.64			
Obstructive sleep apnea	5 (27.8%)	8 (16.0%)	2.02	(0.56-7.25)	0.28			
History of vascular diseases	2 (11.8%)	15 (30.0%)	0.31	(0.06-1.53)	0.15			
Long-standing persistent atrial fibrillation	4 (23.5%)	13 (31.0%)	0.69	(0.19-2.51)	0.57			
History of catheter ablation	0 (0.0%)	5 (9.8%)	2.14	(0.53-8.69)	0.29			
CHA2DS2 VASc score	2 (1 - 3)	2 (1 - 3)	0.88	(0.56-1.38)	0.57			
Echocardiographic features								
Left ventricular ejection fraction (%)	53 +/- 12	54 +/- 8	1.00	(0.94-1.06)	0.86			
Dilated left atrium	11 (68.8%)	29 (76.3%)	0.68	(0.19-2.49)	0.56			
Mitral valve disease	2 (11.1%)	1 (2.0%)	6.25	(0.53-73.57)	0.15			
Catheter ablation features								
Ablation of extra-PVI sites								
Ablation of CFAE	17 (94.4%)	31 (60.8%)	**10.97**	**(1.35-88.99)**	**0.03**	**10.77**	**(1.32-87.66)**	**0.03**
Management of additional lines	1 (14.3%)	4 (18.2%)	0.75	(0.07-8.09)	0.81			
Alcoolization of the vein of Marshall	0 (0.0%)	5 (9.8%)	-	-	-			
CTI ablation	1 (5.6%)	6 (11.8%)	0.44	(0.05-3.94)	0.46			
Sinus rhythm during catheter ablation	3 (16.7%)	13 (25.5%)	0.59	(0.15-2.35)	0.45			
Catheter ablation features								
Periprocedural management								
Use of betablockers	12 (66.7%)	25 (49.0%)	2.08	(0.68-6.40)	0.20			
Use of AAD when catheter ablation	13 (72.2%)	43 (87.8%)	0.36	(0.10-1.38)	0.14			
Management at 3 mont post procedure								
Supraventricular arrhythmia	14 (77.8%)	30 (58.8%)	2.45	(0.71-8.49)	0.16			
Electrical cardioversion	5 (27.8%)	22 (43.1%)	0.51	(0.16-1.64)	0.26			
Left catheter ablation	0 (0.0%)	2 (8.0%)	-	-	-			
Use of AAD	11 (61.1%)	22 (44.0%)	**0.28**	**(0.08-1.02)**	**0.05**	-	-	-

Table 4: Univariate and Multivariate logistic regression models to predict arrhythmia recurrence in form of atypical atrial flutter during the 17.8-month follow-up.

aAFL: atypical atrial flutter; AAD: antiarrhythmic drug; AF: atrial fibrillation; AFL: atrial flutter; CTI: cavo-tricuspid isthmus; PVI: pulmonary vein isolation.

Backward stepwise selection algorithms were used for building up the multivariate logistic regression model.

Discussion

This study is the first to investigate the clinical impact of spontaneous SR restoration during the blanking period in patients after CA for persistent AF and persistent arrhythmia at the end of the procedure. 44.4% patients who had AF at the end of the ablation procedure presented spontaneous SR restoration at the end of the 3-month blanking period. Considering the novel procedural strategy of arrhythmia tolerance at the end of the procedure, SR restoration at 3 months is an independent predictor of AF-free survival during the 17.8-month follow-up, while SR restoration during the ablation procedure was not associated with a better prognosis. Ablation of CFAE was associated with persistent arrhythmia at 3 months, during the long-term follow-up, and the occurrence of atypical AFL.

Current international guidelines recommend a 3-month blanking period following CA procedure for persistent AF, during which early arrhythmia recurrence should not been considered (9,10). However, half of the patients experience supraventricular arrhythmia recurrence during this period (20, 21) due to potential transient mechanisms, such as inflammation (22), autonomic nervous system imbalance (23), and the direct effect of the ablation set (24). The concept of a blanking period has been supported by the fact that 50% of patients experiencing early recurrence are free of long-term arrhythmia (25). Nevertheless, recent data have challenged the consensus view that early recurrence is a transient condition. A meta-analysis suggests that freedom from AF recurrence during the 3-month blanking period is highly predictive of long-term success after CA procedures (26). These results have been recently confirmed (27), refuting early arrythmia recurrence as a transient condition and proposing the shortening of the blanking period to 30 days after CA for persistent AF. As a result, early redo procedures in case of early arrythmia recurrence have been proposed to reduce patient symptoms and improve AF-free survival (28). In this study, we aimed to assess the clinical benefit of a novel procedural and postprocedural management approach regarding the blanking period. Specifically, we proposed tolerating persistent arrhythmia at the end of the index ablation procedure and avoiding periprocedural electrical cardioversion and/or extensive ablation until acute SR restoration. Following this approach, spontaneous SR restoration was quite common, with 44.4% of patients who had persistent arrhythmia at the end of the CA procedure being in SR at the end of the blanking period. Notably, spontaneous SR restoration during the blanking period appears to have clinical value, as patients with SR at 3 months presented with a 2-fold higher long-term AF-free survival. Therefore, this novel approach regarding the blanking period proposes avoiding early redo ablation procedures and assessing patient rhythm at the end of the blanking period. In cases of persistent arrhythmia, a systemic electrical cardioversion and/or redo CA procedure were proposed.

Catheter ablation of AF using thermal energy, such as radiofrequency in this study, results in tissue scarring primarily through tissue necrosis. The goal of tissue necrosis is to create a conduction block line, either as part of pulmonary vein isolation or additional atrial lines. However, tissue necrosis during radiofrequency ablation, which occurs when tissue temperature exceeds 60ºC, leads to the local and systemic release of pro-inflammatory cytokines (29). This local inflammation induces electrical and structural remodeling of the adjacent atrial tissue. Specifically, the pro-inflammatory cascade results in a heterogeneous reduction in conduction velocities, as well as decreases in calcium transients and action potential duration (30). Several mechanisms leading to atrial remodeling adjacent to thermally damaged tissue have been identified, including changes in ionic currents, a decrease and abnormalities in the distribution of connexins 40 and 43 (31), as well as fibrotic mechanisms involving the local recruitment of macrophages (32). These electrical and structural changes, secondary to local inflammation, have a pro-arrhythmic effect. As a result, catheter ablation procedures using thermal energy can have a paradoxical transient pro-arrhythmic effect due to local and systemic inflammation (20). The findings from our study reflect this transient pro-arrhythmic phenomenon. Indeed, while the majority of patients do not revert to sinus rhythm during the endocavitary ablation procedure, a significant proportion are in sinus rhythm after the blanking period, without requiring electrical cardioversion. Our study supports the notion that the efficacy of a persistent AF ablation procedure is difficult to assess in the short term. A consolidation period for the ablation lesions, along with the resolution of local inflammatory mechanisms, is necessary to evaluate the procedure's efficacy at the end of the blanking period.

Although PVI remains the cornerstone of invasive AF therapy (10), various combinations of additional lesion sets and energy sources have been explored in dedicated studies, resulting in significant variations (5, 33–36). The long-standing belief that PVI alone is inadequate for persistent AF was challenged in the STAR-AF-2 trial (5), which randomized persistent AF patients to PVI alone, PVI + linear ablation, or PVI + CFAE ablation. The study found no difference in efficacy among the three groups. A meta-analysis of CA studies similarly showed no difference in AF freedom between PVI alone PVI + additional lesions (53% vs 49%, respectively) (33). PVI as a first-line therapy for persistent AF ablation seems to be sufficient (36) and is the preferred option in most of the European centers (37). Our study also confirms these findings, as no additional lesion set option was associated with better long-term outcomes. Furthermore, CFAE ablation was found to be associated with arrhythmia continuation and recurrence at the end of the 3-month blanking period and during the follow-up. It was also identified as an independent factor of atypical AFL during the follow-up. Ablation of the atrial substrate increases procedure duration, X-ray exposure, and the risk of potential complications. However, promising results have been seen with novel standardized strategies for ablating atrial substrate, such as those based on low-voltage myocardium-guided additional atrial ablation (38) or the extensive LA compartmentalization using ethanol infusion of the vein of Marshall (39). Further randomized trials are necessary to determine the optimal lesion set persistent AF ablation.

The clinical benefit of restoring SR during CA procedure for persistent AF on the long-term arrhythmia-free survival is uncertain. A stepwise approach, involving consecutive PVI, CFAE ablation, and linear ablation, has been proposed with SR restoration at the end of the procedure as the short-term clinical endpoint (7.) Initial data suggest that periprocedural SR restoration could be achieved in most patients and is the main predictor of freedom from recurrent arrhythmia during a 5-year follow-up. However, the success rate of SR restoration during CA for persistent AF in several studies is inconsistent, and this approach may lead to extensive and/or repeated ablation procedures with potential complications (16). Our study challenges the benefit of SR restoration during the CA procedure. Firstly, the success rate of SR restoration using a pragmatic lesion set approach is low, with less than one-third of the patients being in SR at the end of the procedure. Secondly, no association between SR restoration during the index procedure and long-term prognosis was found.

Clinical factors that indicate advanced atrial cardiomyopathy have been identified as predictors of long-term arrhythmia recurrence following CA for persistent AF (16). These factors include long-standing persistent AF, dilated LA (40), structural heart disease, ageing, and obesity. However, in our study, except for the association between long-standing AF and worse clinical outcomes, we did not find any clinical factors of atrial cardiomyopathy to be independent predictors of long-term AF-free survival. Nevertheless, the benefit of peri- and post-procedural AAD use on long-term freedom from arrhythmia suggests the role of advanced atrial substrate in persistent AF patients.

The current study proposes a novel approach of tolerating persistent arrhythmia at the end of the ablation procedure, avoiding periprocedural electrical cardioversion, and assessing the patient's rhythm at the end of the 3-month blanking period. SR restoration during the first 3 months after CA for persistent AF is frequent and seems to predict the long-term success of ablation in this subset of patients. This approach aims to reduce unnecessary and inefficient periprocedural electrical cardioversion, as many patients experience early recurrence following electrical cardioversion at the end of the ablation procedure (18, 20, 41). This strategy also challenges the management of early redo procedures, preventing unnecessary CA and potential complications. Waiting until the end of the blanking period to manage electrical cardioversion in case of persistent arrhythmia leads to select a subpopulation without SR restoration during this period.

The observational design of this study has several limitations that should be considered when interpreting the results. First, the lesion set used during the CA procedure was left to the discretion of the physician, which may have introduced substantial bias in patient selection and treatment. Second, the study was conducted at a single center with a limited patient cohort, which may limit the generalizability of the findings. Third, the study is too small to comment upon procedural predictors of freedom from AF recurrence, particularly since most of these parameters have already been previously studied in dedicated RCT, and also since continuous ECG monitoring or any monitoring >3 days was not utilized in this cohort. Accordingly, the impact of these parameters should be interpretated with caution. The clinical follow-up was managed in a pragmatic manner, which may have led to variability in the timing and frequency of follow-up visits. But this design allowed for the assessment of the proposed therapeutic approach in a real-life manner, which may have important implications for clinical practice.

Conclusion

This study evaluated a novel approach of tolerating arrhythmia continuation after CA for persistent AF and avoiding initial electrical cardioversion. Spontaneous SR restoration at the end of the 3-month blanking period is frequent and an independent predictor of arrhythmia-free survival during the long-term follow-up.

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Disclosures

All authors have declared no conflicts of interest.

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