

Cryoablation for atrial fibrillation and antiarrhythmic drug pretreatment: a single referral center experience

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Abstract. – **OBJECTIVE:** Pulmonary vein isolation (PVI) ablation has emerged as the gold standard of ablative strategies to treat medically refractory paroxysmal and persistent atrial fibrillation (AF). Regardless of the superiority of catheter ablation based on PVI over antiarrhythmic drug therapy, recurrence rates of AF remain higher than desired. PVI via cryoablation has rapidly become a mainstream treatment for AF, due to its effectiveness and fast learning curve. Our objective was to assess the safety and efficacy of cryoablation in a single referral center.

PATIENTS AND METHODS: This is a retrospective analysis of results after cryoablation treatment of AF over three years. 146 patients with AF underwent a cryoablation procedure in our clinical center and were followed-up for three years after the procedure. All patients received cryoablation of the pulmonary veins, although concomitant procedures were performed in 6 patients (re-ablation), including radiofrequency and cryoablation.

RESULTS: Cryoablation was clinically successful in 90.83% of the patients with paroxysmal AF and 60% of those with persistent AF. The clinical success of cryoablation was correlated with pretreatment with amiodarone and in the case of re-ablation. Concerning postoperative complications, major bleeding was correlated with female gender, treatment with rivaroxaban and amiodarone.

CONCLUSIONS: Among large trials, freedom from recurrent AF is about 65% with follow-up limited to 1 to 2 years. PVI via balloon cryoablation is a safe and efficient guideline-based treatment for AF, producing a durable event-free result in most patients out to 3 years with better outcomes than previously reported.

Key Words:

Cryoablation, Pulmonary vein isolation, Atrial fibrillation, Antiarrhythmic, Amiodarone.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia affecting approximately 2% of the general population. In Europe, its prevalence is expected to increase to 2.7-3.3% in the next two decades as a consequence of an aging population, the greater ability to diagnose and suspect AF and the improved ability to treat chronic cardiac and non-cardiac diseases¹. AF is associated with complex cardiac diseases, multiple comorbidities and hemodynamic, hemorrhagic or embolic consequences. These consequences may lead to frequent hospitalizations, permanent disabilities, cognitive disturbances, and absences from work and death. Therefore, AF is a relevant item of expenditure for the national health care systems^{1,2}.

Pulmonary vein isolation (PVI) has emerged as the gold standard of ablative strategies to treat medically refractory paroxysmal and persistent atrial fibrillation (AF) and remains the cornerstone of AF ablation. The venous origin of ectopic beats triggering AF has been demonstrated by Haïssaguerre et al since 1998³. Despite the fact that catheter ablation based on PVI is superior to antiarrhythmic drug therapy, recurrence rates of AF remain higher than desired⁴. PVI via cryoablation has rapidly become a mainstream treatment for AF, due to its effectiveness and fast learning curve⁵.

This retrospective study aims to review our experience with patients who underwent cryoablation and to evaluate the safety and efficacy of cryoablation in a single referral center.

Patients and Methods

This study is a retrospective assessment of consecutive subjects who underwent cryoballoon-based catheter ablation of AF by four electrophysiologists at Onassis Cardiac Surgery Center from 2013 to 2015. All participants provided informed consent, and the study protocol was approved by the respective institutional review boards. Patients were brought to the electrophysiology laboratory in a fasted state off all antiarrhythmic drug therapy. Under local anesthetic, a decapolar diagnostic catheter was inserted into the coronary sinus via the femoral approach. After a single transeptal puncture, the 28 mm cryoballoon (Arctic Front or Arctic Front Advance, Medtronic Inc., Minneapolis, MN, USA) was introduced into the left atrium via a 14F steerable sheath (FlexCath, Medtronic Inc., Minneapolis, MN, USA). Pulmonary vein mapping was performed using an eight-pole transluminal circular mapping guide (Achieve, Medtronic Inc., Minneapolis, MN, USA). Catheter positioning was assessed by transluminal contrast injection with the goal of complete pulmonary vein occlusion by the inflated balloon before the lesion delivery. To discriminate between PV, and atrial potentials, stimuli were delivered from the coronary sinus. Cryo energy was applied for 180 to 240 seconds for at least two times with minimum tolerated temperature of -55 degrees Celsius. Cryoapplication duration was impacted by assessment for phrenic nerve dysfunction, balloon nadir temperature, and time to isolation when measured. Only the 28 mm cryoballoon was used. PVI was reassessed 30 minutes after the final application at each vein. Ablation of PV potentials, dissociation of PV potential or exit of entry were accepted as endpoints of the procedure. If PVI could not be achieved, the targeted pulmonary vein was again subjected to cryoablation. Heparin bolus was administered during the procedure targeting an activated clotting time of >300 s. All patients underwent transthoracic echocardiography (TTE) to rule out pericardial effusion after the procedure. The patients were treated with oral amiodarone for 3 months, oral anticoagulation for at least 3 months and after that based on the individual CHA₂DS₂-VASC score. The patients attended outpatient clinic follow-up at 3, 6, 12 months and 6-month intervals after that. During these visits, a 12-lead surface electrocardiogram (ECG) and 24h-Holter ECGs were performed. Recurrence was defined as symptomatic and documented

episodes of AF/AT lasting > 30s. The primary endpoint was defined as recurrence of any symptomatic and documented atrial arrhythmia >30 s following a blanking period of 3 months. Secondary endpoints were procedure-related complications such as death from any cause, major and minor bleeding, pulmonary vein stenosis, left atrial arrhythmias, phrenic nerve palsy, pericardial effusion, cerebral embolism or atrial-esophageal fistula.

Data were collected from patient medical charts, operative notes, and pathologic examination records. Follow-up data were gathered from outpatient clinic files and with direct telephone contact with the patients or their families.

A total of 146 patients were identified, and 125 patients were successfully contacted and interviewed. Patients were queried about recurrent symptomatic AF, the recurrent AF diagnosis, the perception of symptom resolution, re-ablation procedure, and subsequent hospitalizations for AF (apart from any ablation procedure admission).

For all patients, a chart review of the procedure was created. The information included the type of AF (paroxysmal or persistent), previous electrical or pharmacological cardioversion for AF and, the subjective frequency of the AF before the procedure. The chart review provided information about the presence of precipitating factors such as coronary artery disease, hypertension, and cardiomyopathy, and the presence and names of anticoagulant and antiarrhythmic drugs before or after the procedure. The exact ablation procedure, the number of pulmonary veins present and ablated and the presence of any complications of the procedure were also included. All patients provided verbal consent through telephone contact.

Statistical Analysis

Statistical Analysis was performed using SPSS 23.0 (Mac OS Version) (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY, USA). Continuous variables are expressed as a mean \pm standard deviation, while nominal/ordinal variables in absolute or percentage value (%). Distribution of all continuous variables was tested for normality with the parametric test Shapiro-Wilk and graphically with *p-p* plots. The success rate of the procedure was examined with the utilization of chi-square test. Correlations between variables in cross-sectional design were evaluated using Pearson's correlation coefficient. The level of statistical significance was predefined at 0.05.

Results

A total of 146 patients were followed-up for a mean of 3 years after the cryoablation procedure. The mean age of the patients was 60 years, and the group was divided equally between men and women. Before the ablation, 5 patients had persistent AF, and 120 had paroxysmal AF. This index AF ablation procedure was the second procedure for 6 patients.

Many patients (80%) were on an anticoagulant before the procedure, including dabigatran (10%), warfarin (25%), rivaroxaban (25%), and apixaban (40%). Similarly, many (70%) were on an antiarrhythmic medication at the time of evaluation for the ablation procedure (although all antiarrhythmic medication was held before the procedure), which included flecainide (30%), amiodarone (40%), propafenone (30%) (Table I).

All patients in this study underwent PVI cryoablation. The mean procedural and fluoroscopy times were 72.3 ± 5.5 (50-90), and 14 ± 3.3 (15-25) minutes respectively. Acute procedural success (absence or dissociation of all PV potentials, as confirmed by bi-directional block using a circular mapping catheter after a waiting period) was achieved in 99.5 % (581/584) of the pulmonary veins intervened. Cryoablation was clinically successful in 90.83% of the patients with paroxysmal AF ($p < 0.001$) and in 60% of those with persistent AF ($p = 0.655$). There were complications in 5 patients, all of which resolved within 30 days. The complications included one report of atrial flutter, two reports of major bleeding and two reports of minor bleeding following the procedure. Six patients had another ablation procedure, and for 5 of these 6, the next procedure was performed at our institution. In two patients with a repeat ablation procedure, there was a reconnection of the pulmonary veins.

Table I. Patient demographics and medication characteristics.

| Characteristic | Patients (n = 125) | |
|----------------|--------------------|-------|
| Gender | Male | 70.4% |
| | Female | 29.6% |
| Anticoagulant | Dabigatran | 10% |
| | Rivaroxaban | 25% |
| | Apixaban | 40% |
| | Warfarin | 25% |
| Antiarrhythmic | Flecainide | 30% |
| | Amiodarone | 40% |
| | Propafenone | 30% |

In terms of pairwise associations, clinical success of the cryoablation was correlated with paroxysmal AF status ($r = 0.176$, $p = 0.05$) and inversely with persistent AF ($r = 0.176$, $p = 0.05$), treatment with amiodarone ($r = 0.195$, $p = 0.029$) and in the case of re-ablation ($r = 0.263$, $p = 0.003$). With respect to post-operative complications, major bleeding was correlated with female gender ($r = 0.197$, $p = 0.028$), treatment with rivaroxaban ($r = 0.33$, $p < 0.001$) and amiodarone ($r = 0.262$, $p = 0.003$) (Table II).

Discussion

In agreement with previously published studies, our analysis demonstrates that cryoablation for atrial fibrillation is effective for the treatment of paroxysmal AF whereas long-term clinical outcome in patients with persistent AF is only moderate⁶⁻⁹.

The main finding of our study was that, with long-term follow-up of an ablation procedure using cryoballoon, freedom from recurrent AF and hospitalization for atrial arrhythmias was observed in 90.83% of subjects. Most were either free of AF symptoms or had a reduced burden after a follow-up of nearly 3 years. The pretreatment

Table II. Statistically significant Pearson's correlation coefficients (r) between variables.

| | | r | p | |
|-------------------------|----------------------------|--------|--------|--------|
| Clinical success | Paroxysmal AF [†] | 0.176 | 0.05 | 90.83% |
| | Persistent AF [†] | -0.176 | 0.05 | 60% |
| | Re-ablation | -0.263 | 0.003 | 50% |
| | Amiodarone | -0.195 | 0.029 | 75% |
| Major bleeding | Female | 0.197 | 0.028 | 5.405% |
| | Gender | | | |
| | Rivaroxaban | 0.33 | 0.0001 | 12.5% |
| | Amiodarone | 0.262 | 0.003 | 8.333% |

[†]AF: Atrial Fibrillation.

use of amiodarone contributed to higher success rates. Amiodarone can prolong atrial fibrillation cycle length at every step of the ablation and reduce the number of complex fractionated atrial electrogram sites identified. Amiodarone can also reduce the time spent on the procedure, while not affecting the long-term recurrence rate of atrial arrhythmias¹⁰. The combined approach of cryoablation and amiodarone can assist in the reduction of the ablated substrate amount while maintaining clinical success. This is opposite to the common practice of discontinuing antiarrhythmic drugs well before the procedure to allow a complete substrate ablation in the atria.

Complication rates were acceptably low, and no procedural-related issues emerged late in follow-up^{11,12}. The majority of complications were of bleeding relevance and were correlated with female gender, use of rivaroxaban and amiodarone. When AF recurred, there was a finding in the pulmonary veins, consistent with either a reconnection or incomplete ablation at the index procedure^{13,14}. All patients with recurrence underwent a successful second ablation procedure^{13,15}. Re-ablation procedures were correlated with higher success rates and resulted in greater and more durable outcomes¹⁶.

The majority of publications on AF and cryoablation have focused on freedom from 30 seconds of AF during 3 to 12 months post ablation^{6-9,17}. More recent reports have focused on cryoablation for somewhat longer times and have shown a 65-75% rate of freedom from AF for one to two years post ablation^{11,18-20}. This study demonstrated a higher success rate over a longer time of observation. The study was an observational retrospective single-center study, involving multiple operators. 21 patients in the consecutive series could not be reached. In this study, the recurrence of AF was assessed through medical history, and a conventional systematic approach to AF monitoring was performed (ECG, 24h Holter monitoring)¹⁹. Our study has some limitations. This is a single-center, retrospective study with a relatively small group of patients. Therefore, these results need to be validated in a larger, prospective study.

Conclusions

Cryoablation is an effective method to treat atrial fibrillation. Cryoablation represents the ideal therapy that can restore sinus rhythm without the adverse effects of antiarrhythmic drugs.

Successful AF cryoablation results in significant improvements in symptoms, quality of life, left ventricular function (HF patients) and exercise tolerance. Cryoablation is a procedure with fast learning curve and low complications rate. Patients with the highest success rate are those with normal structural hearts and paroxysmal atrial fibrillation. Patients who benefit the most are those without precipitating factors and limited atrial fibrillation substrate. Patients with persistent atrial fibrillation develop frequent recurrence episodes after cryoablation. Pretreatment with amiodarone leads to higher success rates, whereas female gender, rivaroxaban, and amiodarone were correlated with higher bleeding risk. All large trials report freedom from recurrent AF at about 65% with follow-up limited to 1 to 2 years. Our analysis demonstrated that PVI via balloon cryoablation is a safe and efficient guideline-based treatment for AF, producing a durable event-free result in most patients out to 3 years with better outcomes than previously reported.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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