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Pulmonary vein isolation by circumferential radiofrequency lesions in atrial fibrillation. From substrate to clinical outcome

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Summary. - Circumferential ablation around pulmonary vein ostia by CARTO system was performed in 98 patients with paroxysmal and 29 with permanent atrial fibrillation (AF). Preablation and postablation activation, propagation and voltage maps were obtained. A total of 135 ± 18 radiofrequency pulses were delivered. After a follow-up of 14.7 ± 3.3 months, 84 patients with paroxysmal and 22 with chronic AF are in sinus rhythm and 75 of them without antiarrhythmics. Only the area extent of low voltage potentials within and just around the lesions distinguished patients with and without successful ablation. Pulmonary vein isolation is an effective procedure to cure resistant AF; the extent of lesion area around pulmonary vein ostia may be crucial in predicting the outcome.

Key words: atrial fibrillation, catheter ablation, mapping.

Riassunto *(Isolamento della vena polmonare mediante lesioni a radiofrequenza in fibrillazione atriale. Dal substrato all'impatto clinico).* - E' stata effettuata l'ablazione RF circonferenziale degli osti delle vene polmonari utilizzando il sistema non fluoroscopico CARTO in 98 pazienti con fibrillazione atriale parossistica e 29 con FA cronica. Sono stati calcolati i tempi di attivazione, di propagazione e le mappe di voltaggio prima e dopo ablazione. Sono state effettuate 135 ± 18 erogazioni. Dopo un follow-up di 14 ± 3.3 mesi, 84 pazienti con FA parossistica e 22 con FA cronica sono in ritmo sinusale anche senza farmaci (75%). L' unico predittore di successo è stato l'estensione dell'area di basso voltaggio intorno alle lesioni. L'isolamento delle vene polmonari rappresenta una procedura efficace nella cura della fibrillazione atriale e l'area di lesione sembra essere cruciale nel predire i risultati.

Parole chiave: fibrillazione atriale, ablazione transcatetere, mappaggio.

Introduction

Atrial fibrillation (AF) is the most common of all sustained cardiac arrhythmias that occurs progressively with aging. Unfortunately, our current therapeutic strategy is frequently disappointing because it is frequently resistant to antiarrhythmic agents. Often, the presence of the arrhythmia has to be accepted and only measures to control the ventricular rate and to prevent thromboembolic events have to be applied. Dissatisfaction with pharmacological therapy resulted in growing interest in nonpharmacological treatment of the arrhythmia, including His-bundle ablation and pacing, preventive atrial pacing, the implantable atrial defibrillator, and linear biatrial catheter ablation. However, at this point in time, the treatment of patients with resistant AF is evolving from a palliative approach to a curative one. Our recent preliminary experience in 26 patients demonstrates that pulmonary veins ablation represents a new approach to cure both paroxysmal and permanent AF; indeed, after a follow-up of > 6 months 85% of the patients were AF-free [1]. We report herein the long-term results of circumferential radiofrequency lesions around pulmonary vein ostia in 127 consecutive patients with resistant atrial fibrillation.

Methods

Study population

Patients were enrolled who had paroxysmal AF with documented daily sustained (> 1h) episodes despite the use of antiarrhythmic drugs at therapeutic doses (2.9 ± 1) or symptomatic chronic AF for > 6 months resistant to both pharmacological and electrical cardioversion. All patients had to be taking effective oral anticoagulation for > 4 weeks. Diagnostic workup included serial Holter recordings, transthoracic and transesophageal echocardiography, laboratory tests, and thyroid function evaluation. Written, informed consent was obtained before the study from each patient according to a protocol approved by the Institutional Human Research Committee.

Catheter positions

Antiarrhythmic drugs (except amiodarone) and digoxin were discontinued for ≥ 5 half-lives before the study. As described previously [1], quadripolar 6F catheters were positioned in the coronary sinus, right atrium (RA), and

right ventricle. The patients were anticoagulated with heparin as soon as the catheters were placed to maintain a partial thromboplastin time of 60 to 90 seconds.

Mapping process

As described previously [1, 2], a nonfluoroscopic navigation system (CARTO: Biosense Webster) was used to generate 3D electroanatomic left atrium (LA) maps and deliver radiofrequency (RF) energy. In brief, via a transeptal approach the navigator catheter was inserted into the left atrium and placed 2 to 4 cm into each pulmonary vein (PV) and slowly pulled back. Along pullback, multiple locations were recorded to tag the vein. The ostium was identified by fluoroscopic visualization of the catheter tip entering the cardiac silhouette with simultaneous impedance decrease and appearance of atrial potential. Three locations were recorded along the mitral annulus to tag valve orifice. LA maps were obtained by sequentially acquiring a minimum of 50 points. In patients in sinus rhythm (SR) at the beginning of the procedure, maps were acquired during pacing from the coronary sinus (CS) or RA appendage at a cycle length (CL) of 600 ms. Each endocardial location was recorded while a stable catheter position was maintained, as assessed by both end-diastolic stability (a distance < 2 mm between 2 successive locations) and local activation time (LAT) stability (an interval < 2 ms between 2 successive LAT). When split potentials were recorded, the LAT was derived from the steeper of the two. For patients in AF, maps were acquired to assess the distribution and types of electrograms by a previously reported method [3]. Local CL were automatically analyzed and displayed as histograms, which were classified as follows: type A, defined as fairly regular activation with a clear isoelectric baseline; type B, irregular activation with perturbations of baseline and/or highly fragmented electrograms; and type C, alternation between A and B. In all patients voltage maps were also calculated, namely color-coded maps expressing the average voltage of endocardial electrical signals in each region. In patients in sinus rhythm propagation maps were also obtained.

Radiofrequency ablation

As described previously [1, 2], RF pulses were delivered in unipolar mode to a cutaneous ground patch via the distal catheter electrode. Since all 4 pulmonary veins may serve as a source of AF [4], our end point was the creation of circumferential lines of conduction block around each PV. These lines consisted of contiguous focal lesions deployed at a distance of ≥ 5 mm from the ostia (Fig. 1). With a maximum temperature setting of 60 °C, RF energy (up to 50 W) was applied for 60 to 120 seconds until local electrogram amplitude was reduced by 80%. During AF, the same power titration technique was used, but current was always delivered for 60 to 120 seconds. If there was an impedance rise, or the patient had cough, burning pain, or severe bradycardia, RF delivery was stopped.

Remap process and lesion validation

In patients in SR postablation remap was performed utilizing the preablation anatomic map for the acquisition of new points to allow accurate comparison of pre- and post-RF activation sequence. In patients in AF, after restoration of SR, the remap was done with the anatomic map acquired during AF, to maintain the same landmarks and lesion tags for reliable lesion verification. Lesion validation required acquisition of 2 maps during CS and RA pacing for the lateral and septal PV, respectively. The rationale was to pace from a site close to the lesions and shorten conduction time to the ablation site, thereby allowing detection of delayed activation inside the circular line.

The following criteria were used to define line continuity:

1) low peak-to-peak bipolar potentials (< 0.05 mV) inside the lesion, as determined by local electrogram analysis and voltage maps (Fig. 1);

2) LAT delay > 30 ms between contiguous points lying in the same axial plane on the external and internal sides of the line, as assessed by activation maps. Changes in activation spread were also evaluated with propagation maps.

In addition, we measured in the postablation maps the low-voltage areas, namely those showing endocardial potentials with an amplitude < 0.05 mV.

Every map was obtained both during CS pacing and during right atrial appendage (RAA) pacing, according to the principle that to assess changes in activation or impulse propagation caused by RF lesions it is necessary to pace from a region close to the lesion line. Therefore, septal PV lesions were evaluated during RAA pacing, and lateral PV lesions during CS pacing.

Voltage map analysis

Whenever the ablation line was complete, a dramatic voltage decrease was observed by voltage map not only in the ablated area but also outside the lesion line. We measured the total low-voltage areas as the sum of the 4 areas with < 0.05 mV voltage potentials at each of the pulmonary veins.

Postablation management

After ablation, patients underwent 24 to 48-h telemetry monitoring. Most patients (76.3%) were discharged without the need for antiarrhythmic therapy. Of the remaining (23.7%) patients, amiodarone,

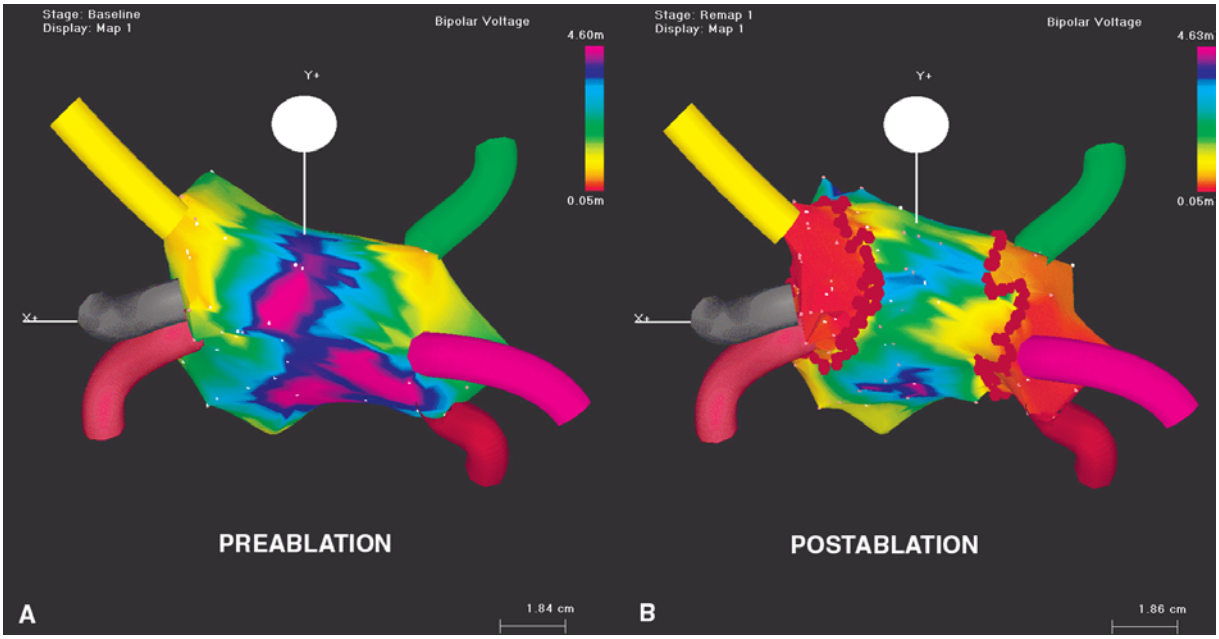

Fig. 1. - Voltage maps. Posteroanterior view: A) preablation; B) postablation remap showing peak-to-peak bipolar electrogram amplitude. Red represents lowest voltage. Postablation, areas inside and just around lesions show low-amplitude (< 0.05 mV) electrograms.

flecainide, and propafenone were administered because frequent ventricular and supraventricular ectopic beats. Other cardiovascular drugs including digitalis, betablokers, and calcium-antagonists were prescribed if necessary. Warfarin was continued for 3 months.

Follow-up

Clinical follow-up consisted of outpatients visits. Holter monitoring was performed at discharge, monthly for 3 months, and then every 2 months and on symptom recurrence). Transthoracic and transesophageal echocardiogram were performed within 6 months after ablation to assess LA dimensions and Doppler mitral flow pattern to evaluate possible pulmonary vein stenosis. The procedure was considered successful if no recurrences of AF lasting > 30 seconds were present during postdischarge follow-up.

Statistics

The data were presented as mean ± SD. The χ-square test was applied for categoric variables. Student t test was used to compare the means; a value of $p < 0.05$ was considered statistically significant.

Results

From November 1998 to May 2000 we studied 127 patients (106 men and 21 women with a mean age of 51.4 years), with resistant atrial fibrillation, either paroxysmal (group A; no. = 98) or chronic (group B no. = 29); the clinical characteristics are summarized in Table 1. The patients with paroxysmal AF had daily attacks of clinically documented AF lasting from 2 to 10 hours. These episodes were refractory to 3 ± 1 antiarrhythmic drugs; 33/127 patients had other associated diseases (Table 1).

Mapping and ablation procedure

Until November 1999 we performed a total of 35 procedures while from December 1999 to May 2000 we performed 92 procedures. The overall procedure duration was 179.9 ± 64.3 minutes (238.1 ± 52.9 and 162.5 ± 56.9 in 1999 and 2000, respectively $p < 0.001$). Fluoroscopy time was 46.6 ± 35.6 (75.9 ± 27.9 and 37.87 ± 32.98, in 1999 and 2000, respectively $p < 0.001$). Preablation map comprised 110 ± 38 points (range 72 to 150 points). A total of 135 ± 18 RF pulses were delivered; sinus rhythm was acutely restored during ablation in 60% of the patients; in most of them (67%) RF was being delivered around the superior lateral PV, although this was not the initial site of ablation in all patients. In patients who were still in AF after completion of ablation, the arrhythmia was terminated by direct current shocks. After ablation complete isolation was documented by absence of discrete electrical activity (voltage < 0.01 mV) at all sites inside the lesions in 82% of the PV treated (499 PV). Such lesions were associated with marked LAT delay. Incomplete lesions were dichotomized into

those with LAT delay > 30 ms in 49 PV (10%) and those without delay in 38 PV (8%). The sum of areas relative to the 4 PV ranged from 13178 to 18 745 mm^2 (average 15 987 ± 1867 mm^2).

Clinical outcome

No patient developed intolerable pain or severe cough requiring RF delivery cessation; one patient had a transient complete AV block during RF delivery. Two patients had hemopericardium but they recovered well after pericardiocentesis. There were no strokes or other thromboembolic events. Five patients had mild pericardial effusion managed medically. During the first 48 hours from ablation, 10 patients developed spontaneous terminating AF episodes lasting from 7 min to 2 hours; all patients were discharged in SR; 2-4 months after ablation 8 patients with paroxysmal AF and 4 with chronic AF had brief episodes of palpitations that in 8 cases were documented as AF. Five patients had mild exertional dyspnea after ablation, which resolved 2-4 months later. In patients with paroxysmal AF predischarge echocardiography demonstrated unchanged LA transport function. Of the patients with permanent AF, mitral A waves were detectable in all patients who returned to SR during ablation. During serial follow-up visits, all patients without recurrences showed preserved LA contraction. Transesophageal echocardiography showed no high-velocity turbulence near the ostia suggesting no PV stenosis either acutely or at repeated follow-up controls

After a mean follow-up of 14.7 ± 3.3 months, 106/127 patients (84 with paroxysmal and 22 with chronic AF) remained in stable SR; 75 of them were no longer taking antiarrhythmic agents and the remaining 31 patients required the use of antiarrhythmic drug therapy for frequent ectopic beats. Of the unsuccessful patient group, 14 patients with paroxysmal AF had sporadic nonsustained asymptomatic AF with 1 type of antiarrhythmic drug (which failed to control AF before ablation). Anticoagulants were interrupted in all patients in SR at 4 month follow-up.

Table 1. - Clinical characteristics

Heart disease	Group A (no.)	Group B (no.)
No disease	68	26
Ischemic heart disease	14	3
Mitral valve prolapse	2	
Mitral stenosis	4	
Mitral regurgitation	3	
Hypertrophic cardiomyopathy	3	
Dilated cardiomyopathy	4	

Patients with successful AF ablation vs *patients with unsuccessful AF ablation*

Patients with successful paroxysmal (group A1) and chronic AF (group B1) and patients with unsuccessful paroxysmal (group A2) and chronic AF (group B2) did not differ from each other concerning age, structural heart disease, left ventricular end-diastolic diameter, ejection fraction, and percentage of PV successfully isolated (Table 2); however, in successful patient group with both paroxysmal and chronic AF the postablation low voltage area was significantly larger ($p < 0.01$) than in patients with unsuccessful ablation procedure (groups A1 *vs* A2 and B1 *vs* B2, respectively; Table 2); in addition, the patients with chronic AF and successful outcome had significantly larger low voltage area than those with paroxysmal AF and successful outcome (A1 *vs* B1; $p < 0.05$); no statistical difference in all parameters was found between the patient group with unsuccessful ablation procedure (A2 *vs* B2, p = NS; Table 2).

Discussion

This study describes the long-term results of a new ablative technique around and outside the PV ostia by creating circumferential lesions in 127 patients with both paroxysmal and chronic AF. This is the first report about long-term efficacy, feasibility and safety of this approach in a large group of patients with resistant AF.

Pulmonary vein ablation in paroxysmal AF

The pulmonary veins have been shown to trigger paroxysm of AF [4-7]. These studies indicate an important role of pacemaker activity in or around the pulmonary veins as a trigger for paroxysmal AF and in these cases, ablation of the focus may lead to disappearance of the recurrence of the arrhythmia [4-7]. Unfortunately, ectopic activity in the pulmonary vein may not be present during electrophysiologic study, even when provocative pharmacological or pacing procedures are performed. On the other hand, ectopic activity may arise in > 1 pulmonary vein [7] making focal ablation a less attractive method and for this reason we isolated each pulmonary vein by creating circumferential RF lesions around their ostia [1]. Recently, in patients with drug-resistant paroxysmal AF RF ablation was directed at specific segments of PV ostia to minimize the risk of PV stenosis [7]; with this approach, 31/70 patients (44%) had recurrence of AF but a reablation session was necessary in 29 patients with an overall success rate of 73% after a mean follow-up of 4 ± 5 months. In most patients the ectopy was related to a previously ablated PV or to previously untargeted PV [6]. With our approach

Table 2. - Comparison of patients with successful RF ablation (A1 = paroxysmal AF; B1 = chronic AF) *vs* patients with unsuccessful RF ablation (A2 = paroxysmal AF; B2 = chronic AF)

Parameter	A1	A2	A1 *vs* A2	B1	B2	B1 *vs* B2	A1 *vs* B1	A2 *vs* B2
No. of patients	84	14		22	7			
Age	50.9 ± 10	52.6 ±12	NS	49.3 ± 7	52.1 ± 10	NS	NS	NS
Disease	26 *(a)*	4 *(b)*	NS	2 *(c)*	1 *(d)*	NS	NS	NS
LA diameter	39.2 ± 6.1	39.4 ± 5.2	NS	40.1 ± 4.4	42.5 ± 6.6	NS	NS	NS
LVEDD	51.5 ± 5.4	52.2 ± 3.4	NS	52.1 ± 4.5	50.2 ± 2.2	NS	NS	NS
LVEF (%)	60 ± 7	63 ± 9	NS	54 ± 9	60 ± 3	NS	p < 0.001	NS
Pv isolated (%)	78.5 ± 9	82 ± 7	NS	81.4 ± 9	83 ± 5	NS	NS	NS
Low voltage area (mm^2)	16152 ± 2140	13432 ± 2350	p < 0.01	17134 ± 1535	15125 ±1345	p < 0.01	p < 0.05	NS

(a) Coronary artery disease (13 patients), mitral regurgitation (3), hypertrophic cardiomyopathy (3),dilated cardiomyopathy (4), mitral stenosis (3). *(b)* Coronary artery disease (1 patient), mitral valve prolapse (2), mitral stenosis (1). *(c)* Coronary artery disease (2 patients). *(d)* Coronary artery disease (1 patient).RF: radiofrequency; AF: atrial fibrillation; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction.

84/98 patients with refractory paroxysmal AF were AF free after a mean follow-up of 14 months. The 14 unsuccessful patients had sporadic asymptomatic episodes of AF with type 1 antiarrhythmic drugs which failed to control AF before ablation.

Pulmonary vein ablation in chronic AF

To being the most common site of arrhythmogenic foci that trigger the onset of AF, the unique electrophysiologic characteristics of the pulmonary veins may serve to perpetuate established AF. Because of the very short-duration refractory periods that are measured within the pulmonary veins, these structures may serve as a site of high frequency activation due to reentrant activation with small wavelengths. Catheter ablation strategies that are designed to ablate and reablate the site of triggering foci at PV ostia have been recently reported in fifteen cases in whom PV were the dominant triggers reinitiating chronic AF [8]; a single ablation session was performed in 7 patients and 8 underwent 2 or 3 sessions because of recurrence of AF; ablation was directed at the same source due to recovery of local PV potential or at a different PV; 60% of the patients were in stable SR without antiarrhythmic drugs at follow-up of 11 ± 8 months. Conversely, our idea was that catheter strategies that are designed to electrically isolate the pulmonary veins from the bulk of the left atrium are likely to definitively control the mechanism of the arrhythmia. Indeed, with this approach 22 of 29 patients with chronic resistant AF were free of AF after a single session procedure.

Pulmonary vein ablation in paroxysmal vs *chronic AF*

In our experience, similar results were obtained in patients with paroxysmal and chronic AF. A total of 106/127 patients (84%) were AF-free after a mean follow-up of 14 months; in particular, RF ablation was successful in 84/98 patients (85%) with paroxysmal AF and in 22/29 patients (75%) with chronic AF. There were no clinical predictors differentiating patients with and without a successful RF ablation procedure. On the other hand, in patients with chronic AF submitted to cardiac surgery for severe mitral valve disease and dilated atria, SR may be restored in 80% of patients clearly demonstrating that atrial size does not play a determinant role in restoring and maintaining SR [9]. Conversely, in our experience by using electrophysiologic criteria, the circular lines of lesions were complete in 82% of all PVs treated but there was no relationship between lesion completeness and outcome. The only information that allowed differentiation between patients with and without a successful RF ablation was the area extent of low voltage potentials around PV. Patients who underwent successful ablation had significant larger ($p < 0.01$) lesion areas than patients with unsuccessful outcome suggesting that the extent of ostial ablation necessary to electrically disconnect PV may play a key role in predicting favorable outcome. In addition, the comparison of subgroup A1 versus B1 shows that in patients with successful outcome the areas of voltage fall are significantly larger in patients with chronic AF (B1) further suggesting the key role of lesion area in affecting the outcome.

Pulmonary vein ablation and disappearance of AF mechanism(s)

The muscular wall of the left atrium may extend up to a few centimeters around the PV, more so in the superior than the inferior PV. There may be marked differences in diameter, wall thickness, and the extension of cardiac tissue in and around the PV. Focal ablation of triggering foci may be relatively effective, but outcome was not always successful, and paroxysmal AF recurred. RF energy ablation can be delivered distally into the PV, or at the ostium, with the end point of distal disconnection [8]. Since the topography and activation of myocardial extensions to PV as well as their autonomic innervation extension are unknown, focal ablation alone may not be able to simultaneously disconnect all triggers involved in both initiating and perpetuating AF. These observations could explain why a single session procedure with a focal approach frequently results in unsuccessful outcome. Conversely, our good long-term results with a single session procedure may be explained by the fact that RF energy circumferentially directed around PV ostia induced lesion areas around and outside PV ostia. Similar long-term efficacy was observed in patients with both paroxysmal and chronic AF raising the question about reversibility of electrophysiologic changes in the atrium induced by our approach. As a result, our experience suggests that the mechanisms surrounding the favorable effect of circumferential lesions around pulmonary vein ostia are complex; the circular lines of lesion were complete in most patients but there was no relationship between lesion completeness and outcome; on the contrary, in successful patient group with both paroxysmal and chronic AF (groups A1 and B1) the areas of low voltage (< 0.05 mV) were larger than in unsuccessful patient group (groups A2 and B2); of interest, within patients with successful group (groups A1 and B1) the lesion areas were significantly larger in those with chronic AF (group B1) suggesting that only the removal of a relatively large area may simultaneously eliminate different sources triggering (paroxysmal) and maintaining (chronic) AF:

- by destroying focal driving rotors ("mother waves");
- by preventing the egress from pulmonary vein ostia of impulses arising from venous automatic foci;
- by interrupting critical reentry pathways of circuits;
- by exerciting some denervation effect.

The efficacy of PV isolation supports a common pathogenesis in paroxysmal and chronic AF involving both focal activity and reentry with a spectrum of different clinical presentation.

Feasibility and safety

RF application around the pulmonary vein ostia did not result in major complications. The first 35 procedures performed in 1999 lasted 238.1 ± 52 minutes while the last 92 performed in 2000 lasted 162.5 ± 56 minutes suggesting that the time required to make circular lesions is significantly reduced overtime. Obviously, technical developments may help to further speed up isolation of all 4 pulmonary veins for extensive application of this approach. RF applications around the PV orifices were well tolerated in all patients. One patient experienced a transient episode of AV block during RF applications. No thromboembolism occurred. No case of PV stenosis occurred during the follow-up.

Clinical outcome

Uncertainty exists about long-term results with regard to arrhythmia recurrence [4-9]. With this approach 106/127 patients (84 with paroxysmal and 22 with chronic atrial fibrillation) were free of AF 14.7 ± 3.3 months after the procedure; in addition, of the 106 patients, 75 were no longer taking antiarrhythmic agents and the remaining 31 required antiarrhythmic therapy for frequent ectopic beats.

Study limitations

Since our approach is limited to the left atrium, possible right atrial foci cannot be completely excluded as responsible for AF contributing to failure of the ablation procedure in some cases.

Conclusions

The results of this large series of patients demonstrate the long-term success and safety of circumferential RF ablation of PV ostia to definitively cure a majority of patients with both paroxysmal and chronic resistant atrial fibrillation. The extent of lesions area around PV ostia may be crucial in predicting the outcome especially in patients with chronic atrial fibrillation; this approach may modify the natural history of paroxysmal *versus* chronic AF; increasing experience significantly decreases the time required to make circular lesions around PV ostia without risk of complication. These results provide important information for extensive application of this method for definitively curing AF.

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