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Medium-term results of cryoballoon ablation of the pulmonary veins in patients with paroxysmal and persistent atrial fibrillation. First experience of a Spanish center

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Abstract
Purpose Cryoballoon ablation of the pulmonary veins (CAPV) is a new technique that could have similar results to radiofrequency procedures, but with fewer complications. We analyzed the outcomes and safety of this technique in a consecutive cohort of patients with atrial fibrillation (AF).
Methods A total of 63 patients with paroxysmal (n=40) or persistent (n=23) AF were studied. Patient follow-up was performed at 3 months and then every 6 months with 72-h continuous electrocardiographic recordings.
Results A total of 262 pulmonary veins were treated; 60.3 % of the cases presented normal pulmonary vein drainage with 4 pulmonary veins, and 23.8 % of the cases presented a common left-sided antrum. Complete isolation of all veins was achieved in 95.2 % of cases with 10.3±2.8 (mean±standard deviation) applications per patient. Transient right phrenic nerve injury was the most common complication (4.7 %). Median follow-up was 5.5 months. The probability of being free of recurrence at 1 and 2 years was, respectively, 86.2 and 72.2 % for paroxysmal AF and 49 and 36.4 % for persistent AF (P=0.012). Patients with structural heart disease experienced recurrence more often than patients with a normal heart (62.5 versus 24.5 %; P=0.03).
Conclusions CAPV appears to be a safe and effective procedure for the treatment of patients with AF, particularly those with paroxysmal AF and no structural heart disease.

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Keywords Atrial fibrillation · Ablation · Cryoballoon · Cryothermia

Abbreviations
AF Atrial fibrillation
CAPV Cryoballoon ablation of the pulmonary veins

1 Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia in the general population [1]. Its prevalence increases with age and other cardiovascular risk factors and its morbidity and mortality are considerably higher, leading to significant health costs [2]. Given the characteristics of the current population, the condition is considered one of the major cardiovascular health problems that could become pandemic in the twenty-first century [3]. At present, antral isolation with pulmonary vein radiofrequency ablation is considered a first-line treatment to maintain sinus rhythm in patients with paroxysmal AF who have no structural heart disease and are resistant to antiarrhythmic drugs [4]. This interventional approach has proven to be superior to conventional antiarrhythmic therapy in terms of long-term success and complications [5–7]. However, the technical requirements, long learning curve, and potential technique-related complications have driven the development of new approaches based on creating circumferential lesions with single-shot applications and using new energy sources for pulmonary vein isolation [8]. Among these new approaches, pulmonary vein cryoablation with a nitrous oxide balloon is the most widely used and has shown promising results in the main series published [9–16]. Furthermore, the technique appears to

be equal to or superior to conventional techniques, although the results of randomized clinical trials are still pending [17].

We present the initial experience and medium-term results of the first published Spanish series with follow-up of patients with paroxysmal and persistent AF who underwent cryoballoon ablation of the pulmonary veins (CAPV).

2 Method

Consecutive patients with paroxysmal or persistent AF eligible for their first procedure of pulmonary vein ablation according to the current indications were included [4]. In the case of paroxysmal AF, patients had presented more than two documented episodes of AF and were refractory to at least one antiarrhythmic drug. Before the procedure was scheduled, all patients underwent cardiac magnetic resonance imaging or computed tomography (CT) to characterize the left atrial anatomy and pulmonary venous drainage, and written informed consent was obtained

2.1 Procedure

Before the procedure, patients were admitted to the hospital on the morning of the procedure and underwent transesophageal echocardiography to rule out the presence of thrombi in the left atrium. Under deep sedation with propofol, local anesthesia, and via the right femoral vein, a quadripolar electrode catheter was advanced to the coronary sinus for left atrial recording and pacing. Using a single transseptal access and the Müllins technique, a deflectable 15-F sheath (FlexCath®, Medtronic CryoCath, Kirkland, Quebec, Canada) was advanced toward the left atrium. A 10.5-F cryoballoon of 23 or 28 mm in diameter (Artic Front®, Medtronic CryoCath, Kirkland, Quebec, Canada) was introduced through the deflectable sheath and used for the ablation. To record electrical activity and pacing inside the pulmonary veins, a decapolar circular mapping electrode catheter (Lasso® Biosense Webster, Diamond Bar, CA, USA) was exchanged for the cryoballoon and introduced through the deflectable FlexCath® sheath in the first 27 patients. In all other patients, a 3.3-F octapolar mapping electrode catheter of 15 mm in diameter (Achieve™, Medtronic, Minneapolis, MN, USA) was used (Fig. 1). The proximal two thirds of the Achieve™ electrocatheter was considered stiff enough to support the cryoballoon and served as a guidewire for catheterization of the pulmonary vein. If proper vein catheterization was impossible, the catheter was replaced with a 0.035-in. guidewire (Lunderquist Extra Stiff, Cook Medical, Limerick, Ireland). In patients who presented AF at the start of the procedure, synchronized electrical cardioversion was performed. Once a pulmonary vein was catheterized, the cryoballoon was inflated and advanced to the vein ostium; contrast venography was performed to confirm vein occlusion (Fig. 2). In cases in which the Achieve™ catheter was used, the catheter was shifted

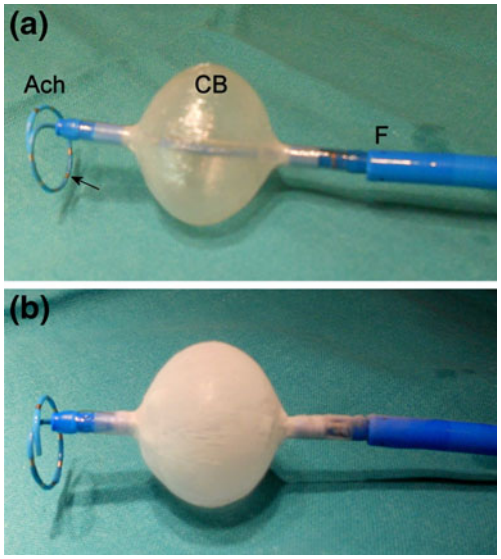


Fig. 1 The system used for CAPV is shown **a** before and **b** during cryothermal energy application. The cryoballoon (*CB*) is introduced through the FlexCath® (*F*) sheath. The Achieve™ (*Ach*) circular electrode catheter runs through the interior of the cryoballoon and has eight electrodes to record activity inside the pulmonary vein (*arrow*)

proximally to record potentials inside the vein. Afterwards, at least two applications of cryothermal energy of 300 s were given until correct electrical isolation of the vein was demonstrated. A minimum effective temperature was considered to be a cutoff point of −40 °C [18] or a temperature at which the entrance block at the vein was visualized. The left pulmonary veins were treated first, in descending order, followed by the right veins in the same order. During the right pulmonary vein applications, the phrenic nerve was stimulated through the superior vena cava to alert to the possibility of phrenic paralysis during stimulation. If phrenic nerve paralysis was observed, application was halted immediately. When complete occlusion of the vein was not achieved (particularly in the case of inferior pulmonary veins), maneuvers reported in the literature to increase contact between the balloon and the venous ostium during application (grind-down, hockey-stick, or big-loop maneuvers) were performed [14]. When pulmonary vein potentials could be recorded during application, entrance block of electrical activity to the vein as an endpoint of the application was considered (Fig. 3a). Once all applications had been carried out, the pulmonary veins were mapped to show the entrance block of electrical activity to the interior thereof, as well as exit block by demonstrating local capture inside the vein during pacing in its interior, with no evidence of atrial capture (Fig. 3b). In addition, special attention was paid to spontaneous activity dissociated from the vein (Fig. 3c). The entire procedure was carried out with sufficient intravenous heparin lock to achieve an activated coagulation time above 300 s, started immediately after transseptal puncture. Following ablation, anticoagulation was maintained with sodium heparin or low-molecular-weight heparin until correct oral anticoagulation was achieved.

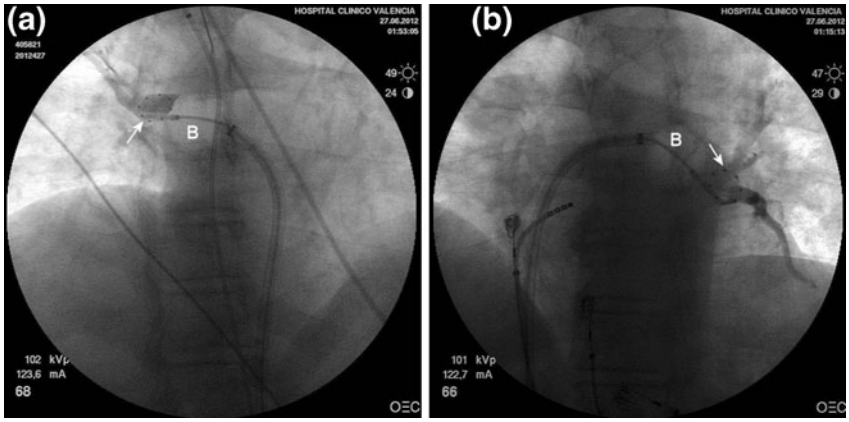


Fig. 2 **a** Radioscopic image in right anterior oblique projection showing a venography of the right superior pulmonary vein. **b** Left anterior oblique view showing a left venography of a patient with a common left-sided antrum. In both images, the *white arrow* indicates the position of the Achieve™ circular electrode catheter inside the pulmonary vein. *B* cryoablation balloon

2.2 Postprocedure anticoagulant and antiarrhythmic therapy

Following CAPV, oral anticoagulation was maintained for at least 3 to 6 months if AF did not recur and then individualized according to the patient's embolic risk, based on the CHA_2DS_2-VASc score [19]. Likewise, antiarrhythmic therapy with flecainide or propafenone was maintained for at least 3 months unless contraindicated, in which case sotalol, amiodarone, or dronedarone was used.

2.3 Follow-up

Patients were followed up in the arrhythmia clinic at 3 months and every 6 months thereafter, with follow-up consisting of a clinical interview, 12-lead electrocardiogram (ECG), and continuous 72-h ECG recording. As in other studies, in patients with a device capable of storing electrograms, the follow-up was based on an analysis of the episodes stored in the device [20] (Fig. 4). Patients were given instruction on proper electrocardiographic documentation if any episodes of palpitations occurred. Recurrence was considered to be proven AF lasting longer than 30 s [11, 15, 21, 22]. Patients with recurrent, sustained, or symptomatic AF were given an opportunity to undergo a second procedure, although only the outcomes and clinical progress after the initial procedure were analyzed in this study. As in other studies, we established a blanking 3-month period during which any paroxysmal AF episodes detected were not considered recurrences [13, 15, 16]. To calculate the survival curve, early recurrences within the first 3 months were only considered to exist when the patient continued to present episodes of AF after this period.

2.4 Statistical analysis

The results are expressed as the mean±standard deviation. Categorical data were compared using the chi-square test or the Fisher exact test. AF recurrence-free survival was estimated by the Kaplan–Meier method and compared to survival curves obtained using the log-rank test. A P value≤ 0.05 was considered to be statistically significant. All analyses were performed using SPSS version 15.0.

3 Results

3.1 Population characteristics

A total of 63 patients were included; the main epidemiologic characteristics of the population are summarized in Table 1. A high percentage of patients presented at least one cardiovascular risk factor: high blood pressure (32.8 %), diabetes (4.9 %), dyslipidemia (23 %), overweight (77.8 %), and obesity (mean body mass index, 27.75±3.46) (18.9 %). Only 1.7 % were diagnosed with sleep apnea–hypopnea syndrome (SAHS), and 17.2 % were at least moderately active sporty. The postdiagnosis time of AF progression was above 2 years in 80.3 % of patients, with a mean of 1.7 antiarrhythmic drugs unsuccessfully tested per patient (including beta blockers). Among patients included with structural heart disease, the most common was idiopathic dilated cardiomyopathy (37.5 % of all heart disease), followed by hypertrophic cardiomyopathy (25 %). Only 6.3 % of the population presented left ventricular dysfunction, 19.4 % presented left ventricular hypertrophy, and 38.5 % presented left atrial enlargement.

The most common pulmonary vein drainage pattern was 2 left and 2 right veins with drainage independent of the left atrium (observed in 38 patients, 60.3 % of cases). The remaining 25 cases presented some kind of variant of normality: a common left-sided antrum in 15 (23.8 %) patients, a common right-sided antrum in 1 patient, and accessory right pulmonary vein in 9 patients (14.2 %), 1 of whom also presented common left pulmonary antrum. An accessory left pulmonary vein was observed in only one patient.

3.2 Ablation procedure

The mean total procedure time was 180±32 min, with a mean fluoroscopy time of 30.7±22 min. Synchronized

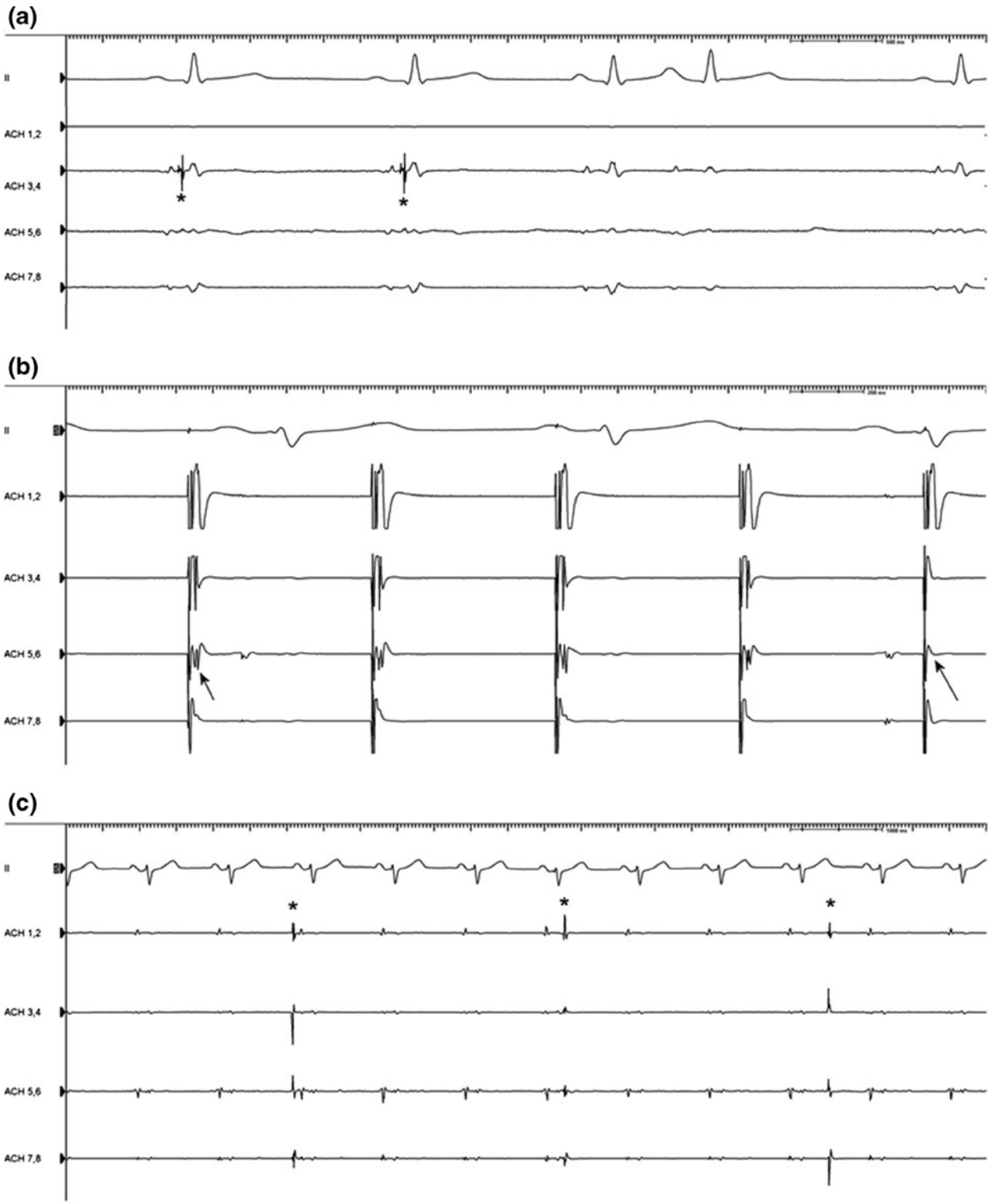


Fig. 3 The electrocardiographic LII surface lead and the recordings from four electrode pairs of the Achieve™ electrode catheter are shown. **a** Entrance block of electrical activity to the left superior pulmonary vein during the application of cryothermal energy in sinus rhythm. The *asterisks* show the recording of the venous electrical potentials located between far-field signals of the atrium and the left ventricle. The third complex shows the sudden disappearance of the vein potential, which is indicative of entrance block to the vein. **b** Post-ablation pacing in the pulmonary vein with a cycle length of 400 ms through the Achieve™ catheter. The *black arrow* indicates the local capture electrogram inside the pulmonary vein without exit from the activity to the rest of the atrium. Note the absence of local electrogram of the last paced beat (*second arrow*) showing the presence of local capture in the preceding paced beats. **c** The *asterisks* show spontaneous rhythm of the pulmonary vein at 25 bpm that does not capture the left atrium after ablation

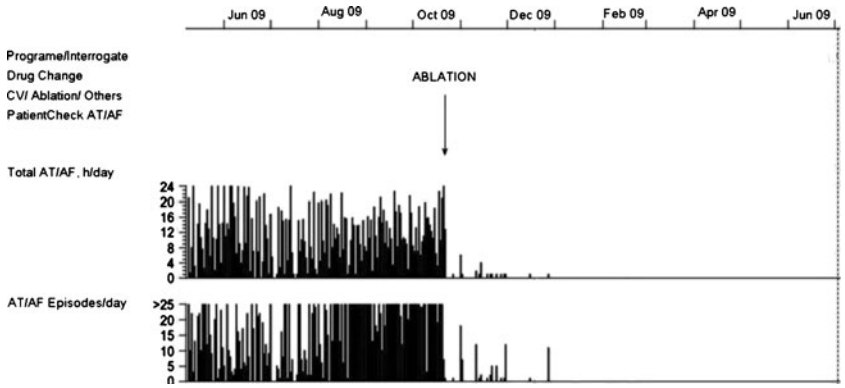


Fig. 4 Recording of the arrhythmic burden stored by the device in a patient who underwent cryoablation of the pulmonary vein and had a pacemaker. Note the high arrhythmic burden that she presented before cryoablation and the dramatic reduction in the burden during the post-ablation blanking period (3 months). Afterwards, no new episodes of AF were recorded. *AF* atrial fibrillation, *AT* atrial tachycardia, *CV* cardioversion

electrical cardioversion was performed at the start of the procedure in 22.2 % of cases (7.5 % of patients initially diagnosed with paroxysmal AF and 65.2 % of patients diagnosed with persistent AF). The ablation procedure was completed in 61 of the 63 patients (96.8 %). In one case, the procedure was not completed due to the recurrent appearance of transient phrenic paralysis, and in the second case, due to loss of transseptal access. When the Achieve™ electrode catheter was used, optimal occlusion was achieved with the cryoballoon by using only the catheter as a guidewire in 47.6 % of cases and the potentials inside the pulmonary vein were monitored during ablation in 57.7 % of veins, with vein isolation subsequently confirmed in the remaining cases. A 28-mm cryoballoon was used in 59 of the 63 cases (93.6 %).

A total of 621 cryothermal energy applications were performed in 262 veins; the mean number of applications per patient was 10.3±2.8 (range, 8–21). Correct isolation of all pulmonary veins was observed in 96.9 % of cases (95.2 % of left superior, 96.8 % of left inferior, 100 % of right superior, and 93.6 % of right inferior pulmonary veins). In all patients with a common antrum (15 left-sided and 1 right-sided), correct isolation of the antrum was achieved.

Table 1 Population characteristics

Number of patients (*n*)	63
Paroxysmal/persistent AF	40/23
Men/women	49/14
Age (years)[a]	49±11
CVRF≥1 (*n*)	27
Heart disease (*n*)	8
Mean EF (%)[a]	59±10
LA diameter (mm)[a]	39±10
Mean follow-up (months)[a]	12.2±10

AF atrial fibrillation, *CVRF* cardiovascular risk factors, *EF* ejection fraction, *LA* left atrium

[a] Mean±standard deviation

3.3 Acute complications

Periprocedural complications occurred in 9.52 % of cases; the most frequent was right phrenic paralysis (4.7 %). In two of these three cases, the paralysis was transient and recovery was immediate when cryothermal energy was stopped. In the third case, the persistence of phrenic paralysis that occurred during cryothermal energy in the right inferior pulmonary vein required that the procedure be ended, although no immediate clinical repercussions were observed and there was radiologic recovery at the 3-month follow-up visit. There was one case of pericardial effusion with no clinical repercussions that required preventive discontinuation of oral anticoagulation. Five days after oral anticoagulation was withdrawn, the patient presented a transient ischemic accident with subsequent complete recovery. The procedure had to be discontinued in one case of hemoptysis; the pulmonary CT scan subsequently revealed the presence of a small perialveolar hemorrhage in the upper left lobe of no clinical importance that showed spontaneous resolution at successive follow-up visits. These complications appeared in the first 24 patients treated, but not in the last 39. Local vascular complications were uncommon, and no cases required transfusion of blood products or specific therapeutic attitudes. No complications occurred related to the use of 23-mm cryoballoon.

3.4 Follow-up

Among the patients included, two patients (one with paroxysmal AF and one with persistent AF) were followed up at their referring hospital because it was in another province. The median follow-up of the remaining 61 patients in the

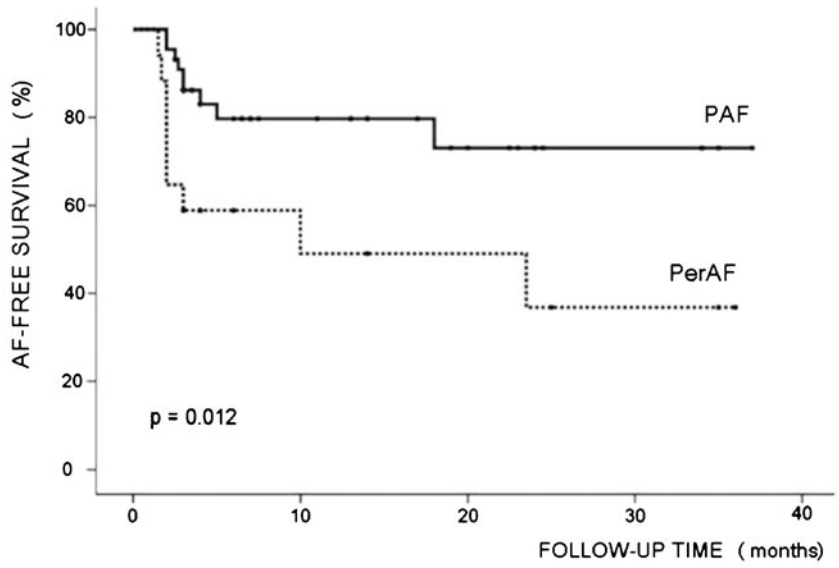
arrhythmia clinic was 5.5 months, with an interquartile range of 2.6–16.6 months. A total of 34 patients completed at least 12 months of follow-up. The survival curves are shown in Fig. 5. The estimated probability of being free of AF recurrence at 1 year of follow-up was 86.2 % in patients with paroxysmal AF and 49 % in patients with persistent AF, and 72.2 and 36.4 %, respectively, at 2 years (log rank P=0.012). Among patients in whom at least one pulmonary vein remained connected at the end of the procedure, 71.42 % presented AF recurrence during follow-up.

Among all patients with no recurrence, 6.8 % of patients with paroxysmal AF and 5.2 % of those with persistent AF were still receiving antiarrhythmic therapy. Two patients with paroxysmal AF presented atypical flutter during follow-up; one of them subsequently presented AF recurrence. The second patient was successfully treated with radiofrequency ablation and remained in sinus rhythm on follow-up. Patients with structural heart disease presented AF recurrence more often than those without heart disease (62.5 versus 24.5 %; P= 0.03). The multivariate analysis showed no variable independently associated with recurrence.

4 Discussion

Ablation is a well-established indication for the treatment of patients with paroxysmal AF refractory to antiarrhythmic drugs [4], and some studies have shown promising outcomes for CAPV as first-line treatment in these patients [20]. After the initial results reported by a Spanish group with a series of 5 patients [21], we present our initial experience and the medium-term results of CAPV in a group of 63 patients with paroxysmal or persistent AF. Although some series include only patients with paroxysmal AF [12, 13, 16], most include patients with both paroxysmal and persistent AF [9–12, 14, 15, 22], which allowed the outcome of the technique to be compared between the two groups, while waiting for results from more consistent studies. The results of our series are in line with previously published experience and increase the body of evidence about the safety and effectiveness of this technique.

The baseline characteristics of the study population are practically identical to those of other series in terms of the prevalence of cardiovascular risk factors and the echocardiographic parameters. However, our population is slightly younger compared to other series, which may be probably due to the preference given to young patients in the AF ablation program in our center. The associated morbidities in our population are indicative of the role of SAHS. In our series, only 1.7 % of the patients were diagnosed with SAHS. However, a series of patients who underwent CAPV reported by Bitter et al. [22] used polysomnography to screen all patients not diagnosed with SAHS and found an elevated prevalence of the disorder (29 % of patients),



AT-RISK PATIENTS

Months	3	6	12	18	24	30	36
PAF	32	21	14	12	9	4	3
PerAF	15	9	6	4	4	3	3

Fig. 5 AF-free survival curves. The table below shows the number of recurrence-free patients who have completed follow-up at the 3- to 36-month visits. *AF* atrial fibrillation, *PAF* paroxysmal atrial fibrillation, *PerAF* persistent atrial fibrillation

which was also shown to be an independent predictive factor of post-ablation recurrence. Therefore, SAHS screening should be considered in these patients, probably improving the long-term results of ablation.

A major limitation to isolation success inherent in the technique is its dependence on pulmonary venous anatomy (pulmonary vein orientation ostium shape and position) [11, 23]. In our series, the most common pulmonary venous drainage pattern was four veins, and a common left-sided antrum was found in a similar percentage to that of other studies. Although this variant has been related to a lower percentage of isolation success [11], in our series, the presence of this anatomical variant, as in other studies [23], was not related to a lower isolation rate even in the antrum of larger diameter than the cryoballoon. In most cases, the 28-mm cryoballoon was used regardless of the pulmonary vein diameter. This option, which is a widespread trend, is due in part to various factors, including the lower rate of complications reported (particularly right phrenic nerve paralysis) when using the 28-mm cryoballoon, compared to the 23-mm cryoballoon [17], as well as the extent of the injury—comparable, according to voltage mapping studies, to injuries occurring in wide antral ablation of the pulmonary vein with radiofrequency [24]. The preferential use of the 28-mm cryoballoon in our series could explain the lower incidence of phrenic nerve paralysis compared to that found in the meta-analysis by Andrade et al. [17]. Nevertheless, we did not have any complication in the four patients treated with the 23-mm cryoballoon. On the other hand, all phrenic paralyses reverted immediately, except for one case which reverted at 3 months of follow-up, and all were asymptomatic. The usual acute complications of the technique appeared in only the first 24 patients (probably in relation to the learning curve for the procedure) and at a comparable percentage to other series [17].

The probability of being recurrence-free was 86 and 49 % for paroxysmal and persistent AF at 1 year of follow-up and 72.2 and 36.4 % at 2 years, respectively. These results are very similar to those obtained by other groups [9, 12–16]. Nonrandomized studies that compared the efficacy of ablation of the pulmonary veins to that of radiofrequency ablation showed no significant differences between the two strategies in terms of recurrence [14, 25]. However, we will have to wait for the results of the first randomized study, which is being started at this time.

5 Conclusions

Pulmonary vein cryoablation with a nitrous oxide balloon is a safe and effective procedure for the treatment of patients with AF, particularly in paroxysmal AF and in the absence of heart disease.

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