



Double factor single shot to diminish complications in cryoballoon ablation procedures for atrial fibrillation

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Abstract

Purpose Cryoballoon ablation (CBA) has become a standard treatment for recurrent atrial fibrillation (AF). There is need for improved CBA protocols. We aimed to demonstrate that a new protocol including minimum temperature (minT) reached could reduce procedure times and complications.

Methods A new double factor protocol (DFP), based on the performance of one single shot per vein with variable duration, and conditional bonus shot, determined by time-to-effect (TTE) and minT, was compared with the conventional protocol (CP), with at least two shots per vein. Procedure parameters, complications, and efficacy were compared.

Results We prospectively included 88 consecutive patients treated with the DFP. These were compared to the previous consecutive 69 patients treated with CP. All procedures were performed with 28-mm second-generation balloon. Acute pulmonary vein (PV) isolation was similar (98.6% vs. 98.9% in CP vs. DFP, $p = 0.687$). Procedure and ablation times favored DFP over CP (120 vs. 134 min, $p = 0.003$; and 1051 vs. 1475 s, $p < 0.001$; respectively). A composite of major and minor complications was significantly reduced in the DFP compared to the CP (18.8% vs. 6.8%, $p = 0.02$; respectively). Within a follow-up of 18 months, freedom from AF was 79.7% in CP and 78.4% in DFP (Log-rank 0.501). Paroxysmal AF and absence of PV potentials predicted better arrhythmia outcomes (HR 2.14 for paroxysmal vs. persistent, $p = 0.031$; and HR 1.61 for absence vs. presence of PV potentials, $p = 0.01$).

Conclusions The novel DFP results in reduced complication rates and procedure times, with similar success rates compared with a conventional strategy.

Keywords Atrial fibrillation · Cryoballoon procedure · Optimized protocol

1 Introduction

Pulmonary veins (PV) isolation has emerged as the cornerstone of atrial fibrillation (AF) ablation procedures [1]. However, despite the advent of different techniques and the high rate of acute PVI, there are still serious limitations in terms of long-term results, mostly related to reconnection of pulmonary veins [2, 3]. Techniques based on the performance

of wide applications, led by the first-generation cryoballoon (CB1, Arctic Front, Medtronic, Minneapolis), have spread worldwide with great success since 2010 [4]. In 2012, a second-generation cryoballoon (CB2) became available (Arctic Front Advance, Medtronic, Minneapolis), with improved acute and long-term outcomes [5, 6], comparable to those obtained by radiofrequency ablation [7, 8].

Cryoablation was first introduced with cryocatheter ablation of focal, non-complex arrhythmias. These experiences provided the basis for AF cryoballoon procedures, with particular tools and protocols adapted and improved specifically for AF pathophysiology [9]. Cryotherapy in AF procedures can be delivered in a single shot or in two or more shots. PV isolation is frequently achieved during the first shot, and the rationale for delivery of additional shots is based on the potential for a deeper lesion by means of sequential freeze/thaw cycles, resulting in increased mechanical and biochemical cellular disruption. Key parameters that determine lesion depth are balloon contact, cryotherapy delivery time, and minimum temperature (minT) reached during

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ablation. Duration of applications has progressively shortened as experience and studies accumulated, and when the improved CB2 was introduced. Several studies now advocate an alternative to a fixed duration with a variable duration depending on the time until PVI, called time-to-effect (TTE), which is a parameter that can predict reconnection of the vein [10]. Some non-randomized [11] and randomized [12, 13] studies with optimized protocols have already shown a reduction in the procedure times with no effect on the efficacy endpoints. The minT reached during ablation mostly depends on the proper occlusion of the PV antrum, although the CB2 is much less contact-dependent [14]. Ideally, temperature should reach below $-40\text{ }^{\circ}\text{C}$ during the first 60 s. However, a temperature below $-55\text{ }^{\circ}\text{C}$ within the first 30 s should be avoided in order to prevent complications, as it suggests a deep insertion of the balloon within the PV. All protocols of cryoballoon ablation (CBA) must balance efficacy with safety, since deeper lesions achieved by longer cryotherapy delivery times and lower temperatures increase the risk of collateral damage to the esophagus, lungs, and right phrenic nerve.

We hypothesized that a protocol with restricted cryoablation delivery time and conditional bonus shot, adapted not only to the TTE, but also to the minT reached within the first 60 s, named double factor protocol (DFP), could decrease procedure times and improve safety, while providing similar PVI rates and long-term freedom from AF recurrences.

2 Methods

All patients undergoing a first CBA procedure for recurrent symptomatic AF during 2015 and 2016 were included. The second half of the study population were prospectively assigned to the new DFP and compared with the previous conventional protocol (CP). All procedures were performed by two well-experienced operators with more than 200 AF ablation procedures performed each. In case of concomitant common flutter ablation, procedure and fluoroscopy times utilized for cavo-tricuspid isthmus ablation were subtracted for analyses purposes. Patients had follow-up at 1, 3, and 6 months after the procedure and every 6 months thereafter. A 12-lead ECG and a 24-h Holter monitor were performed at the first four visits, and additional 7-day Holter monitoring was performed in case of symptoms or frequent supraventricular ectopy. Patients were also instructed to visit emergency services whenever they experienced symptoms suggestive of arrhythmia relapses. A cardiac CT or MRI scan was performed before the procedure and repeated after 6 months in all patients. Antiarrhythmic drugs were continued during the 3 months blanking period but were withdrawn early if there were no AF recurrences. Continuation of oral anticoagulation was indicated according to the CHA2DS2VASc score.

2.1 Cryoballoon procedure

The CBA procedure has been previously described [15, 16]. Anticoagulation is not discontinued, including NOAC use. Briefly, with the patient under conscious sedation and under infusion of unfractionated heparin aiming an activated clotting time (ACT) of 250–300, a single trans-septal puncture is performed using a standard long sheath (Lamp, St. Jude Medical, St. Paul, MN), guided by intracardiac echo (ViewFlex, St. Jude Medical). The transeptal sheath is exchanged over guidewire for a 15F deflectable introducer (Flexcath, Medtronic, Minneapolis, MN), and the CB2 (Arctic Front Advance, Medtronic) is introduced together with the inner circular mapping catheter (Achieve, Medtronic) into the antrum of each PV. All procedures are performed under the guidance of a three-dimensional reconstruction of the left atrium and the pulmonary veins, extracted from a cardiac CT or MRI scan, and using an esophageal temperature probe with multiple thermocouples and adjustment to balloon position. Cryoenergy delivery was stopped in case of temperature drop under $26\text{ }^{\circ}\text{C}$. Right phrenic nerve was monitored with palpation and fluoroscopy while pacing. Cryotherapy was performed according to one of the protocols described below.

2.2 Ablation protocols

PV isolation was defined by the persistent elimination or dissociation of PV potentials visualized by the circular mapping catheter (Achieve catheter). TTE was defined as the time to PV isolation during ablation. MinT was the minimum temperature reached during ablation. Thaw time was not used in this protocol because it was not consistently collected. The CB2 was repositioned between freezes only in case of failure to isolate the PV, late PV isolation, or early recurrence of the conduction.

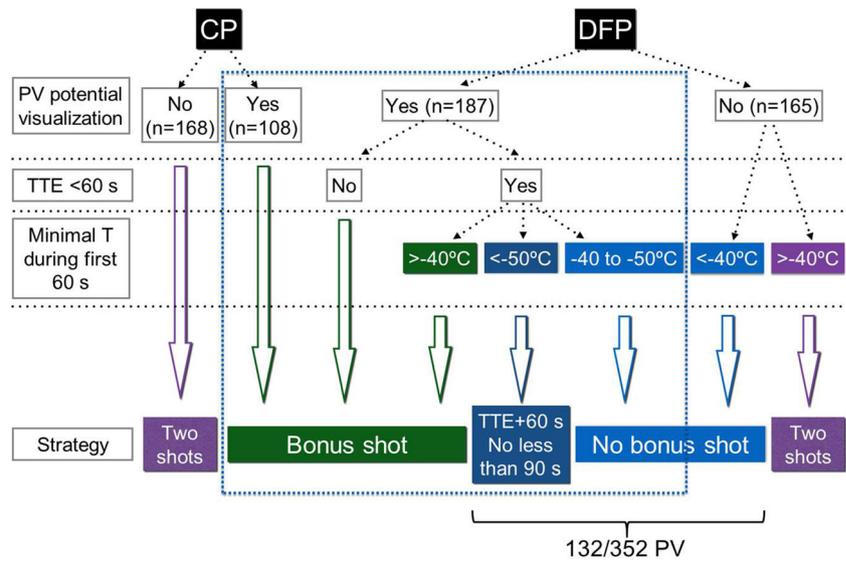
Patients were assigned to one of the following groups:

- Conventional protocol (CP): patients received at least two shots of 180 s per vein. If the first shot resulted in PV isolation, regardless of TTE or minT, an additional 180 s bonus shot was given.
- Double factor protocol (DFP): patients received one shot plus a bonus shot conditional to TTE and minT (see Figs. 1 and 2):

1. If PV potentials were visualized:

- If TTE was $< 60\text{ s}$ and minT below $-50\text{ }^{\circ}\text{C}$: cryotherapy delivery time was extended for an additional 60-s interval after TTE (but no less than 90 s total); no bonus shot was delivered.
- If TTE was $< 60\text{ s}$ and minT between -50 and $-40\text{ }^{\circ}\text{C}$: cryotherapy was delivered during 180 s in a single shot; no bonus shot was delivered.

Fig. 1 Study flowchart. Number of PVs with or without visualization of PV potentials in each protocol and number of PVs treated with only one application in the DFP. CP, conventional protocol; DFP, double factor protocol; PV, pulmonary vein; T, temperature; TTE, time to effect



- If TTE was < 60 s and minT above -40 °C: two shots were delivered. The first shot was 180 s, and the second one was 90–180 s, depending on the quality of the application.
 - If TTE was > 60 s, irrespective of minT: two shots were delivered. The first shot was 180 s, and the second one 90–180 s, depending on the quality of the application.
 - If PV isolation was not achieved during the first shot: at least two 180 s shots were delivered.
2. If PV potentials were not visualized:
- If minT was < -40 °C: a single shot of 180 s was delivered, with no bonus shot.
 - If minT was > -40 °C: two shots of 180 s were delivered.

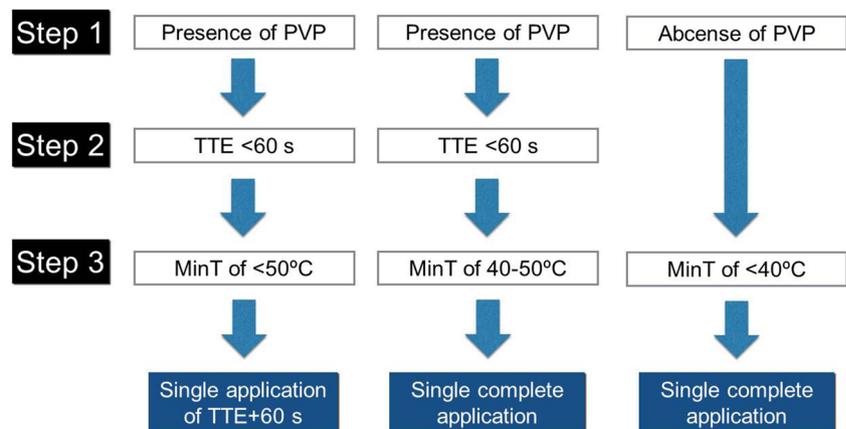
2.3 Endpoints

The primary short-term efficacy endpoint was PV isolation. Secondary short-term efficacy endpoints included total

procedure, fluoroscopy, and cryotherapy times. Long-term efficacy endpoints were freedom from symptomatic documented AF relapses lasting at least 30 s.

The primary safety end point was a composite of major and minor complications. Major complications included CBA-related death, stroke/transient ischemic attack, cardiac effusion/tamponade, pulmonary hemorrhage, atrial-esophageal fistulae, persistent phrenic nerve palsy after the conclusion of procedure, radiologic pulmonary vein stenosis > 50%, and any need for surgery. Minor complications included transient phrenic nerve palsy (resolved during the procedure), radiologic pulmonary vein stenosis < 50%, and groin hematoma not requiring invasive intervention, blood product transfusion, or extended hospitalization. Cryoenergy-related complications included those complications exclusively related to balloon freezing (associated with application time and minT). All serious adverse events were pre-specified and physicians were required to report them.

Fig. 2 Study diagram. Diagram showing the only three examples requiring shortened applications with the DFP. MinT, minimal temperature; PVP, pulmonary vein potentials; TTE time to effect



2.4 Statistical analyses

Continuous quantitative variables are presented as mean \pm standard deviation (SD), or as median and interquartile range (IQR) as appropriate. Categorical variables are presented as frequencies or percentages. Quantitative variables were compared with the Student test or the non-parametric Mann-Whitney *U* test, and categorical variables were compared with the chi-square test or Fisher exact test, as appropriate. Long-term efficacy endpoints were analyzed with survival analysis methodology. Cumulative event rates were estimated by Kaplan-Meier estimation, and plots were compared by the log-rank test. Cox-regression models were used to establish predictors associated to AF recurrences after CBA procedure, with the use of a forward stepwise procedure with a criterion of $p < 0.05$ for inclusion and $p > 0.10$ for removal from the model. A p value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 18 software package (SPSS Inc., Chicago, IL).

3 Results

3.1 Population characteristics

We included 157 consecutive patients undergoing CBA procedure for recurrent AF. All procedures were performed with the 28-mm second-generation balloon. Patients were divided into two consecutive groups: the first 69 patients were retrospectively included and treated with the CP of at least two shots per vein, and the following 88 patients were prospectively included in the DFP and treated as described above.

There were no significant differences between both groups regarding baseline characteristics (see Table 1), including type of AF, left atrium diameter, and presence of hypertension or structural heart disease.

3.2 Short-term outcomes

Short-term endpoints were collected in all 157 patients. The primary efficacy endpoint was PV isolation, which was similar for both groups (98.6% vs. 98.9% in CP vs. DFP, $p = 0.687$). Except for the fluoroscopy time, parameters related to procedure times favored DFP over CP: total procedure time (119.8 min vs. 134.6 min, $p = 0.003$); total fluoroscopy time (22.8 min vs 20.1 min, $p = 0.036$); total cryotherapy delivery time in all pulmonary veins (1051 s vs. 1475 s, $p < 0.001$); and total cryotherapy delivery time per each individual vein (see Table 1). No differences were recorded regarding minT achieved in each vein nor in the proportion of veins with identified PV potentials (see Table 1). No significant cooling in the esophagus was registered in any patient; the minimum temperature observed was 21 °C at the end of an application.

Patients undergoing CP received an average of 8.5 applications, compared to 6.5 applications in patients undergoing DFP ($p < 0.001$).

Major procedure-related complications occurred in 6 patients (3.8%), with no significant differences between groups: 4 in CP and 2 in DFP ($p = 0.23$). Major complications from CP were one atrial-esophageal fistula presumably related to very low temperatures reached in the left inferior PV (−59 °C), which presented 2 weeks after the procedure with endocarditis, disseminated embolism and death of the patient before surgery, one transient ischemic attack due to air embolism, one ischemic stroke, and one pericardial effusion not requiring drainage. Major complications from DFP were one massive tamponade during balloon manipulation in the left superior PV, requiring urgent surgery, and one pericardial effusion during transeptal puncture, not requiring drainage. Regarding minor complications, transient asymptomatic phrenic nerve palsy was observed in 8 patients (5.1%) and resolved intra-procedure in all cases: 6 patients in the CP and 2 patients in the DFP, without significant differences ($p = 0.074$). Other minor complications were two groin hematomas and one pulmonary vein stenosis of $< 50\%$ in the CP; and one groin hematoma and one PV stenosis of $< 50\%$ in the DFP (see Table 2). Cryoenergy delivery-related complications (phrenic nerve palsy, atrial-esophageal fistula, pulmonary vein stenosis) were seen in 11 patients: 8 patients in CP and 3 patients in DFP, with a significant 62% reduction ($p = 0.047$) with DFP. A composite of all major and minor complications was observed in 19 patients: 13 patients in CP and 6 patients in DFP, resulting in a significant 54% reduction ($p = 0.02$) with DFP.

3.3 Long-term outcomes

The follow-up period was 18 months for both groups, with no patients lost in follow-up. Thirty-eight percent of all patients received additional Holter monitoring due to palpitations or frequent ectopy, which had a 30% yield of diagnosing AF recurrences.

Freedom from AF at 18 months did not differ between groups: 79.7% in CP vs. 78.4% in DFP (Log-rank 0.501; see Fig. 3b), with 1.22 procedures in CP and 1.13 procedures in DFP ($p = 0.09$).

3.4 Predictors of sinus rhythm maintenance

The only two variables predicting a better outcome were the type AF (HR 2.15 for paroxysmal vs. persistent; CI 1.07–4.32; $p = 0.031$; see Fig. 3c) and the absence of PV potentials before ablation (HR 1.61 for absence vs. presence of PV potentials; CI 1.13–2.29; $p = 0.01$). No further clinical or procedural (see Table 3) characteristics were found to be associated with long-term sinus rhythm maintenance, including CBA

Table 1 Population and procedure characteristics

	CP (n = 69)	DFP (n = 88)	p
Age (years; ave. ± SD)	53.8 ± 10.2	55.7 ± 8.7	0.21
Female sex (%)	23.2	35.2	0.07
Hypertension (%)	40.3	37.9	0.51
Persistent AF (%)	30.4	20.5	0.11
Duration AF (months, ave. ± SD)	57.2 ± 49.4	46.7 ± 41.4	0.15
LAD (mm; ave. ± SD)	41.7 ± 5.7	41.6 ± 6.6	0.90
LVEF (% ave. ± SD)	62.9 ± 8.7	59.5 ± 9.3	0.52
SHD (%)	18.8	12.5	0.19
Previous AF ablation (%)	7.2	4.5	0.35
CHA2DS2VASc Score < 2 (%)	69.6	72.4	0.41
Common left ostium (%)	20.3	14.8	0.24
Max LSPV diameter (mm; ave. ± SD)	16 ± 2	17 ± 4	0.21
Max LIPV diameter (mm; ave. ± SD)	17 ± 3	16 ± 3	0.32
Max RSPV diameter (mm; ave. ± SD)	18 ± 2	18 ± 3	0.60
Max RIPV diameter (mm; ave. ± SD)	16 ± 3	17 ± 3	0.07
Fluoroscopy time (minutes; ave. ± SD)	20.1 ± 7.9	22.8 ± 7.9	0.036
Procedure time (minutes; ave. ± SD)	134.6 ± 33.7	119.8 ± 28.0	0.003
Total therapy time (seconds; ave. ± SD)	1475 ± 372	1051 ± 346	<0.001
Total therapy time in LSPV (seconds; ave. ± SD)	377 ± 113	305 ± 145	0.002
Total therapy time in LIPV (seconds; ave. ± SD)	375 ± 111	266 ± 123	<0.001
Total therapy time in RSPV (seconds; ave. ± SD)	328,116±	259 ± 151	0.003
Total therapy time in RIPV (seconds; ave. ± SD)	353 ± 93	237 ± 110	<0.001
Min LSPV temp (°C ave. ± SD)	48 ± 7	47 ± 7	0.7
Min LIPV temp (°C; ave. ± SD)	46 ± 7	47 ± 8	0.8
Min RSPV temp (°C; ave. ± SD)	52 ± 7	50 ± 8	0.2
Min RIPV temp (°C; ave. ± SD)	45 ± 9	48 ± 7	0.06
Identified LSPV potentials (%)	52.6	61.4	0.19
Identified LIPV potentials (%)	56.1	55.7	0.55
Identified RSPV potentials (%)	52.6	58.0	0.32
Identified RIPV potentials (%)	30.0	37.5	0.22

AF atrial fibrillation, ave. average, CP conventional protocol, DFP double factor protocol, LAD left atrium dilation, LIPV left inferior pulmonary vein, LSPV left superior pulmonary vein, LVEF left ventricle ejection fraction, min minimum, RIPV right inferior pulmonary vein, RSPV right superior pulmonary vein, SD standard deviation, SHD structural heart disease, temp temperature

protocol, TTE, minT, and application time, taken globally or in each vein.

4 Discussion

4.1 Conventional cryotherapy protocols

When CBA was first introduced, initial protocols delivered at least two 5-min shots per vein. After an initial period, protocols were modified to applications of 4 min [4], which became accepted as standard practice. The first large study assessing the performance of the CB1 was the STOP-AF, which was based on 4-min protocols and reported acute isolation of all veins in 83% of patients and maintenance of sinus rhythm in

57.7% of patients at 1 year with a single procedure. These results were improved with the arrival of the CB2, achieving acute isolation rates of 84% with the first 4-min shot (compared to 51% [17] with the CB1). Procedures were performed with two 4-min shots per vein, and maintenance of sinus rhythm was 73% at two years after a single procedure [18]. An interesting study using this protocol reported 91% persistent PV isolation during a second procedure routinely performed 3 months after the first procedure [19].

Experimental canine studies have shown no significant differences in the rate of PVI, complications, or transmural injury caused by applications of 2 min [20] or 3 min [21] compared to 4 min. However, the latter were associated with greater intimal proliferation, suggesting a higher potential risk of vein stenosis. These results translated to comparable acute and

Table 2 Complications

	Major complication	Minor complication
Conventional protocol		
Patient 1		-Transient phrenic nerve palsy
Patient 2	-Atrial-esophageal fistula with endocarditis and death	
Patient 3		-Groin hematoma
Patient 4		-Transient phrenic nerve palsy
Patient 5	-Transient ischemic attack due to air embolism	-Transient phrenic nerve palsy
Patient 6		
Patient 7	-Ischemic stroke	-Transient phrenic nerve palsy
Patient 8		
Patient 9		-Transient phrenic nerve palsy
Patient 10	-Pericardial effusion not requiring drainage	
Patient 11		
Patient 12		-Transient phrenic nerve palsy
Patient 13		-Groin hematoma
Double Factor Protocol		
Patient 1		-Transient phrenic nerve palsy
Patient 2		-Transient phrenic nerve palsy
Patient 3	-Tamponade during balloon in the LSPV	
Patient 4	-Pericardial effusion not requiring drainage	
Patient 5		-Groin hematoma
Patient 6		-Pulmonary vein stenosis < 50%

LSPV left superior pulmonary vein

chronic clinical outcomes when abbreviated protocols spread in clinical practice [22]. Thus, the use of two 3 min applications has emerged as the most common current protocol in the majority of EP laboratories. On the other hand, protocols using a single application of 3 or 4 min have proved equally effective, with an acute isolation rate of 91–94% and maintenance of sinus rhythm in 72–82% of patients at 1-year follow-up. In addition, safety of these abbreviated protocols has been also demonstrated, with only a 2–3.5% incidence of phrenic nerve injury [23–25]. Two studies directly compared the performance of one vs. two applications, with similar efficacy and rate of complications, but with improved procedural times in the group of one single application [26, 27].

4.2 Optimized protocols

Optimized protocols are emerging with the rationale of offering safer procedures without a reduction in the effectiveness. These protocols use a variable cryotherapy time conditioned to the results of the first application [26]. However, to date, the only parameter consistently predicting good long-term results with a single application has been the achievement early PV isolation [11–13]. Initial results of our protocol [28] with 79 patients showed shorter procedure and cryotherapy times, and a trend to fewer complications in the optimized therapy group, without significant differences in 8-month maintenance of

sinus rhythm (85 vs. 80% in the conventional vs. optimized group, respectively).

4.3 Main findings

In this study, we included 157 consecutive patients undergoing CBA for recurrent AF. Patients from CP ($n = 69$) were treated with two cryotherapy applications per vein, with an additional bonus shot at the discretion of the operator, and patients from DFP ($n = 88$) were treated according to the new protocol, where a single shot cryotherapy application was delivered per vein, with duration determined by TTE and minT. An additional bonus shot was delivered, again on a conditional basis determined by TTE and minT. Of note, this is the first CBA protocol using the minT as a determinant factor, together with the TTE, in order to adjust the delivery of cryoenergy.

The primary short-term efficacy endpoint was PV isolation, which was similar for both groups (98.6% vs. 98.9% in CP vs. DFP, $p = 0.687$). Procedure efficacy endpoints revealed shorter procedure and therapy times in DFP compared to CP (total procedure time of 119.8 min vs. 134.6 min, $p = 0.003$, respectively; total cryotherapy time of 1051 s vs. 1475 s, $p < 0.001$, respectively).

Interestingly, this reduction in procedure and cryotherapy time was accompanied by a reduction in the total complication rate. There were no differences in major complication rates

Fig. 3 Survival analyses. Panel **a** shows total population survival curve for freedom from atrial fibrillation recurrences at 18 months. Panel **b** shows survival curves for freedom from atrial fibrillation recurrences at 18 months for each protocol group. No differences were observed between groups. Panel **c** shows survival curves for freedom from atrial fibrillation recurrences at 18 months depending on type of AF. Significant differences were observed with better outcomes in the paroxysmal group. AF, atrial fibrillation; CP, conventional protocol; DFP, double factor protocol

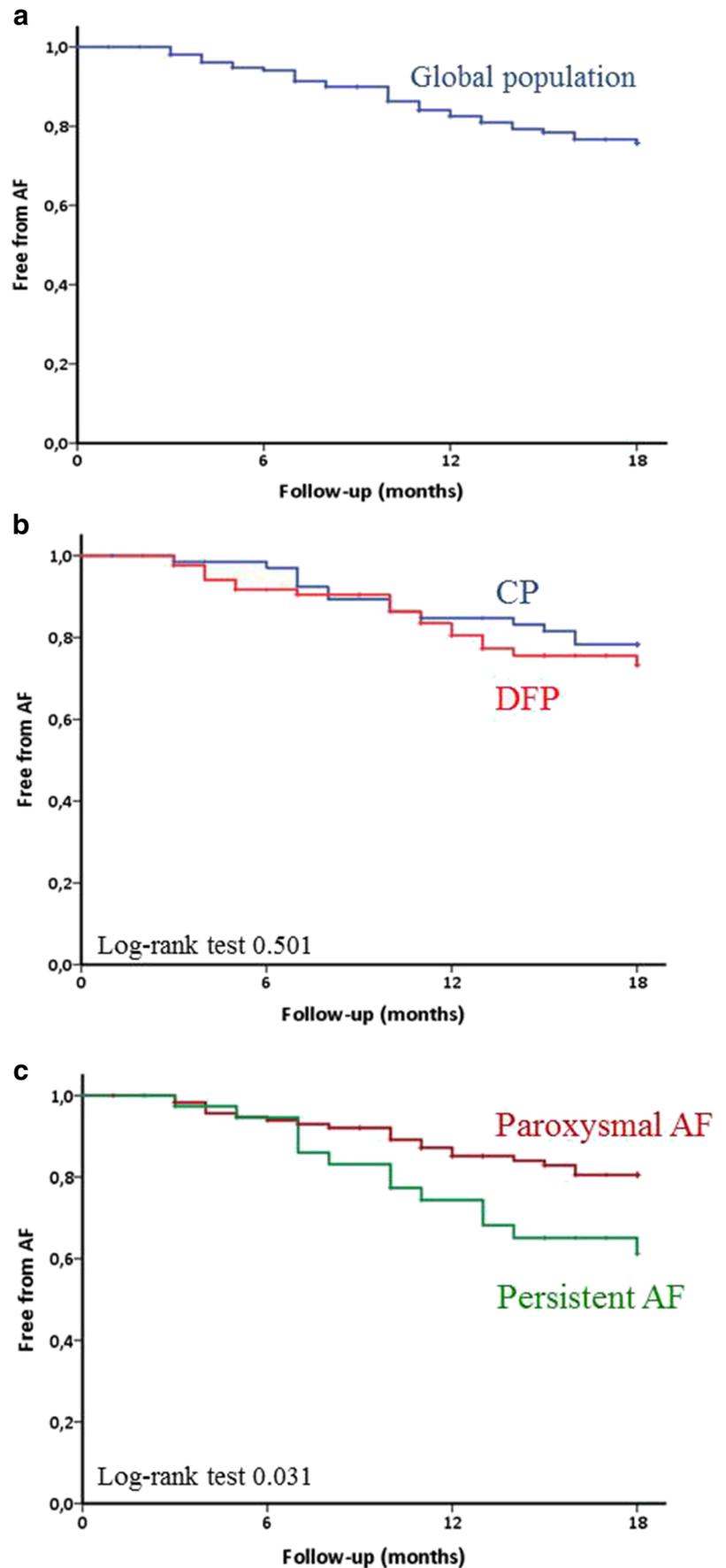


Table 3 Clinical and procedural predictors

	HR	CI	<i>p</i>
Age (per year)	0.997	0.96–1.03	0.88
Gender (women)	0.570	0.25–1.31	0.19
Hypertension	1.357	0.59–3.13	0.47
Diabetes mellitus	0.849	0.25–2.80	0.79
Obesity	0.686	0.25–1.86	0.46
Structural heart disease	0.971	0.37–2.51	0.95
Left ventricle dysfunction (> 50%)	0.986	0.35–2.87	0.98
Left atrium dilation (> 40 mm)	1.1741	0.81–3.74	0.16
CHA2DS2VASC Score (per point)	0.858	0.63–1.16	0.323
AF type (paroxysmal AF)	2.153	1.07–4.32	0.03
CBA protocol	1.273	0.64–2.54	0.49
AF evolution time (per month)	0.999	0.99–1.01	0.86
Left common PV ostium	1.264	0.55–2.90	0.58
Procedure therapy time (per minute)	1.026	0.99–1.01	0.50
Therapy time in LSPV (per second)	1.001	0.99–1.01	0.73
Therapy time in LIPV (per second)	1.000	0.99–1.01	0.80
Therapy time in RSPV (per second)	1.000	0.99–1.01	0.32
Therapy time in RIPV (per second)	0.998	0.99–1.01	0.57
Minimal temperature (°C)	1.01	0.98–1.03	0.57
TTE time (seconds)	1.00	0.99–1.02	0.72
Absence of PV potentials	1.608	1.13–2.30	0.01

AF atrial fibrillation, CBA cryoballoon ablation, LIPV left inferior pulmonary vein, LSPV left superior pulmonary vein, PV pulmonary vein, RIPV right inferior pulmonary vein, RSPV right superior pulmonary vein, TTE time to effect

and no difference in transient phrenic nerve palsy rates between the two groups. On the other hand, a composite of cryoenergy delivery-related complications (phrenic nerve palsy, atrial-esophageal fistula, pulmonary vein stenosis) was less frequent with the new protocol: 8 patients in CP and 3 patients in DFP, resulting in a significant 62% reduction ($p = 0.047$). The incidence of any complication (major/minor; cryoenergy delivery related/venous access related) was lower with the new protocol: 13 patients in CP and 6 patients in DFP, resulting in a significant 54% reduction ($p = 0.02$). These results are in agreement with recent studies [12–14] showing a similar or lower complications rate with abbreviated protocols based on the TTE.

The primary long-term efficacy endpoint, freedom from symptomatic AF recurrences at 18 months, did not differ between groups, 79.7% in CP vs. 78.4% in DFP (Log-rank 0.501).

4.4 Long-term predictors for sinus rhythm maintenance

The only clinical predictor of long-term maintenance of sinus rhythm after CBA was paroxysmal AF (HR 2.15 for

paroxysmal vs. persistent; CI 1.07–4.32; $p = 0.031$). We did not observe any other significant clinical predictor, including CBA protocol. Similarly, AF evolution time, hypertension or left atrium dilation did not predict outcomes either, probably due to the inclusion in this study of a relatively healthy population.

In terms of procedure characteristics, the absence of PV potentials before the ablation was the only predictor of long-term maintenance of sinus rhythm (HR 1.61 for absence vs. presence of PV potentials; CI 1.13–2.29; $p = 0.01$), probably reflecting a less arrhythmogenic substrate. This is in disagreement with previous studies with good results associated to the observation of PV potentials even in >90% of the veins, allowing for a real-time disconnection assessment as a standard strategy [29]. In our study, PV potentials were observed in approximately 60% of the veins. We believe in such scenario DFP can provide better results since its algorithm includes not only the TTE, but also the minT, which is not based in the observation of PV potentials. No other procedural characteristics were found to predict long-term sinus rhythm maintenance in our study, including application time. To summarize, no long-term benefit was associated with a colder application, faster PV disconnection time, or longer application time.

5 Limitations

Since the two groups were collected consecutively in a non-randomized fashion, it could be argued that the learning curve could have favored the results among patients in DFP. However, the two operators were well-experienced and trained in CBA procedures as they were early adopters of cryoballoon ablation since inception. Furthermore, no changes were introduced in CBA procedures except for cryotherapy protocol. Secondly, in our series we were able to see PV potentials in approximately 60% of the veins. This is a common issue in several labs [30], partially related with a reduced resolution of the Achieve catheter compared to the previous conventional circular PV mapping catheters. The adoption of a more systematic stepwise mapping approach with the Achieve catheter during ablation probably could have increased the PV visualization, which could have improved our DFP results and modified the predictors for sinus rhythm maintenance, particularly the absence of PV potentials as a positive predictor. We did not include the use of internal loop recorders. The systematic use of these devices could have improved the detection of more asymptomatic episodes of AF relapses. Lastly, the relatively small sample size may not have allowed the finding of other well-recognized predictors, such as TTE. Larger randomized prospective studies should be performed in order to confirm our findings.

6 Conclusions

A novel tailored cryoballoon ablation protocol, which takes into account not only the TTE but also the minT, results in a shorter and safer procedure, without diminishing acute and long-term efficacy endpoints. This observation needs to be evaluated further in larger randomized, prospective studies.

Compliance with ethical standards

All authors have read and approved the submission. No financial support has been received from any institution or industry. The study was conducted following the Declaration of Helsinki. Informed consent was obtained from all patients participating in the study.

References

- Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33(21):2719–47.
- Ouyang F, Antz M, Ernst S, Hachiya H, Mavrakis H, Deger FT, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. *Circulation*. 2005;111(2):127–35.
- Cappato R, Negroni S, Pecora D, Bentivegna S, Lupo PP, Carolei A, et al. Prospective assessment of late conduction recurrence across radiofrequency lesions producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. *Circulation*. 2003;108(13):1599–604.
- Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol*. 2013;61:1713–23.
- Di Giovanni G, Wauters K, Chierchia GB, Sieira J, Levinstein M, Conte G, et al. One-year follow-up after single procedure cryoballoon ablation: a comparison between the first and second generation balloon. *J Cardiovasc Electrophysiol*. 2014;25:834–9.
- Chierchia GB, Di Giovanni G, Ciconte G, de Asmundis C, Conte G, Sieira-Moret J, et al. Second-generation cryoballoon ablation for paroxysmal atrial fibrillation: 1-year follow-up. *Europace*. 2014;16:639–44.
- Schidt M, Dorwarh U, Andresen D, Brachmann J, Kuck KH, Kuniss M, et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. *J Cardiovasc Electrophysiol*. 2014;25:1–7.
- Kuck KH, Fühnkranz A, Chun KR, Metzner A, Ouyang F, Schlüter M, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J*. 2016;37(38):2858–65.
- Dubuc M, Roy D, Thibault B, Ducharme A, Tardif JC, Villemare C, et al. Transvenous catheter ice mapping and cryoablation of the atrioventricular node in dogs. *Pacing Clin Electrophysiol*. 1999;22(10):1488–98.
- Ferrero-de Loma-Osorio A, Izquierdo-de Francisco M, Martínez-Brotons A, Sánchez-Gómez JM, Mascarell-Gregori B, Ruiz-Ros V, et al. Medium-term results of cryoballoon ablation of the pulmonary veins in patients with paroxysmal and persistent atrial fibrillation. First experience of a Spanish center. *J Interv Card Electrophysiol*. 2013;37(2):189–96.
- Aryana A, Kenigsberg DN, Kowalski M, Koo CH, Lim HW, O'Neill PG, et al. Verification of a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation: results from the Cryo-DOSING study (Cryoballoon-ablation DOSING Based on the assessment of time-to-effect and pulmonary vein isolation guidance). *Heart Rhythm*. 2017;14(9):1319–25.
- Chun KR, Stich M, Fühnkranz A, Bordignon S, Perrotta L, Dugo D, et al. Individualized cryoballoon energy pulmonary vein isolation guided by real-time pulmonary vein recordings, the randomized ICE-T trial. *Heart Rhythm*. 2017;14(4):495–500.
- Ferrero-de Loma-Osorio Á, García-Fernández A, Castillo-Castillo J, Izquierdo-de-Francisco M, Ibáñez-Criado A, Moreno-Arribas J, et al. Time-to-effect-based dosing strategy for cryoballoon ablation in patients with paroxysmal atrial fibrillation: results of the plusONE multicenter randomized controlled noninferiority trial. *Circ Arrhythm Electrophysiol*. 2017;10(12).
- Su W, Kowal R, Kowalski M, Metzner A, Svinarich JT, Wheelan K, et al. Best practice guide for cryoballoon ablation in atrial fibrillation: the compilation experience of more than 3000 procedures. *Heart Rhythm*. 2015;12:1658–66.
- Marti-Almor J, Bazan V, Vallès E, Benito B, Jauregui-Abularach ME, Bruguera-Cortada J. Long-term outcome on cryoballoon ablation of atrial fibrillation in a low-volume center. *Rev Esp Cardiol*. 67:577–8.
- Martí-Almor J, Jauregui-Abularach ME, Benito B, Vallès E, Bazan V, Sánchez-Font A, et al. Pulmonary hemorrhage after cryoballoon ablation for pulmonary vein isolation in the treatment of atrial fibrillation. *Chest*. 2014;145:156–7.
- Fühnkranz A, Bordignon S, Schmidt B, Gunawardene M, Schulte-Hahn B, Urban V, et al. Improved procedural efficacy of pulmonary vein isolation using the novel second-generation cryoballoon. *J Cardiovasc Electrophysiol*. 2013;24(5):492–7.
- Metzner A, Heeger CH, Wohlmuth P, Reismann B, Rillig A, Titz RR, et al. Two-year outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon: lessons from the bonus freeze protocol. *Clin Res Cardiol*. 2016;105(1):72–8.
- Reddy VY, Sediva L, Petru J, Skoda J, Chovanec M, Chiltovova Z, et al. Durability of pulmonary vein isolation with cryoballoon ablation: results from the sustained PV isolation with Arctic front advance (SUSPIR) study. *J Cardiovasc Electrophysiol*. 2015;26(5):493–500.
- Andrade JG, Dubuc M, Guerra PG, Landry E, Coulombe N, Leduc H, et al. Pulmonary vein isolation using a second-generation cryoballoon catheter: a randomized comparison of ablation duration and method of deflation. *J Cardiovasc Electrophysiol*. 2013;24(6):692–8.
- Takami M, Lehmann HI, Misiri J, Parker KD, Sarmiento RI, Johnson SB, et al. Impact of freezing time and balloon size on the thermodynamics and isolation efficacy during pulmonary vein isolation using the second generation cryoballoon. *Circ Arrhythm Electrophysiol*. 2015;8(4):836–45.
- Chierchia GB, Di Giovanni G, Sieira-Moret J, de Asmundis C, Conte G, Rodríguez-Mañero M, et al. Initial experience of three-minute freeze cycles using the second-generation cryoballoon ablation: acute and short-term procedural outcomes. *J Interv Card Electrophysiol*. 2014;39(2):145–51.
- Ciconte G, de Asmundis C, Sieira J, Conte G, Di Giovanni G, Mugnai G, et al. Single 3-minute freeze for second-generation cryoballoon ablation: one-year follow-up after pulmonary vein isolation. *Heart Rhythm*. 2015;12(4):673–80.
- Wissner E, Heeger CH, Grahn H, Reissmann B, Wohlmuth P, Lemes C, et al. One-year clinical success of a “no-bonus” freeze

- protocol using the second-generation 28 mm Cryoballoon for pulmonary vein isolation. *Europace*. 2015;17(8):1236–40.
25. Miyazaki S, Hachiya H, Nakamura H, Taniguchi H, Takagi T, Hirao K, et al. Pulmonary vein isolation using a second-generation cryoballoon in patients with paroxysmal atrial fibrillation: one-year outcome using a single big-balloon 3-minute freeze technique. *J Cardiovasc Electrophysiol*. 2016;27(12):1375–80.
 26. Tebbenjohanns J, Höfer C, Bergmann L, Dedroogh M, Gaudin D, von Werder A, et al. Shortening of freezing cycles provides equal outcome to standard ablation procedure using second-generation 28 mm cryoballoon after 15-month follow-up. *Europace*. 2016;18(2):206–10.
 27. Ciconte G, Sieira-Moret J, Hacıoglu E, Mugnai G, Di Giovanni G, Velagic V, et al. Single 3-minute versus double 4-minute freeze strategy for second-generation cryoballoon ablation: a single-center experience. *J Cardiovasc Electrophysiol*. 2016;27(7):796–803.
 28. Vallès E, Cabrera S, Alcalde O, Benito B, Jiménez J, Poveda P, et al. Adapted single shot for cryoballoon procedures optimization in atrial fibrillation. Roma: Abstract in Congress of the European Society of Cardiology; 2016.
 29. Boveda S, Providência R, Albenque JP, Combes N, Combes S, Hireche H, et al. Real-time assessment of pulmonary veins disconnection during cryoablation of atrial fibrillation: can it be “achieved” in almost all cases? *Europace*. 2014;16(6):826–33.
 30. Stabile G, Tondo C, Curnis A, Lunati M, Manfrin M, Molon G, et al. Efficacy of cryoballoon ablation in patients with paroxysmal atrial fibrillation without time to pulmonary vein isolation assessment. *Int J Cardiol*. 2018;18:32170–3 In press.