ISSN : 0974 - 7532 Volume 5 Issue 1

Research & Reviews in

BioSciences

Trade Science Inc.

Regular Paper

RRBS, 5(1), 2011 [16-20]

Clinical study of ablating persistent atrial fibrillation: An analysis of its methods and outcomes

Guo Fang-Ming[1]*, Wang Xiao-Huan[2], Li Guang-Ping[3], Li Li[2]

[1]Department of Cardiovascular Center, China-France Friendship Hospital & Yantai Hill Hospital, Yantai, (CHINA)

[2]Department of Cardiovascular Center, The People's Hospital in Gansu Province, Lanzhou, (CHINA)

[3]Department of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, (CHINA)

E-mail: guofmcn@yahoo.com.cn

Received: 21st December, 2010 ; Accepted: 31st December, 2010

ABSTRACT

Objective: Ablation of circumferential pulmonary vein is an effective method for treating atrial fibrillation (AF), however, it has been found a lower rates of success in persistent AF compared to paroxysmal AF. The aim of this study is to assess whether left atria circumferential ablation (LACA) combined with complex fractionated atrial electrograms ablation is more effective in patients with persistent atrial fibrillation, and to explore the risk factors of atrial fibrillation recurrence. **Methods:** All pulmonary veins (PVs) in 51 patients with persistent AF were isolated completely by LACA under Ensite NvaX mapping system. Complex fractionated atrial electrograms (CFAEs) were mapped and eliminated if induced AF needed to persist for >1 min after above procedure, and further redo-isthmus ablation were necessary in patients with pre-existing atrial flutter. The primary end point was incidence of AF recurrent in 10 months following-up. **Results:** After LACA, 20 of the 51 patients (39.2%) was successful terminated AF, and another 18 patients (34.0%) required additional CFAEs ablation in one area of LA. The others (13 patients) needed two or more area CFAEs ablation though only 7 of 13 patients had AF terminated. All patients with typical AFL had cavo-tricuspid isthmus ablated. During 10.1 ± 3.1 months follow-up, 14 patients had AF recurred including LACA (nine patients), LACA + one area CFAEs ablation (four patients) and LACA + CFAEs ablation in two or more area (one patient). By stepwise regression analysis (sle=0.3 sls=0.05) including all the variables evaluated at baseline, pre-existing APL (HR=3.616, P=0.0278), left atrium enlargement (HR 1.256, P=0.0037) and CFAEs eliminated (HR=0.399, P=0.0209) were main factors for the recurrent (P=0.0002) in this model. **Conclusions:** Combined LACA + CFAEs ablation is more effective in controlling persistent atrial fibrillation than LACA alone. CFAEs and pre-exsiting AFL and left atrium enlargement are main risk factors for the recurrent events.

KEYWORDS

Atrial fibrillation;
Atrial flutter;
Pulmonary veins;
Fractionated atrial electrograms;
Outcomes.

INTRODUCTION

Atrial fibrillation(AF) and atrial flutter (AFL) often co-exist in the same patient and may degenerate into each other[1-5]. Pulmonary veins (PVs) often initiate and /orperpetuate an episode of AF as well as AFL, and pulmonary vein antrum isolation (PVAI) is sufficient to control both arrhythmias[6-8]. However, the recurrence of AF is more common after PVAI especially for the first two months in patients with persistent atrial fibrillation. In present study, We manage persistent AF with different methods, including left atria circumferential ablation (LACA) to encircle the PVs, complex fractionated electrograms (CFAEs) ablation to eliminate AF, and additional AFL ablation in patients with typical right AFL, to establish whether additional CFAEs ablation is required in these patients.

METHODS

Study population

We studied 51 patients with persisitent AF, which is not self-terminating within seven day or was terminated by either electrical or pharmacologic coverison. Thirty-six were men, with mean age of 55.5±9.6years. Most of these patients had a long history of AF (5.8±4.0years) and had failed at least two previous antiarrhythmic drugs (mean, 2.8±0.6) in preventing AF recurrence before the procedure. Thirty patients had hypertension and six patients had coronary artery disease. The mean left ventricular ejection fraction was 56.9 ±5.2, and the mean left atrial dimension was 40.8±4.3 mm. Patients with valvlar heart disease were excluded in this study. All antiarrhythmic medications except amiodarone were discontinued four to five half-lives before the procedure. All patients had effective anticoagulation for =1 month, and transesophageal echocardiography was performed to exclude left atrial thrombus before ablation.

Study protocol

All patients underwent left atria circumferential ablation with an end point of electrical isolation of PVs. If the procedure was performed during AF and the patient converted to sinus rhythm during ablation, atrial pacing was performed on five occasions for 10 s at cycle lengths of 200 to 220 ms and programmed atrial stimulation was performed with a single atrial extra stimulus to determine whether AF or another arrhythmia was inducible. If after ablation the patient remained in AF, CFAEs ablation was performed. And if the patient had a history of typical AFL or occurrence atypical AFL during operation, AFL ablation was then undergone.

Left atria circumferential ablation

The ablation procedure was performed in the fasting state after written informed consent was obtained. The techniques used for LACA have been previously described[9]. In brief, the following catheters were introduced via the right femoral vein for electrophysiological study: (1) A steerable quadripolar catheter (Xtrem; Ela Medical) was positioned in the coronary sinus (CS) for atrial pacing; (2) double transseptal puncture was performed under intracardiac echocardiography guidance, After transeptal catheterization, heparin was infused to maintain an activated clotting time of 300 to 350 s; (3) A circular mapping catheter (Lasso; Biosense Webster, USA) was advanced to the antrum of each pulmonary vein (PV); (4) tubular models of the pulmonary veins and three-dimensional replica of the left atrium (LA) were reconstructed using EnSite NavX (St. Jude Medical, USA) mapping system; (5) a cool saline irrigated-tip ablation catheter (Celsius Thermocool, Biosense Webster) was used. (6)Left atrial ablation was performed 1 to 2cm from the pulmonary vein ostia to encircle the left- and right-sided pulmonary veins. A 70-W Stockart generator (Biosense Webster) was set to deliver RF lesions up to 70W and 55°C.

The end-point of this procedure was electrical isolation of PV validated by circular mapping catheter.

CFAEs ablation

If Induced AF needed to persist for >1 min after LACA, the areas with CFAEs in LA could be located and ablated[10]. Radiofrequency applications were delivered with the maximal temperature of 55°C to 60°C at the catheter tip. The end points were either conversion of AF to normal sinus rhythmeither and noninducible AF, or complete elimination of the areas with CFAEs. If the arrhythmias were not successfully terminated, transthoracic cardioversion was performed.

AFL ablation

In patients with history of typical right AFL, bidirectional block was demonstrated by pacing at different sites. In patients with atypical AFL during the procedure, LA access was obtained via trans-septal puncture and electroanatomic mapping, and entrainment mapping was repeated in the LA. Block across the line was demonstrated using the 3-D mapping system when possible. Double potentials with a separation of 100 ms were required along the ablation line. To assess the success of the ablation, inducibility of AFL was tested after ablation using both programmed and burst pacing.

Follow-up

All patients were seen in an outpatient clinic at 2, 5, 10 months after ablation. Patients were asked to transmit their rhythm three time per day and every time they had symptoms compatible with arrhythmia. In addition, patients were asked to contact the doctor practitioner whenever they experienced symptoms. No patients was lost to following up, the mean duration of follow-up was 10.1±3.1 months. Warfarin (international normalized ratio 2 to 3) was restarted in all patients the day of ablation and was continued for a minimum of four months.

Statistics

For continuous variables Student's t-test, and for categorical variables, chi-square test or Fisher exact test, were used, as appropriate. Univariate and multivariable Cox proportional hazard analysis were used to assess risk factors of AF recurrence for covariates respectively. Those with a p value<0.20 at univariate analysis were entered into the multivariable model, further analyzed with stepwise to estimate the final predictors of the AF recurrence. Significance between models was calculated by the likelihood ratio test. In multivariable analysis, a p value<0.05 was considered statistically significant. All statistical analyses were performed using SAS version 8.1 (SAS Institute Inc., Cary, NC, USA). Statistical significance was determined when P< 0.05. AF -free survival curves were constructed by Kaplan-Meier analysis.

RESULTS

Ablation results

All left- and right-sided pulmonary veins were isolated successfully in all patients. Left atria circumferentia ablation had terminated the AF in 20 of 51 patients (39.2%), and in no case was it reinducible, though 3 patients had concomitant AF recurrence and a second LACA was performed. In 18 patients (35.3%), AF terminated after additional CFAEs ablation was only delivered one area of LA (the roof, 12 patients; the septum, 6 patients). In remaining 13 patients, in whom entrainment mapping the CFAEs were distributed in two or more areas (interatrial septum and coronary sinus, 5 patients; septum and the roof of the left atrium, 3 patients;=3 areas, 5 patients), radiofrequency application terminate the AF in 7patients. In 2 patients(3.9%), AF degenerated into AFL during ablation, the arrhythmia termination in those patients required block across the line between left subpulmonary vein and mitral isthmus using the Ensite NavX mapping system, after which the AF and AFL were no longer inducible. In 4 patients, radiofrequency application failed to terminate the arrhythmia despite ablating the CFAEs in the aspect of the right atrium.

All 12 patients with cavo-tricuspid isthmus depended APL had successfully performed and no complication related to AFL or AF ablation was noted.

Longitudinal analysis

Clinical characteristics of patients

All subjects were devided into two groups according to the reccurrence of AF, The baseline characteristics of the study population listed in TABLE 1. Subjects of recurrent group showed to have larger left atrial dimension, more patients with history of AFL than normal group. No differences were found between groups with regard to other parameters, including self-terminating time and duration of AF, age, sex, smoking, left ventricular eject fraction.

TABLE 1 : Prevalence of clinical characteristics of two groups on atrial fibrillation (n=51)

	Normal group (n=37)	Recurrent group (n=14)	P
Age, year	54.1±9.2	58.9±10.1	0.1122
Men, %	25, 66.6	11, 78.6	0.4415
Duration of AF, years	5.9±4.3	5.6±3.5	0.7713
Lasting time, weeks	9.5±4.0	11.4±3.9	0.1501
Smoking, %	20, 54.1	8, 57.1	0.8432
CAD, %	6, 16.2	3, 21.4	0.6630
Hypertension, %	27, 73.0	12, 85.7	0.3384
Atrial flutter, %	5, 13.5	7, 50.0	0.0061*
LA diameter(mm)	39.8±4.1	43.3±3.7	0.0088*
LVEF, %	56.6±5.7	57.7±4.2	0.5671

Note: AF= atrial fibrillation, CAD=coronary artery disease, LA=left atrium, LVEF=left ventricular eject fraction
*** statistic significance**

Following-up results

In a mean 10.1 ± 3.1 months follow-up of 51 study participants, there were 14 patients recurred: only left atria circumferential ablation (9 of 20 patients, 45.0%), LACA and CFAEs ablation in one area (4 of 18 patients, 22.2%), LACA and CFAEs ablation in two or more area (1 of 13 patients, 7.7%). Kaplan-Meier survival curves for patients with persistent atrial fibrillation found that the arrhythmia free rate of LACA ablation is significantly lower than that of combining CFAEs ablation ($p < 0.001$, Figure 1), and the more area of CFAEs ablated, the less AF recurred ($P < 0.001$). Univariate Cox proportional hazard analysis showed that AFL, LA diameters and CFAEs were statistically significant risk factors ($p < 0.05$) of AF recurrence. Multivariate Cox analysis identified that LA diameters and CFAEs

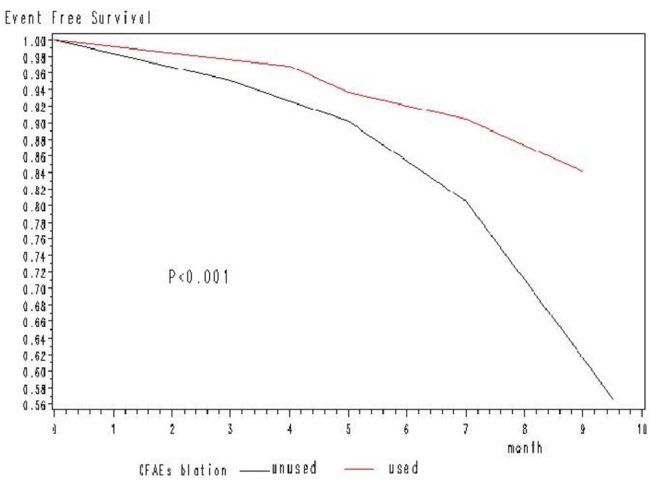

Figure 1 : Kaplan-Meier survival curves for patients with persistent atrial fibrillation. The arrhythmia free rate of LACA ablation is significantly lower than that of combining CFAEs ablation (p< 0.001).

TABLE 2 : Univariate and multivariate association between all baseline variables and the recurrence of atrial fibrillation

	Univariate analysis				Multivariate analysis			
	Hazard ratio	95% HR confidence limits		P	Hazard ratio	95% HR confidence limits		P
Age	1.046	0.990	1.104	0.1097	1.016	0.953	1.082	0.6343
Sex	1.575	0.439	5.647	0.4858				
Duration of AF	0.982	0.856	1.127	0.7913				
Lasting time	1.117	0.971	1.285	0.1203	1.202	0.981	1.474	0.0765
Smoking	1.170	0.406	3.373	0.7710				
CAD	1.454	0.405	5.214	0.5657				
Hypertension	1.861	0.416	8.316	0.4163				
Atrial flutter	4.373	1.511	12.652	0.0065*	2.986	0.977	9.125	0.0550
LA diameter	1.140	1.018	1.277	0.0228*	1.235	1.051	1.452	0.0105*
LVEF	1.031	0.935	1.137	0.5397				
CFAEs ablation	0.454	0.214	0.963	0.0394*	0.355	0.160	0.787	0.0108*

Note: AF= atrial fibrillation, CAD=coronary artery disease, LA=left atrium, LVEF=left ventricular eject fraction, CFAEs= fractionated atrial electrograms
*** statistic significance**

as independent predictors ($P=0.0076$) of AF recurrence (TABLE 2). While further analysis with stepwise selection (stepwise sle=0.3 sls=0.05) to determine the final predictors of AF recurrence were AFL (HR=3.616, P=0.0278), LA diameters (HR 1.256, P=0.0037) and CFAEs (HR=0.399, P=0.0209).

DISCUSSION

The main finding of this study is that patients with persistent AF have lower recurrence after CFAEs ablation following LACA compared with the patients without CFAEs ablation, though the immediate results of two methods were similar. Further AFL ablation is needed in the patients with atypical history of AFL. In our study, CFAEs and AFL were found to be independent indicators in addition to LA size in a group of persistent atrial fibrillation patients after ablation.

Arrhythmogenic foci within the pulmonary veins (PVs) often initiate and/or perpetuate an episode of AF, providing the rationale for PV isolation as a method of eliminating AF, and now radiofrequency catheter ablation has recently been proposed as an alternative treatment for drug-refractory paroxysmal and persistent AF[11-14]. To avoid incidence and functional characteristics of pulmonary vein stenosis, LACA to encircle the PVs, an effective method compared with PV isolation[15] was performed in this study. However, LACA only successfully terminated 39.9% persistent AF. The resluts indicated that the mechanisms of triggering persistent AF are not only relaying on potential activation of pulmonary veins.

CFAEs are atrial electrograms that are fractionated and composed of two deflections or more and/or have a perturbation of the baseline with continuous deflections from a prolonged activation complex as shown in the atrial septum, and found mostly in areas of slow conduction and/or at pivot points where the wavelets turn around at the end of the arcs of functional blocks during intraoperative mapping of human AF[16,17]. Nademanee, K et al. showed that areas with CFAEs represent a defined electrophysiologic substrate and are ideal target sites for ablations to eliminate AF and maintain normal sinus rhythm. In this study, we provide evidence for the hypothesis that CFAEs following unsuccessful LACA were eliminated by ablation, AF could no longer be sustained in the majority of the patients. The findings also confirm those of Verma et al.[18] that the combination of PVI + CFE had the best outcome compared with either of the other two arms in a population of high-burden paroxysmal/persistent AF patients after either one or two procedures. In addition, most patients after LACA represent and ablate just one regional area of CFAEs, however, unlike previous studies[19,20], the left atrial roof is the most common site for CFAEs. That different AF patients and CFAEs mapping time may be responsible for the different results[21]. Recent investigations demonstrate that recurrence of AF after electrogram-guided ablation is usually due to PV tachycardias[22], in the existing body of study demonstrating the risk of CFAEs for AF reccurence, our findings are in line with other recent investigations demonstrating common mechanisms of recurrent atrial arrhythmias[23].

It is well recognized that AFL and AF often co-exist[1,5], though the reasons for co-existence are not entirely clear. In our study, 23.5% (12 of 51) AF patients have pre-existing AFL, which were controlled by LACA and cavo-tricuspid isthmus ablation. However, 58.3% (7 of 12) AFL patients experienced AF reoccurrence after the procedure, though a cavotricuspid isthmus ablation after PV isolation reduces inducibility of atrial arrhythmias[24]. Those may partly support the ideas that a considerable number of patients have AF recurrence after ablation of typical AFL[24]. Furthermore, according to our finding, co-exist status of AFL and AF raise the risk for the arrhythmia recurrence.

Study limitations

First, a relatively small sample size was a limitation of the present study.our data need confirmation in future studies. Yet, statistical significance in our study was achieved despite the limited sample and independent of clinical variables, thus suggesting that CFAEs and pre-exiting AFL can actually play important role in risk stratification. Second, we did not include long-standing persistent AF patients (more than 1 year), which limits the applicability of our results.

In Conclusion, combined PVI + CFAEs ablation is an effective strategy to terminate persistent atrial fibrillation. However, CFAEs, pre-exsiting AFL and left atrium enlargement are main risk factors for the recurrence of the arrythmia.

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