Pulmonary Vein Isolation Using Transvenous Catheter Cryoablation for Treatment of Atrial Fibrillation Without Risk of Pulmonary Vein Stenosis

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OBJECTIVES
We sought to evaluate the efficacy and safety of pulmonary vein (PV) isolation using transvenous cryoablation for the treatment of atrial fibrillation (AF).

BACKGROUND
Although electrical isolation of PVs with radiofrequency energy for the treatment of AF is feasible, it is associated with a significant risk of PV stenosis. Cryoablation is a new alternative therapy allowing ablation of tissue while preserving its underlying architecture.

METHODS
In 52 patients with paroxysmal (n = 45) or persistent (n = 7) AF, PV isolation using the CryoCor cryoablation system (CryoCor Inc., San Diego, California) was performed. A 10F deflectable transvenous catheter was performed as guided by ostial PV potentials. Cryoablation was applied twice at each targeted site (2.5 to 5 min/application). Computed tomography (CT) of the thorax was performed at baseline and at 3 and 12 months to evaluate for PV stenosis.

RESULTS
All targeted PVs were completely isolated in 49 (94%) of 52 of patients. Of 152 PVs targeted, 147 (97%) were successfully isolated (mean 3.0 PVs isolated per patient). After a mean period of 12.4 ± 5.5 months of follow-up, 37 (71%) of 52 patients had no recurrence of AF or were clinically improved, including 29 patients (56%) who had no recurrence of AF (n = 11) or without the use of anti-arrhythmic drugs. At 3 and 12 months, the CT scan showed no evidence of PV stenosis associated with cryoablation in any patients.

CONCLUSIONS
Transvenous catheter cryoablation is an effective method to create PV electrical isolation for the treatment of AF. A clinically satisfactory result can be achieved in 71% of patients with AF, without the risk of PV stenosis.

Radiofrequency (RF) energy application, applied either focally to eliminate the triggering foci in the pulmonary veins (PVs) or circumferentially to isolate the PVs from the left atrium, has resulted in a cure of atrial fibrillation (AF) in 50% to 70% of patients (1–5). However, the procedure with RF energy has a significant risk of mortality and morbidity, including systemic embolism (2% to 5%), PV stenosis (3% to 8%), pericardial effusion, cardiac tamponade, phrenic nerve paralysis, and pro-arrhythmia (intra-atrial re-entry tachycardia) (4–12). Additionally, multiple procedures are required in 9% to 49% of patients to achieve clinical efficacy, highlighting the challenge to determine a successful acute end point (4–6). Although RF energy has become the gold standard for catheter ablation in the majority of cardiac arrhythmias, PV ablation by heating has potential limitations: 1) RF energy produces tissue disruption, which increases the risk of perforation and thromboembolism (9,13); and 2) RF energy induces inhomogeneous, dense fibrosis and shrinking of the tissue, leading to PV stenosis (5–8,10,11,14). Therefore, evaluation of new energy sources that may overcome these limitations is of clinical importance.

One such alternative energy source is cryothermal energy. Previous clinical studies regarding the surgical treatment of arrhythmias have demonstrated that cryoablation is a safe and effective method for ablating cardiac tissues (15,16). Pathologic studies in animals (17,18) and humans (19) have shown that cryolesions are well delineated, transmural, homogeneous, and without inflammation. Cryothermal energy creates minimal endothelial/endocardial disruption and preserves the underlying tissue architecture. Therefore, the lesions are minimally thrombogenic and arrhythmogenic, and cryoablation of the PV should have a low risk of PV stenosis (16). The advent of percutaneous catheter cryoablation, which avoids the risks associated with open-heart surgery (20), may provide an important alternative to RF ablation for the treatment of AF. The initial early results of a novel catheter-based cryoablation system (CryoCor Inc.,
San Diego, California) for the treatment of supraventricular tachycardias, including AF, have been reported recently (21). In this report, we present the long-term results in patients treated with this catheter cryoablation technique to isolate PVs for the treatment of AF, with particular emphasis on the potential of this technique to avoid PV stenosis.

**METHODS**

**Patient population.** The subjects of this prospective study consisted of 52 patients enrolled consecutively at three participating clinical centers. Forty-one were men, with a mean age of 50 ± 11 years. Atrial fibrillation was paroxysmal in all patients during the initial enrollment for this study; however, AF became persistent (defined as present for ≥1 month and requiring cardioversion for termination) in seven patients by the time of the procedure. A mean value of 11 AF episodes within six weeks preceding the procedure. Eight patients had previously failed ≤1 anti-arrhythmic drugs and at least two anti-arrhythmic drugs had been ineffective in preventing AF recurrence before the procedure. Twenty-eight patients (54%) had no structural heart disease, 17 had arterial hypertension, 5 had coronary artery disease, 1 had dilated cardiomyopathy, and 1 had valvular heart disease. The mean left ventricular ejection fraction was 0.61 ± 0.08 (range 0.39 to 0.82), and the mean left atrial size was 4.0 ± 0.7 cm (range 2.1 to 5.2 cm).

Patients were included if they had symptomatic AF resistant to ≥2 anti-arrhythmic drugs and at least two documented AF episodes within six weeks preceding the procedure. There was a mean value of 11 ± 11 episodes of AF per month in patients with paroxysmal AF, as documented by a transtelephonic event recorder one month before the procedure. Eight patients had previously failed RF ablation of AF resistant to ≥2 anti-arrhythmic drugs and at least two documented AF episodes within six weeks preceding the procedure.

**Electrophysiologic procedure.** Patients enrolled signed a written consent form that was approved by the local ethics committee. Before the procedure, all patients were orally anticoagulated to a therapeutic international normalized ratio of 2 to 3 for at least three weeks and had a transesophageal echocardiogram to exclude the presence of a left atrial thrombus. Patients with persistent AF were converted to sinus rhythm by internal or external cardioversion during the procedure. In each patient, a decapolar catheter was positioned in the distal coronary sinus to record, pace, and confirm entrance conduction into the left PVs. Double trans-septal catheterization was performed, and intravenous heparin was administrated to achieve an activated clotting time of >250 s. Venograms of all targeted PVs were obtained both before and after the ablation procedure. A deflatable, 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 deflatable, 10F cryoablation catheter (CryoCor Inc.) was inserted into the left atrium through a 10F to 12F, 65-cm-long sheath (DAIG, St. Jude Medical Inc., St. Paul, Minnesota, or Cook Inc., Bloomington, Indiana) and was used to perform the ablation.

**Cryoablation procedure.** Segmental isolation of PVs, as guided by the recording of PV potentials with the Lasso catheter, was performed using the CryoCor cryoablation system (4,22). Whenever feasible, all PVs with PV potentials recorded at their ostium were targeted for isolation. 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. 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, 2.5 to 5 min of cryoablation was delivered twice (Fig. 1). If no changes in the electrogram were observed after 45 s, despite a catheter tip temperature of <−70°C, the application was stopped and the catheter was repositioned. The early procedural end point was complete electrical isolation of PVs based on abolition of all ostial PV potentials or complete entrance conduction block into the PV (Fig. 2).

**Post-ablation management.** All patients were monitored for 24 to 48 h and received anticoagulant therapy (warfarin) and the same anti-arrhythmic drugs as before the ablation for at least 3 months after the procedure. Before three months, the continuation of anti-arrhythmic drugs and anticoagulation was left to the discretion of the physician.

**Spiral computed tomographic (CT) scan.** A contrast-enhanced spiral CT scan of the thorax with three-dimensional reconstruction was performed within 1 month before the ablation procedure and at 3 and 12 months follow-up to define the anatomy of the PVs and to measure the diameter of the ostia of the PVs (Fig. 3). The same radiologist (B.G.) reviewed all pre- and post-cryoablation images in a blinded manner. The diameter of the ostia of the PVs was determined for each patient in a pairwise manner to maintain consistency in the measurements. In addition, the radiologist was asked to indicate the presence, location, and degree of any discrete luminal narrowing observed. All measurements were made both for treated and untreated veins to compare inter-observation variability.

**Follow-up.** The patients were seen in the outpatient clinic every four to six weeks and then every two to three months after the procedure. All patients were given an event monitor recorder to document the frequency of symptomatic AF episodes. A successful outcome was defined as no recurrence of symptomatic AF in the most recent six months of follow-up, independent of treatment with an anti-arrhythmic drug that had been ineffective before the procedure. A mean number of 3 AF episodes during the initial enrollment for this procedure. There was a mean value of 11 AF episodes within six weeks preceding the procedure.
**Figure 1.** Isolation of the left superior pulmonary vein (PV). A decapolar ring catheter (PV1-2 to PV10-1) is positioned at the ostium of the left superior PV. Recordings of the surface electrocardiographic leads I, aVL, and V1 and the cryoablation catheter (Cryo Dis) are shown during distal coronary sinus (CS Dis) pacing. After initial cryoablation applications at the earliest activation sites (*) of the PV potential at electrodes 9-10 (Baseline), the PV activation sequence changes and the local endocardial activation time at electrodes 9-10 increases from 60 to 130 ms (Cryo 9-10). Further cryoablation applications at the earliest activation sites (*) of the PV potential at electrodes 3-4 resulted in complete electrical isolation without any PV potential (Cryo 3-4).

**Figure 2.** An example of exit block of the pulmonary vein (PV) potential after isolation of the left inferior PV using cryoablation. Isolation of the PV is confirmed by abolition (but there are still potentials visible) of all PV potentials as recorded by the decapolar ring catheter (PV1-2 to PV10-1). Exit block of the PV potential (arrow) is observed during spontaneous discharge inside the PV. CS Dis = distal coronary sinus; Cryo Dis = cryoablation catheter.
ablation. Patients who had at least a 50% reduction of AF episodes (frequency multiplied by average episode duration) in the most recent six months on event recordings, compared with the month before ablation, were considered clinically improved.

Statistical analysis. Continuous measures are expressed as the mean value ± SD and were compared with a t test for paired or unpaired data, as appropriate. Dichotomous variables were compared using the chi-square test with Yates’ correction. The CT data were compared using two-way analysis of variance to detect the effect of vein size, treatment, and follow-up duration. Statistical significance was set at p < 0.05.

RESULTS

Cryoablation of PVs. Successful electrical isolation was achieved in 147 (97%) of the 152 targeted veins. These included 48 (96%) of 50 left superior pulmonary veins (LSPVs), 44 (96%) of 46 right superior pulmonary veins (RSPVs), 38 (97%) of 39 left inferior pulmonary veins (LIPVs), and 17 (100%) of 17 right inferior pulmonary veins (RIPVs) in which isolation was attempted. There were no significant differences in the efficacy of the vein isolation procedure across the PVs (p > 0.05). All targeted PVs were completely isolated in 49 (94%) of the 52 patients with an average of 3.0 ± 0.9 veins treated per patient. The reasons for failure to completely isolate the targeted PVs were transient phrenic nerve paralysis in one patient and the inability to maintain stable sinus rhythm in two patients with persistent AF. The mean procedure time was 7.5 ± 2.0 h (range 3.5 to 13 h), and the mean fluoroscopic time was 114 ± 44 min (range 44 to 263 min). In one patient in whom cryoablation did not successfully isolate all veins with PV potentials due to the console failure, RF ablation of the LIPV was performed at the index procedure.

A mean of 48.3 ± 16.6 (range 10 to 79) cryoablation applications were delivered per patient, and there was a median of 13.9 (range 4.3 to 26) applications per vein (7.7 ± 2.3 sites). The overall mean percentage of effective cryoablation applications was 70 ± 15% (range 43% to 100%). The mean temperature achieved at target sites during effective applications (−77.5 ± 4.5°C) was significantly lower than that during ineffective applications (−71.2 ± 5.0°C, p < 0.01). The mean number of cryoablation applications needed to achieve isolation of the LIPV (7.7 ± 4.4) and the RIPV (7.6 ± 6.3) was significantly lower than that for the LSPV (12.5 ± 5.9, p < 0.05) and RSPV (10.1 ± 5.2, p < 0.05).

Follow-up results. After a mean follow-up of 12.4 ± 5.5 months (range 1 to 19.8 months), 29 (56%) of 52 patients had no recurrence of AF. Eighteen (62%) of these 29 patients were not taking anti-arrhythmic drugs at the time of the last follow-up. At 12 months of follow-up, 16 (62%) of 26 patients had no recurrence of AF. In patients with paroxysmal AF, 26 (58%) of 45 patients were free of arrhythmia, including 16 off anti-arrhythmic drugs. In patients with persistent AF, successful long-term AF control was achieved in 3 (43%) of 7 patients, including 2 patients off anti-arrhythmic drugs.

The remaining 23 patients had one or more recurrences of AF, with or without concomitant atrial flutter, identified by the patient symptom report and/or by an event recorder electrocardiogram. When AF recurred, it occurred with a median time to the first recurrence of 2 days (range 1 to 21
days). Of the 23 patients, 7 additional patients were clinically improved after the cryoablation procedure and were having at least a 50% reduction in the frequency and duration of episodes while taking previously ineffective anti-arrhythmic drugs (mean improvement 72 ± 15%, median 73%, range 50% to 98%). Using the same criteria of frequency and duration, the remaining 15 patients had improvement no better than a 15% reduction in AF episodes (mean 4 ± 4%, median 0%, range 0% to 15%). Based on these criteria, 37 (71%) of the 52 patients had adequate control of their arrhythmia after the cryoablation procedure.

Five patients underwent a repeat cryoablation procedure. One patient had a residual PV potential at the ostium of the LSPV and RSPV, proximal to the previous ablation sites. Both PVs were completely isolated at a more proximal site by cryoablation. In one patient, foci outside the PVs, at the superior vena cava, and at the ostium of the coronary sinus were found. The third patient had one vein with recurrence of PV potentials. All three patients had successful cryoablation. Two patients developed a typical atrial flutter and underwent successful cavo-tricuspid isthmus cryoablation. After a repeated procedure, one patient had no episodes in the most recent six months of follow-up, and the remaining four patients were clinically improved as of the last follow-up.

**PV Stenosis.** There was no acute PV stenosis or thrombosis observed in any treated PVs, based on the second venogram performed after the procedure. All patients were questioned for symptoms of PV stenosis at 3, 6, and 12 months of clinical follow-up. Only three patients reported symptoms suggestive of PV stenosis during follow-up—namely, shortness of breath (n = 2) or a new cough (n = 1). All three patients underwent a lung perfusion scan to determine possible stenosis. Of the three patients, one was diagnosed with a pulmonary embolus (see Complications section), and the other two had no anomalies on the scan. Furthermore, these three patients did not have evidence of PV stenosis noted on the CT scan obtained at the next follow-up interval.

All patients had a spiral CT scan performed before the procedure; 47 (96%) of 49 patients and 19 (73%) of 26 patients who completed 3 and 12 months of follow-up, respectively, had a repeated CT scan obtained. In 7 patients, a repeated CT scan was not performed at 3 (n = 3) and 12 months (n = 7) of follow-up because of allergic reactions to contrast agents on their baseline scan (n = 2), patient refusal (n = 3), and performance of the surgical maze procedure (n = 2 at 3 and 5 months of follow-up). A transesophageal echocardiogram was performed in those showing no increase in Doppler flow at the PVs suggestive of stenosis. In 3 patients, 3 CT scans (1 at 3 months and 2 at 12 months) were only evaluated by the local center due to technical difficulties in transferring these scans to the core laboratory facility. At the local center, no luminal irregularities or narrowing were observed in these three patients; however, their data are not included in the summary data presented subsequently.

A total of 196 PVs were evaluated, of which 123 (63%) had cryoablation performed. The mean diameter of all the treated PVs was 15.5 ± 3.6 mm (n = 123) before the procedure, 15.2 ± 3.6 mm (n = 123) at 3 months of follow-up, and 14.6 ± 3.6 mm (n = 46) at 12 months of follow-up (p = 0.32). In 17 patients who had paired CT data at 3 and 12 months, there were no significant differences in the percent change in PV diameter between the treated and untreated PVs (n = 28) at 3 months (−2.5 ± 10.3% vs. −0.7 ± 10.3%, p = 0.47) and 12 months of follow-up (−6.6 ± 12.9% vs. −9.4 ± 15.0%, p = 0.41). As analyzed by two-way analysis of variance for time and treatment effect, there were also no changes in the PV ostial diameter due to the treatment effect noted (p > 0.05), and over time, both treated and untreated PVs significantly decreased in size (p < 0.05) (Fig. 4).

Regarding the anatomic positions of treated PVs, the ostial diameter of the LSPV (n = 41; 17.3 ± 3.8 mm), RSPV (n = 35; 15.9 ± 2.2 mm), and RIPV (n = 14; 15.8 ± 3.4 mm) was significantly larger than that of the LIPVs (n = 33; 12.9 ± 3.3 mm; p < 0.05) on the baseline CT scan. At 3 and 12 months of follow-up, there were no significant serial changes in the ostial diameters of the LSPVs (17.0 ± 3.6 mm vs. 16.7 ± 3.5 mm after 12 months [n = 16]; p > 0.05), RSPVs (15.3 ± 2.4 mm vs. 14.7 ± 2.6 mm after 12 months [n = 15]; p > 0.05), LIPVs (12.4 ± 3.3 mm vs. 11.3 ± 2.5 mm after 12 months [n = 12]; p > 0.05), and RIPVs (15.5 ± 2.9 mm vs. 16.6 ± 1.5 mm after 12 months [n = 3]; p > 0.05) (Fig. 5).

Three PVs in three patients were reported to have discrete luminal narrowing of <25%, noted both before and after cryoablation, and remained unchanged through follow-up. These luminal irregularities were likely caused by previous RF ablation (n = 2) or an anatomic variant (n = 1). In one patient who received both RF and cryoablation in the index procedure, 75% narrowing was noted in the LIPV, which was treated with RF alone. No significant narrowing was noted in the LSPV, a vein that was treated with cryoablation. Otherwise, there was no evidence of discrete luminal irregularities, generalized narrowing, or other signs of stenosis in any other treated PVs.
Complications. Some of the early procedure-related complications have been reported previously (21). One patient had a peri-procedural ischemic event with left-sided hemiplegia, occurring at the end of the procedure during PV angiography. After 12 months of follow-up, his neurologic status had significantly recovered. One patient with a history of coronary artery bypass surgery developed a pulmonary embolism two months after the procedure. During this event, the patient was inadequately anticoagulated. Another patient developed an arteriovenous fistula that required surgical repair. Finally, one patient had transient phrenic nerve paresis during a cryoablation application in the RSPV, resulting in premature procedure termination. However, the diaphragmatic movement resumed immediately after termination of cryoablation without sequelae, and there was no damage of the phrenic nerve or loss of diaphragmatic or pulmonary function at 12-month follow-up.

DISCUSSION

The data presented herein show that the novel cryoablation system used in this study allows for the percutaneous delivery of cryothermal energy and is a safe and effective way to perform segmental isolation of PVs for the treatment of AF, without the risk of PV stenosis during long-term follow-up.

Early electrical isolation of PVs, as determined by elimination of all PV potentials and entrance block into the PV, was achieved in 97% of the PVs targeted. During long-term clinical follow-up, 71% of patients with AF had no recurrence of symptomatic episodes or were clinically improved (including 56% without any recurrence of AF), suggesting that cryoablated lesions result in not only short-term but also permanent electrical isolation of PVs. This is consistent with a recent animal study in which catheter cryoaulation could effectively create circumferential lesions (averaging 18 mm in length and 13 mm in width) in the PV (23). In the present study, the long-term clinical efficacy of PV isolation using cryoablation has a 56% success rate, with only 10% of patients undergoing a repeat ablation procedure. This result is comparable to the clinical efficacy of previous studies using RF energy for segmental isolation of PVs (50% to 70%) (4,5,23). However, the prevalence of anti-arrhythmic drug use (38%) in those patients free of arrhythmia recurrence remains high. In this multicenter study, the long-term use of anti-arrhythmic drugs was not controlled. One possible explanation for the reluctance of stopping anti-arrhythmic drugs in some patients, even if they were free of arrhythmia, is due to the high percentage of patients having underlying structural heart disease (46%) and a large percentage of patients in whom a previous PV ablation procedure with RF energy had failed (15%) or who had persistent AF (13%).

Most important is the difference in the safety profile for cryoaulation. The overall procedure complication rate, excluding PV stenosis, of 7.7% (4 of 52 patients) is lower than the rate range (8% to 35%) of voluntarily reported complications in noncontrolled trials using RF energy (1–6,9). In this study, one patient (2%) developed a thromboembolic event associated with PV ablation, and this incidence is similar to previous studies using RF energy (1,4,9,10). Although cryoaulation may be associated with a lower thrombogenic tendency than RF energy (24,25), the thromboembolic risk related to left atrial catheter ablation remains. Like RF ablation (9), cryoaulation can produce phrenic nerve paralysis. Therefore, identification of diaphragmatic movement during pacing with a high current from the tip of the catheter before PV ablation, especially the RSPV, is recommended. As seen in this study, one of the advantages of the use of cryoaulation for PV isolation is that phrenic nerve function recovers after stopping the cryoaulation, which is a form of “ice mapping” for complications.

Most interestingly is the lack of any short- or long-term PV stenosis in the present study. Despite the use of an electroanatomic mapping technique, intracardiac echocardiography, and biplane fluoroscopy to guide the positioning of the mapping and ablation catheters at the PV ostium, up to 5% of patients developed severe PV stenosis after RF ablation (12,26). Patients with severe PV stenosis after RF ablation often presented with respiratory symptoms that frequently led to a misdiagnosis of other common diseases, resulting in erroneous diagnostic and therapeutic procedures. Furthermore, a significant proportion of patients remained symptomatic or developed restenosis after the PV intervention for PV stenosis (12). These highlight: 1) the difficulty in defining the most proximal extent of the ostium during PV isolation and effectively isolating all the PVs using RF energy without causing PV stenosis; and 2) the importance of preventing PV stenosis. In the study reported herein, no patients had either physiologic or anatomic PV stenosis as the result of cryoaulation. Three patients did have luminal irregularities that were the result of a previous (n = 2) or concomitant (n = 1) RF ablation procedure.
Study limitations. The first limitation of this study is that the clinical efficacy of the procedure was based on the documentation of symptomatic recurrences of AF. Asymptomatic episodes of AF were not assessed routinely by ambulatory monitoring during follow-up. However, because all of the patients in this study were highly symptomatic before the ablation, no recurrence of their symptomatic AF was considered an acceptable clinical end point. Secondly, before the ablation, no recurrence of symptomatic AF were not assessed routinely by fluoroscopy times necessary for PV isolation were long, although they were still within accepted safe ranges (27). The longer procedure times were due, on the one hand, to the nature of this technique (cryoablation requires longer individual ablation applications of 2.5 to 5 min), a learning curve in the use of this new technique for PV isolation, and, on the other hand, to the additional protocol-oriented procedures (transesophageal echocardiography was used during the procedure by one center and PV angiography before and after cryoablation was mandated by the protocol). Additionally, in some patients, a three-dimensional mapping system was used, further prolonging the procedure in these patients. The procedure and fluoroscopy times will decrease as operators gain experience using this system, with a shorter ablation protocol and further refinement of the catheter designs, such as the use of a balloon catheter to occlude the blood flow of the PV during ablation to improve the efficacy of each cryoablation application. Finally, an electrocardiogram-triggered measurement was not used to determine the PV diameter during CT scanning in this study. Although this might have affected the measurement of the PV luminal diameter, there was no evidence of discrete luminal irregularities, generalized narrowing, or clinical signs of stenosis in any cryoablated PVs, and this would impart an error in the measurement of both treated and untreated veins equally.

Conclusions. Our results suggest that electrical isolation of the PVs using cryoablation is feasible and may prevent arrhythmia recurrence in patients with AF, without the occurrence of PV stenosis over long-term follow-up.

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