Long-Term Follow-Up After Cryothermic Ostial Pulmonary Vein Isolation in Paroxysmal Atrial Fibrillation

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Objectives
This study was designed to evaluate the long-term effect of segmental pulmonary vein (PV) cryoablation in patients with recent-onset paroxysmal atrial fibrillation (PAF).

Background
Patients with PAF have more triggers to initiate and less substrate to sustain atrial fibrillation (AF). Elimination of the potential initiators alone may be sufficient to abolish the arrhythmia.

Methods
Patients with PAF were prospectively recruited from July 2001 to July 2005. If the triggers for AF were identified, PV cryoisolation of the arrhythmogenic vein(s) was performed. Otherwise, all PVs were isolated.

Results
Seventy patients with minimal or no heart disease (54 men; age 40 ± 10 years) were enrolled. The duration of AF was 4 ± 1 year. The left ventricular ejection fraction and left atrial size were 59 ± 8% and 41 ± 5 mm, respectively. An arrhythmogenic PV was found in 10 patients (14%). Complications occurred in 3 patients (4%). No PV stenosis or esophageal injury was detected during a mean follow-up of 33 ± 15 months. Thirty-four patients (49%) achieved complete success (no AF and no antiarrhythmic drugs [AAD]); 15 patients (22%) had no recurrences with AAD; and 8 patients (11%), still with sporadic bursts of AF, improved 50% with AAD. Overall, 82% of the patients benefited from the procedure. Patients in whom the arrhythmogenic PV was identified and isolated had no recurrences.

Conclusions
Pulmonary vein cryoablation is effective in 82% of patients with recent-onset PAF during a mean follow-up of 33 ± 15 (range 15 to 60) months. If the arrhythmogenic PV is identified and isolated, the long-term outcome is excellent, indicating no need to isolate all PVs. (J Am Coll Cardiol 2008;51:850–5) © 2008 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is a disease with different stages. In early stages, paroxysmal and nonsustained episodes are the rule (1,2). In this stage, the triggers, mostly located in the pulmonary veins (PV), are the main culprit of AF (3). Over time, atrial remodeling starts to occur, and more substrate becomes available to sustain longer episodes (4). Therefore, self-perpetuation of AF (AF begets AF) leads to the idea that a treatment strategy employed early in the disease would be more likely to succeed.

The actual ablative techniques are intended to eliminate the triggers (ostial PV isolation 1 by 1 or 2 by 2) and/or to modify the substrate. A technique that modifies the substrate consists of the creation of multiple lines in both atria (5). Adding extensive left atrial linear ablation, although reported to improve overall success rates in a group of patients with more advanced stages of AF, has increased morbidity and mortality (including iatrogenic left atrial flutter, phrenic nerve paralysis, and left atrial-to-esophageal fistula, which is almost universally fatal) (6–8). Many patients with AF and structurally normal hearts are now frequently referred for ablation. In this group, empiric extensive left atrial ablation may not be the best approach because the long-term risk of such extensive lesions is unknown.

Cryothermy has been shown to have some inherent advantages over radiofrequency (RF) ablation. The absence of pulmonary vein stenosis is one advantage (9). But despite cryothermy’s benefits, the great majority of AF ablation is done using RF (10). Our study, OPIPAF (Ostial Pulmo-
nary vein Isolation in Paroxysmal Atrial Fibrillation), was designed to evaluate the effect of a more localized ablation strategy using cryotherapy in patients with PAF in the early stages of the disease.

**Methods**

Seventy patients with drug-refractory, symptomatic PAF were enrolled prospectively from July 2001 to July 2006.

The screening protocol consisted of a review of Holter recordings, daily transtelephonic telemetry (TTM), the number of failed antiarrhythmic drugs (AAD), functional capacity, type of AF, and imaging studies to exclude silent myocardial ischemia. Inclusion criteria required the following: 1) symptomatic PAF; 2) duration of PAF ≤5 years; 3) age ≤65 years; 4) lone AF or minimal heart disease; and 5) left atrial size ≤40 mm and no exposure to amiodarone.

All subjects were given a transtelephonic event recorder and instructed to use it daily (preferably at the same time) and when they had symptoms. This monitoring started 30 days before and continued up to day 180 after pulmonary vein isolation (PVI). From then on, a Holter monitor was used during clinic visits (1, 3, 6, 9, and 12 months) or when patients had symptoms.

A baseline contrast-enhanced spiral computed tomography (CT) scan of the thorax with 3-dimensional reconstruction of the heart was performed within 1 month before the ablation procedure and evaluated blindly by the same radiologist who performed the follow-up study (B.G.).

All the patients in the study signed a written consent form that was approved by the local ethics committee. Before PVI, all patients were orally anticoagulated to a therapeutic international normalized ratio of 2 to 3 for at least 3 weeks and up to 3 months after ablation. All AAD were stopped 5 days before PVI and restarted immediately thereafter. Transesophageal echocardiography (TEE) was performed during the procedure to exclude left atrial thrombus and to aid in the transeptal puncture.

**PV cryoablation.** All patients were studied in the fasting state without sedation, except if external cardioversion was needed (when small doses of midazolam were used). Internal cardioversions were done without sedation. Those patients presenting in AF while in the catheterization room were converted to sinus rhythm by internal or external cardioversion.

During the procedure (but after the transeptal punctures), intravenous heparin was given as a 100–IU/kg bolus dose followed by boluses of 5,000 IU every 1.5 h if needed to keep an activated clotting time ≥300 s. A decapolar catheter was positioned in the distal coronary sinus and a quadripolar catheter in the His bundle region via the femoral route. Double trans-septal catheterization was performed under fluoroscopic and transesophageal guidance.

Left atrial angiography was performed after adenosine administration (11) to visualize the ostia of the pulmonary veins. Together with the left atrial angiography, we used the NavX system (Endocardial Solutions, St. Jude Medical Inc., St. Paul, Minnesota) for virtual reconstruction of the ostia of the veins in the last 20 patients. A deflectable, circumferential decapolar mapping catheter (LASSO, Biosense-Webster Inc., Baldwin Park, California) was advanced into the left atrium and positioned at the ostium of each PV. A deflectable, 10.5-F (6.5-mm tip) cryoablation catheter (CryoCor Inc., San Diego, California) was inserted into the left atrium through a 12-F, 65-cm-long sheath (DAIG, St. Jude Medical Inc., St. Paul, Minnesota; or Cook Inc., Bloomington, Indiana).

Segmental isolation of PV guided by the recording of their potentials with the LASSO catheter was performed using the CryoCor cryoablation system as described previously (12). Efforts were made to identify the arrhythmogenic PV (culprit PV) using adenosine (24 to 40 mg) (Fig. 1) or isoproterenol (1 to 5 μg). If the culprit PV(s) were not identified, all veins with potentials recorded at their ostium were targeted for ablation.

Isolation of the PV was performed during sinus rhythm or coronary sinus pacing by delivering cryoablation at ostial sites that had the earliest bipolar potential. Systematic pacing in the right superior PV region was performed before application to access phrenic nerve capture.

At each effective target site, defined by the abolishment of a PV potential or a change in the PV potential activation sequence during cryothermal application, 3 min of cryoablation was delivered. If no changes in the electrogram were observed after 20 s, despite a catheter tip temperature of −90°C, the application was stopped and the catheter repositioned. The early procedural end point was complete electrical isolation of PV based on abolition of all ostial PV potentials or complete entrance conduction block into the PV.

**After-ablation management.** Every patient was monitored in the hospital for 24 h and oral anticoagulation was restarted the same day as the ablation. The same AAD were continued for at least 3 months after the procedure. After this period, the need for chronic anticoagulation was assessed by the amount of recurrences of AF and the presence of risk factors for thromboembolic events.

All patients had a Holter recording at discharge and during each clinic visit (1, 3, 6, 9, and 12 months) or earlier if they had symptoms. They were instructed to keep a diary of events associated with their transtelephonic monitors. A visual analog scale ranging from zero (indicating no im-
Because of the logistics of the Maastricht area and the presence of a dedicated research nurse (S.P.) who was available to address patients’ concerns and questions at any time, we were able to follow every patient on an individual basis and achieve a $90\%$ compliance rate with daily TTM at the end of 180 days.

To assess the presence of PV stenosis, serial CT scans of the heart were performed at 3, 6 (63 patients), and 12 months (12 patients). In 7 patients, a repeated CT scan was not performed on follow-up because of an allergic reaction to the contrast agent on their baseline scan ($n = 3$) and patient refusal ($n = 4$). A TEE was performed in those individuals showing no increase in Doppler flow velocities suggestive of PV stenosis.

The same radiologist (B.G.) reviewed all before- and after-cryoablation images in a blinded manner. The diameter of the ostia of the PV was determined for each patient in a pairwise manner to maintain consistency in the measurements.

Definitions. Arrhythmogenic veins were considered those that, during AF, had a tachycardia cycle length shorter than the one recorded in the coronary sinus catheter. Induction of AF was attempted first by manipulation of the LASSO catheter inside the vein (mechanical contact); if that did not result in arrhythmias, administrations of adenosine and isoproterenol infusion were used.

According to the 2007 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement on catheter ablation of AF (13), an episode of AF detected by monitoring was considered a recurrence if it had a duration of 30 s or more.

Statistical analysis. Continuous variables are presented as mean $\pm$ SD, where appropriate. In cases of a non-Gaussian distribution, medians and quartiles are given. Categorical variables are expressed as numbers and percentages of patients.

A Kaplan-Meier analysis was used to determine the percentage of patients either free from AF (with or without AAD) or with $\geq 50\%$ improvement after the index PVI.

Results

Our cohort consisted of 70 patients (54 men and 16 women) with PAF who fulfilled the described recruitment criteria of the OPIPAF study.

The mean age was $40 \pm 10$ years (range 21 to 65 years). The mean duration of AF was $4 \pm 1$ year. Patients had failed 1 to 2 AAD before PVI, and most of them had no ($n = 54$ patients) or minimal heart disease ($n = 16$ patients; 11 had arterial hypertension and 5 had a history of coronary artery disease). There was no history of amiodarone use.

The mean left atrial dimension was $38 \pm 2$ (range 33 to 40) mm, with a mean left ventricular ejection fraction of $59 \pm 8\%$.

All targeted PV were successfully isolated (mean of $3 \pm 1$ [range 1 to 4] PV per patient). The following veins had potentials and were isolated: left superior in 63 patients, left inferior in 52 patients, right superior in 57 patients, and right inferior in 16 patients. The right inferior PV was mapped in 32 patients: one-half of them (16 patients) did not have any potentials in this vessel, whereas the other 16 patients had PV potentials that were ablated.

A total of 881 complete cryoapplications were given in 188 veins. A mean of 5 (range 1 to 13) applications were given per PV and 13 (range 3 to 23) applications per patient. No PV stenosis (accessed by serial spiral CT in 63 patients...
and TEE Doppler velocities in 7 patients) or esophageal injury was detected during a mean follow-up of 33 ± 15 (15 to 60) months.

Total procedure time averaged 331 min and fluoroscopy time 88 min. Our long procedure times during PVI are in part due to extensive pacing/pharmacologic maneuvers and other interventions that we used while trying to induce arrhythmias and access end points.

Thirty-four patients (49%) had no AF recurrences without AAD, 15 patients (22%) had no AF recurrences with AAD, and 8 patients (11%) with sporadic AF bursts reported an improvement of >50% with AAD after the ablation. Overall, 82% of patients benefited from the procedure after the index PVI (Fig. 2). Of the 13 patients who did not improve, 10 had a second PVI 6 months after the first procedure. Of those patients, 6 had much improvement in their symptoms. Three patients remained with symptomatic AF and opted for rate control. In 1 patient, a third procedure was needed to ablate a focal tachycardia coming from the left inferior PV. He became asymptomatic.

In only 10 patients (14%), the arrhythmogenic PV(s) could be identified using the criterion of a higher AF rate in the PV than in the coronary sinus or adenosine administration (Fig. 1). When compared with the rest of the cohort, we found no statistically significant differences in their clinical characteristics using t tests or chi-square tests. The characteristics were distributed as follows: one patient had 3 different arrhythmogenic veins, 7 patients had 2 arrhythmogenic veins, and 2 patients had only 1 arrhythmogenic vein. In those patients, no recurrences were observed during long-term follow-up.

**Complications.** Complications were seen in 3 patients (4%). One of our first patients had a cerebral ischemic event with left-sided hemiplegia occurring at the end of the procedure. Factors other than the energy source could have played a role in this event (such as problems with anticoagulation, several exchanges of the sheaths, or long procedure time). Subsequently, this patient recovered all his baseline function.

A second patient developed a pulmonary embolism 2 months after the ablation (when he was also found to be...
inadequately anticoagulated). Although we cannot directly associate this event with the cryoablation, we decided to count it as an adverse effect during our follow-up.

The third patient had transient phrenic nerve paralysis during the application in the right superior PV. However, the diaphragmatic movement recovered immediately after stopping the cryoapplication.

**Discussion**

**Main findings.** Our study shows that a more localized ablation strategy using cryotherapy is effective in 82% of patients with PAF: 49% without AF recurrences without AAD, 22% without AF while receiving AAD, and 11% improved >50% with AAD (sporadic bursts of AF) during a mean follow-up of 33 ± 15 (range 15 to 60) months. The acute complications seen (stroke and transient phrenic nerve paralysis) were within the acceptable range for the procedure and did not result in long-term limitations for the patients.

In those patients in whom the arrhythmogenic PV could be identified and isolated, no recurrences were observed.

Cryothermy is effective as an energy source in AF ablation. Our study shows that 82% of patients with PAF benefited from pulmonary vein cryoisolation during long-term follow-up (Fig. 2). Those results are similar to those obtained with RF (14–19). However, in comparison to RF, cryothermy may have some advantages.

Cryoenergy causes adherence of the catheter tip to the underlying tissue during energy delivery, ensuring accurate lesion creation (20–22). This might be important in avoiding catheter dislocation to areas where complications could occur (such as the posterior left atrium or inside the PV).

Cryoenergy also has the ability to create reversible loss of function, allowing the prediction of the effectiveness and safety of a lesion (23,24). It does not require conscious sedation or anesthesia, as it is painless (25). This not only means more comfort for the patients but also decreases the low but real complications of anesthesia.

Cryothermal ablation preserves the extracellular matrix and endothelial integrity. As a result, it had not been associated with PV stenosis, esophageal perforation, or thromboembolic events during the treatment of AF (26,27). Although the rate of thromboembolic complications during RF ablation of AF is small, such consequences could be dreadful in a relatively young and healthy population.

**Focal approach versus large lesions in the treatment of AF.** All patients in whom we were able to identify which PV was the trigger were cured. Our relatively healthy population (no or minimal structural heart disease, normal left atrial dimension, or PAF) could represent the early stages of AF. At this time, ablation of potential triggers instead of isolation of all PV should be preferred.

A study by Nanthakumar et al. (28) showed that adolescents (without structural heart disease) referred for ablative therapy because of lone AF have an excellent outcome with the focal ablation of distinct foci (most located in the PV). Owing to their age, this population could really represent the first stages of AF, and the success in their treatment corroborates our findings of a more localized approach in a healthier population.

Gerstenfeld et al. (29) have shown a good long-term (18 months) outcome in patients younger than 50 years with PAF undergoing targeted ablation of ≤2 PV with triggered atrial premature beats or AF. Also, a recent report by Oral et al. (30) using a tailored approach to catheter ablation of AF has shown an 80% success rate despite having 40% of patients with evidence of structural heart disease. Although one could say that the group’s study population had already passed the first stages of AF, their results again ratify the success of limited electrophysiologically guided lesions in the percutaneous treatment of arrhythmias.

**Study limitations.** Our daily TTM recorded only fractions of the day and do not represent cardiac rhythm during a 24-h period. Continuous rhythm monitoring would be preferable, but it would be hard to justify implanting a device in this healthy population. After 180 days, we returned to a symptom-guided recording method, which despite being widely used has some disadvantages (poor correlation between symptoms and arrhythmias was shown consistently in 2 studies) (31,32).

Despite being around for a long time in the surgical field, catheter-based cryoablation is still a relatively new technology compared to RF. Also, efficiency is highly dependent on the duration of application and pressure against the myocardial tissues (33,34). This could lead to the concept of longer procedure times when comparing cryoablation to RF. But if we consider total time in the electrophysiology laboratory (including time devoted to anesthesia), cryoenergy and RF procedures are not that different.

Also the identification of an arrhythmogenic PV was not very frequent. In our population, it was identified in only 10 patients (14%). Unfortunately, this represents the reality of most patients with PAF submitted to PVI (29,30).

**Conclusions**

In patients with recent-onset PAF and no (or minimal) structural heart disease, PV cryoablation is effective in 82% of patients: 49% with complete success (no AF and no AAD) and an additional 33% with improvement (22% AF-free with AAD and 11%, still with sporadic bursts of AF, reporting >50% improvement compared to before ablation) during long-term follow-up (mean of 33 ± 15 months). When the arrhythmogenic PV is identified and isolated, the long-term outcome is excellent (100% freedom from AF), indicating no need to isolate all PV. Pulmonary vein isolation alone should be performed in patients early in the process of the disease.

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