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One-year follow-up after second-generation cryoballoon ablation for atrial fibrillation in a large cohort of patients: a single-centre experience

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Aim The second-generation cryoballoon (CB-Adv) is effective in achieving pulmonary vein isolation (PVI) with encouraging results. In this study, we assessed the single-procedure outcome on a 1-year follow-up period in a large sample of patients having undergone PVI for drug-resistant atrial fibrillation (AF) using the CB-Adv.

Methods and Results A total of 393 patients (122 female, 31%; mean age 57.7 ± 12.9 years) with drug-refractory AF undergoing PVI using the novel CB-Adv were enrolled. Follow-up was based on outpatient clinic visits including Holter electrocardiograms. Recurrence of atrial tachyarrhythmias (ATas) was defined as a symptomatic or documented episode >30 s. A total of 1572 pulmonary veins (PVs) were identified and successfully isolated with 1.2 ± 0.3 mean freezes. Mean procedure and fluoroscopy times were 87.1 ± 38.2 and 14.9 ± 6.1 min, respectively. At a mean follow-up of 12 months, freedom from ATas after a single procedure was achieved in 85.8% of patients with paroxysmal atrial fibrillation and in 61.3% of patients with persistent AF (persAF). Similar success rates were observed between bonus freeze and single freeze strategies, 82.5 and 81.8%, respectively ($P = 0.9$). Multivariate analysis demonstrated that persAF ($P = 0.04$) and relapses during blanking period (BP) ($P < 0.0001$) were independent predictors of ATas recurrences.

Conclusion Freedom from any ATa can be achieved in 81.9% of patients after a single CB-Adv procedure in a large cohort of patients. A bonus freeze does not influence the clinical outcome, and reducing the duration of the cryoapplication to 3 min offers excellent results. Persistent AF and arrhythmia recurrence during the BP are strong predictors of AF recurrence.

Keywords Cryoballoon ablation • Second-generation cryoballoon • Atrial fibrillation • Pulmonary vein isolation • 1-Year follow-up

Introduction

The second-generation cryoballoon (CB-Adv; Arctic Front Advance, Medtronic, Minnesota, USA) is a safe and effective for pulmonary vein isolation (PVI).[1] As compared with the first generation, the CB-Adv has been designed with improved technical aspects that result in a larger and more homogeneous freezing zone, ensuing into significantly enhanced procedural and clinical outcomes.[2–4]

This is a retrospective, single-centre study assessing the single-procedure outcome on a 1-year follow-up period in a large cohort of patients having undergone PVI for drug-resistant AF using the

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What's new?

- The largest single-centre study reporting clinical outcome following CB-Adv ablation for drug-resistant atrial fibrillation (AF) on a 12-month follow-up period.
- Recurrence during the blanking period is a major predictor of AF/atrial tachycardia recurrence during the follow-up.
- A bonus freeze does not affect the clinical outcome after a single procedure if compared with a single 3 min freeze approach.

CB-Adv. Potential predictors of arrhythmia recurrence and procedure-related complications are also considered as secondary endpoints.

Methods

Patient population

All consecutive patients with drug-resistant AF who underwent PVI by CB-Adv from June 2012 to December 2014 in our hospital were retrospectively included in this analysis. All patients signed informed consent for the procedure. The protocol was carried out in accordance with the ethical principles for medical research involving human subjects established by Helsinki's declaration, protecting the privacy of all the participants as well as the confidentiality of their personal information. The exclusion criteria were any contraindication for the procedure including the presence of an intracavitary thrombus, uncontrolled heart failure, and contraindications to general anaesthesia.

Pre-procedural management

Prior to the procedure, all patients underwent a 2D transthoracic echocardiogram (TTE) to assess left ventricular ejection fraction and to rule out any structural and/or valvular disease. A cardiac computed tomography (CT) and a transoesophageal echocardiography (TEE) were performed the day before ablation to analyse left atrial and pulmonary vein (PV) anatomy and to rule out any intracardiac thrombus. All antiarrhythmic drugs (AADs) were discontinued at least 3 days before ablation. For patients under novel anticoagulant agents, our practice is to stop anticoagulation as follows: (i) the last dose of rivaroxaban is given in the morning 1 day prior to the procedure, and (ii) the last dose of dabigatran or apixaban is given in the evening 1 day prior to procedure. Warfarin or acenocumarol are not interrupted.

Ablation procedure

All procedures were performed under general anaesthesia and using short-acting neuromuscular blocking drugs for endotracheal intubation. After having achieved left atrial access with a single transseptal puncture, a 100 IU/kg heparin IV bolus was given. A 0.32 French Emerald exchange wire (Cordis, Johnson and Johnson, Diamond Bar, CA, USA) was advanced in the left superior PV, and a steerable 15 French over-the-wire sheath (FlexCath, Cryocath, Medtronic, USA) was positioned in the left atrium (LA). A 20 mm diameter Achieve inner lumen mapping catheter (ILMC) (Medtronic, Minnesota, USA) was sequentially positioned in each PV ostium to obtain baseline electrical information. Then a 28 mm double-walled cryoballoon (Artic Front or Arctic Front Advance, Cryocath) was advanced over the ILMC up to the LA, inflated and positioned in the PV ostium of each vein. Optimal vessel occlusion was considered to have been achieved when selective dye injection showed total contrast retention with no backflow to the atrium. Once occlusion is documented, cryothermal energy commenced. Cryothermal application lasted 4 min, and a bonus freeze following isolation was systematically performed in the initial procedures; later on, all the procedures were performed with a single 3 min application for each vein[5], and a second freeze was delivered in the case of failure to isolate the PV after the first cycle, in the case of nadir temperature greater than $-35^{\circ}C$, and in the occurrence of early PV reconnection. The left-sided veins were treated first, with left superior pulmonary vein (LSPV) first and then left inferior pulmonary vein (LIPV). In the case of a supplementary right-sided vein, the ablation strategy consisted in approaching all branches. In the case of suboptimal occlusion in the lower veins, pull-down manoeuvres were performed to close an unwanted leak. During the initial experience with the second-generation cryoballoon, the right-sided PVs were similarly approached as the first-generation cryoballoon, by strongly wedging the balloon in the venous ostium. However, the freeze extends up to the distal tip of the balloon in the second-generation device. In this setting, occluding the PV by applying a strong pressure hypothetically yields a greater chance of damage to the extracardiac structures. Therefore, the approach was modified later on. When inflated, the balloon's diameter is 26.5 mm and its internal pressure 2–3 PSI. Once the freeze starts, both the diameter and inside pressure increase to 28 mm and 17.7 PSI, respectively. Thus, the technique consists of initially obtaining a complete occlusion of the vein demonstrated by dye injection. The balloon is then retrieved slowly to a more proximal position until a small leak is observed, which is when the freeze commences, and the balloon increases both in volume and pressure. In the first seconds after cryoenergy starts, it is still possible to inject contrast before the inner lumen freezes.

This simple manoeuvre usually eliminates the leak at the more proximal position without the need of further catheter manipulation. If a leak still persists, a slight advancement of the cryoballoon was enough to guarantee venous occlusion. In this setting, a larger and less compliant balloon and the small pressure applied to the device in the PV ostium carry a significantly lower chance of creating a more distal lesion in the vessel. In the case of phrenic nerve palsy (PNP), cryoenergy application was aborted and recovery of diaphragmatic contraction was carefully monitored for 30 min. As from January 2014, an immediate deflation[6] strategy was performed if PNP occurred. Pulmonary vein isolation was documented with the help of a dedicated ILMC (Achieve, Medtronic, USA), evaluating the electrical activity in the PVs. During the whole procedure, activated clotting time was maintained at over 250 s by supplementing heparin infusion as required.

Phrenic nerve monitoring

In order to avoid PNP, a standard decapolar catheter was placed in the superior vena cava in order to pace the right phrenic nerve (PN)

(at 20 mA/1.0 ms pulse width at a cycle length of 1200 ms) during ablation of the right-sided PVs. The reason to pace at such a slow rate is to prevent catheter displacement, due to diaphragmatic contraction in the early phases of cryoenergy application. PN capture was achieved when contraction of the right hemidiaphragm could be observed under fluoroscopic imaging and by manual palpation of the abdomen. The exact position of the optimal PN stimulation was then recorded using fluoroscopy in order to memorize the location. If PN contraction resumed during the procedure, the latter was defined as transient PNP. Conversely, if PNP persisted at the end of the procedure, this complication was defined as persistent.

Assessment of electrical isolation

Pulmonary vein activity was recorded with the ILMC at a proximal site in the ostium prior to ablation in each vein. If pulmonary vein potentials (PVPs) were visible during cryoenergy application, time to isolation was recorded when PVPs completely disappeared or were dissociated from LA activity. If PVPs were not visible during ablation due to a distal positioning of the ILMC, the latter was immediately retracted after completion of the freeze–thaw cycle to a more proximal position in which PVPs had been recorded prior to ablation to record their presence or absence. If needed, pacing from the distal or proximal coronary sinus catheter was performed to distinguish far-field atrial signals from PVP recorded on the mapping catheter, for left- and right-sided veins, respectively.

Post-ablation management

Patients were discharged the day following ablation if their clinical status was stable. After the procedure, the patients were continuously monitored with electrocardiogram (ECG) telemetry for at least 18 h. Before hospital discharge, all patients underwent TTE in order to exclude pericardial effusion. Oral anticoagulation was started the same evening of ablation and continued for at least 3 months. Antiarrhythmic drug treatment was continued for 3 months. The decision to restart AADs after the blanking period (BP) was taken in case of a first episode of recurrence of atrial fibrillation (AF).

Follow-up

After discharge from the hospital, patients were scheduled for follow-up visits at 1, 3, 6, and 12 months. Twenty-four hour Holter recordings were obtained at each follow-up visit. All reports of Holter monitoring or ECG recordings having been performed in referring centres were sent to the Heart Rhythm Management Centre, UZ Brussels for diagnosis confirmation during the follow-up. Furthermore, telephone calls to patients were made during the follow-up. All documented AF episodes of >30 s after the index procedure were considered as a recurrence. A BP of 3 months was applied. All episodes of AF recurrence, including the ones occurring in the BP, were taken into consideration for final analysis.

Statistical analysis

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as mean $\pm$ SD or median and range as appropriate. Event-free survival was estimated by the method of Kaplan–Meier and compared by the log-rank test. Predictors of arrhythmia recurrence were performed using the Cox proportional hazards regression models. The multivariate prediction models for time to recurrence after the final ablation procedure were performed by stepwise regression based on likelihood ratios. For each variable, hazard ratio (HR), 95% confidence interval (CI), and Wald test *P*-values of the final model are displayed. A two-tailed probability value of < 0.05 was deemed significant. Statistical analyses were conducted using the SPSS software (SPSS v22, Chicago, IL, USA).

Results

Baseline population characteristics

A total of 393 consecutive patients (122 female, 31%; mean age 57.7 $\pm$ 12.9 years) undergoing PVI with CB-Adv were included. No patient was excluded based on pre-procedural CT scan anatomical findings. All patients failed $\geq$1 Class I or III AAD. *Table 1* shows baseline clinical and anatomical characteristics of the study population.

Procedural characteristics

All CB-Adv procedures were performed with a large 28 mm balloon, and PVI was successfully achieved in all veins without the

Table 1 Baseline characteristics

	Total procedures (n = 393)
Female gender	122 (31)
Age (years)	57.7 $\pm$ 12.9
Duration from first episode of diagnosed AF (months)	24.7 $\pm$ 18.1
Persistent AF	62 (16)
Hypertension	164 (42)
Dyslipidemia	140 (36)
Diabetes mellitus	35 (9)
Coronary artery disease	30 (8)
Dilated cardiomyopathy	23 (6)
Valvular disease	16 (4)
Absence of cardiomyopathy	307 (78)
Oral anticoagulation	229 (58)
Failed drugs prior to ablation (Classes I and III)	
IC class AAD	209 (53)
III class AADs	184 (47)
Other drugs	
Beta blockers	81 (20)
Calcium antagonists	14 (3)
Left ventricular ejection fraction (%)	58.9 $\pm$ 7.1
Left atrial size (mm)	41.6 $\pm$ 7.0
CHA_2DS_2-VASc score	1.36 $\pm$ 1.33
BMI (kg/m^2)	27.1 $\pm$ 4.5
CT findings	
Discrete common os	21 (6)
Right-sided early branching	16 (4)

Categorical variables are expressed as absolute and percentage (in parentheses). Continuous variables are expressed as mean $\pm$ SD. AF, atrial fibrillation.

need of additional focal catheter applications. Details are shown in *Table 2*. The first 80 patients were treated with 4 min freeze cycles with a systematic bonus freeze. The following 313 individuals were treated with a single 3 min freeze cycle strategy.

Complications

Nine patients (2.2%) experienced procedure-related complications. The most frequently observed was PNP. A detailed list of complications is shown in *Table 3*. A total amount of 31 PNPs (7.9%) were observed; among them, 21 were transient (5.3%) and 10 persistent (2.6%). Among these patients, 6/10 completely recovered within discharge from the hospital, and 3/10 recovered at 2, 3, and 6 months, respectively. One patient (0.25%) still exhibited right diaphragm elevation at the control X-ray at a final follow-up of 20 months and was mildly symptomatic for exertional dyspnoea. Of note, the incidence of persistent PNP decreased, although not significantly, from 2.9% (6/206) to 2.1% (4/187) once an 'immediate deflation' strategy was adopted ($P = 0.7$). Finally, the incidence of phrenic nerve injury was lower in the single application group if compared with patients having undergone a double freeze strategy (6.7 vs. 12%; $P = 0.09$). However, this difference was not significantly different.

Table 2 Procedural characteristics

Mean total procedural time (min)	87.1 ± 38.2
Mean fluoroscopy time (min)	14.9 ± 6.1
Mean number of freeze–thaw cycles in LSPV	1.4 ± 0.3
Mean number of freeze–thaw cycles in LIPV	1.3 ± 0.3
Mean number of freeze–thaw cycles in RSPV	1.2 ± 0.3
Mean number of freeze–thaw cycles in RIPV	1.2 ± 0.3
Mean minimal temperature in LSPV (°C)	−53.2 ± 5.4
Mean minimal temperature in LIPV (°C)	−49.4 ± 5.6
Mean minimal temperature in RSPV (°C)	−54.2 ± 5.7
Mean minimal temperature in RIPV (°C)	−50.1 ± 4.7

Continuous variables are expressed as mean ± SD. LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

Table 3 Major complications in CB-A ablation procedures

	Total procedures ($n = 393$)
Death related to the procedure	0
Atrial-oesophageal fistula	0
Neurologic complications	0
Transient ST elevation	1 (0.25%)
Cardiac tamponade	1 (0.25%)*
Severe PV stenosis	0
Retroperitoneal haematoma	1 (0.25%)
Groin complications	
Femoral pseudoaneurysm	5 (1.27%)**
Symptomatic persisting PNP	1 (0.25%)
Total	9 (2.29%)

PV, pulmonary vein; PNP, phrenic nerve palsy.
* Treated by pericardiocentesis and uneventful.
** One patient requiring surgical treatment.

Follow-up

Clinical follow-up could be obtained in all patients. All patients completed at least two Holter ECG recordings during the follow-up, and more than 85% completed all the scheduled 24 h ECG monitorings. At a mean follow-up of 12.2 ± 3.8 months, the success rate without antiarrhythmic therapy was 81.9% (322/393; considering a BP) and 78.9% (310/393; without considering a BP) in the total study population. Mean time to arrhythmia recurrence was 5.5 ± 3.2 months.

At a mean follow-up of 12 months, freedom from atrial tachyarrhythmias (ATas) off AADs after a single procedure was achieved in 85.8% patients (284/331) with paroxysmal atrial fibrillation (PAF) and in 61.3% of patients (38/62) with persistent AF (persAF) ($P < 0.001$), *Figure 1*.

Similar rates of arrhythmia recurrence were observed between bonus and single freeze strategies, 14/80 (82.5%) and 57/313 (81.8%), respectively ($P = 0.9$).

Atrial arrhythmias recurrences

Considering the BP, 71/393 patients (18.1%) had arrhythmia recurrences: 47/331 (14.2%) among patients with PAF, and 24/62 (38.7%) in patients with persAF ($P < 0.0001$). Of note, 65% of patients that had arrhythmic recurrence during the BP also presented with AF relapses later in the follow-up. Among patients with PAF, ATas recurred as PAF in 40/47 (85.1%), as left atrial tachycardia (AT) in 4/47 (8.5%) and cavotricuspid-dependent flutter in 3/47 (6.4%) of

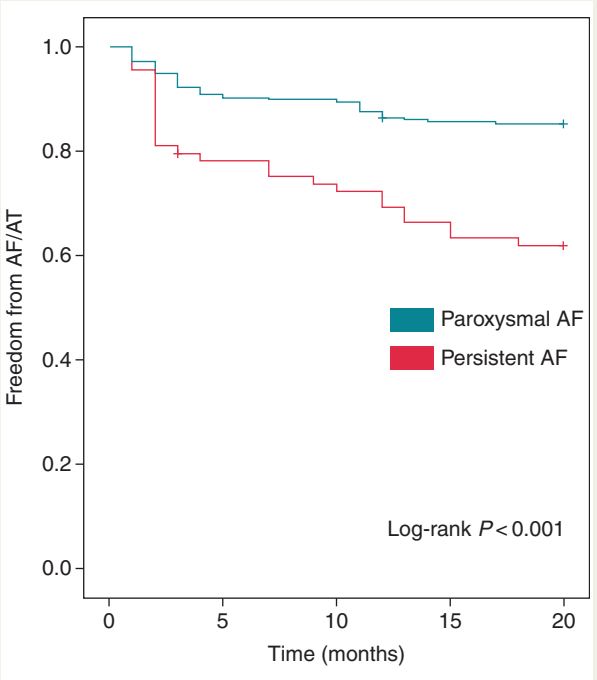

Figure 1 The Kaplan–Meier curve showing freedom from AF/AT in both patients with PAF and persAF after a single CB-Adv procedure.

Table 4 Characteristics of patients with AF recurrence compared with those without AF recurrence

	No recurrence (n = 322)	Recurrence (n = 71)	P-value
Female gender	101 (31)	21 (30)	0.89
Age (years)	57.2 ± 12.3	58.6 ± 12.6	0.40
Duration of symptoms (months)	23.9 ± 15.5	27.3 ± 19.2	0.11
Persistent AF	38 (12)	24 (34)	**<0.0001**
Hypertension	134 (42)	30 (42)	1.00
Dyslipidemia	120 (37)	20 (28)	0.17
Diabetes mellitus	25 (8)	10 (14)	0.11
Coronary artery disease	20 (6)	10 (14)	**0.04**
Dilated cardiomyopathy	16 (5)	7 (10)	0.16
Left ventricular ejection fraction (%)	59.1 ± 7.3	57.7 ± 11.5	0.19
Left atrial size (mm)	41.7 ± 7.2	43.2 ± 8.6	0.12
CHA_2DS_2-VASc score	1.34 ± 1.28	1.34 ± 1.53	0.98
BMI (Kg/m^2)	26.4 ± 4.1	28.1 ± 5.3	**0.003**

Categorical variables are expressed as absolute and percentage (in parentheses). Continuous variables are expressed as mean ± SD. AF, atrial fibrillation.

patients. Twenty-seven patients (27/47; 57.4%) underwent repeat procedure due to recurrent drug-resistant AF symptoms. Patients with left AT and right-sided flutter all underwent redo RF ablation. At the repeat procedure, permanency of PV isolation could be documented in 76% of veins. Specifically, persistence of PVI was observed in 89% of LSPV, 74% of LIPV, 67% of right inferior pulmonary vein (RIPV), and 74% of right superior pulmonary vein (RSPV). Of note, 27% of patients presented with complete isolation in all four veins at the repeat procedure. In the latter, isoproterenol infusion was performed in order to unmask and ablate potential non-PV foci.

After the BP, in patients with persAF symptomatic arrhythmia, recurrence was documented as PAF in 12/24 (50%), as persAF in 10/24 (42%), and as left AT in 2/24 (8%). Patients with documented AT were all scheduled for a RF procedure in order to ablate the clinical arrhythmia without prior cardioversion. Of 24 patients having recurrences, 9/24 (37%) underwent a second procedure because of recurrent drug-refractory ATas. Indication to a repeat procedure was due to PAF in 3 patients (33.3%), persAF in 4 (44.4%), and left AT in 2 (22.2%). In patients presenting with PAF, reisolation of the reconnected PVs was performed. Individuals presenting with persAF underwent reisolation of the reconnected PVs linear ablation and complex atrial fractionated electrograms (CAFE) ablation. Of note, the three patients that underwent redo ablation for PAF also received cavotricuspid isthmus ablation for documented typical right atrial flutter. Left atrium to PV reconnection was found in at least 1 right-sided PV in 4/9 (44.4%) patients, and in at least 1 left-sided PV in 3/9 (33.3%) individuals. Two patients presented with persistent isolation of all four veins. In the two patients with AT, a roof-dependent LA flutter was confirmed by electroanatomical mapping, while a RIPV reconnection could be documented in the other. Both patients underwent successful ablation.

Predictors of arrhythmia recurrence

Comparison of the baseline characteristics of patients with and without AF recurrence showed high incidence of recurrence in patients with high body mass index (BMI), persAF, and coronary artery disease, $P = 0.003$, <0.0001, and 0.04, respectively (*Table 4*).

After a single procedure, univariate predictors of recurrence were persAF duration, BMI, and arrhythmia recurrences during the BP. In the multivariate analysis, only persAF and relapses during the BP independently predicted arrhythmia recurrences (*Table 5*). For each additional month of persAF, the risk of arrhythmia recurrence increased by 1.4 times (HR 1.37, 95% CI 1.03–2.05; $P = 0.04$), while having a recurrence during the BP the risk increased by 10.9 times (HR 10.88, 95% CI 5.72–20.01; $P < 0.0001$).

Discussion

To the best of our knowledge, this is the largest single-centre study reporting clinical outcome following CB-Adv ablation for drug-resistant AF on a 12-month follow-up period. The main findings of our study are as follows: (1) freedom from any ATa can be achieved in 81.9% of patients after a single CB-Adv procedure; (2) a bonus freeze did not influence the clinical outcome; and (3) persAF, BMI, and relapses during the BP predicted arrhythmia recurrence. However, on the multivariate analysis, only persAF and arrhythmia recurrence during the BP were found to be significant predictor.

At 12-month follow-up, 81.9% of 393 patients were free of arrhythmic recurrence after a single procedure with the CB-Adv. This is in line with recent articles analysing mid-term outcomes of the second-generation cryoballoon device.[7–10] However, the latter were all conducted on a limited number of patients. Our findings underline once more the reproducibility and efficacy of this novel technique in a significantly larger cohort of patients. The CB-Adv has been launched on the market with significant technological improvements if compared with its predecessor.[7] The number of refrigerant jets has been doubled, and the latter have been positioned more distally on the catheters shaft. These modifications have led to more homogeneous and circumferential lesions around the PV

Table 5 Univariate and multivariate Cox regression analyses for AF recurrences

Variable	Beta coefficient	HR for AF recurrence	*P*-value
Univariate analysis			
Age (years)	0.001	1.00 (0.98–1.02 95% CI)	0.93
BMI (kg/m^2)	0.06	1.06 (1.01–1.12 95% CI)	0.02
Duration of symptoms (months)	0.006	0.98 (0.97–1.02 95% CI)	0.17
Arterial hypertension	0.09	1.09 (0.66–1.78 95% CI)	0.73
Left atrial diameter (mm)	0.03	1.03 (0.99–1.08 95% CI)	0.17
Coronary artery disease	0.45	0.64 (0.32–1.25 95% CI)	0.19
BP recurrences	2.45	11.62 (7.18–18.80 95% CI)	<0.0001
Persistent AF	0.78	2.19 (1.30–3.70 95% CI)	0.003
Multivariate analysis			
BMI (kg/m^2)	0.001	1.00 (0.95–1.05 95% CI)	0.86
BP recurrences	2.47	10.88 (5.72–20.01 95% CI)	<0.0001
Persistent AF	0.24	1.37 (1.03–2.05 95% CI)	0.04

AF, atrial fibrillation; HR, hazard ratio; BP, blanking period; CI, confidence interval.

antrum if compared with the first-generation device.[11,12] This translated in significantly better clinical outcomes,[13] probably due to a higher rate of permanent PVI in the long term.[14] In addition, a recent publication by Kennisberg *et al.*[15] analysed the extension of the lesions after CB-Adv ablation showing that the latter extended proximally in the PV antra affecting a large portion of the posterior wall of the LA. These very wide lesions might also potentially target extra-PV foci or structures such as the ganglionated plexi, which might play an additional role in triggering and maintaining AF.[16] Finally, it should be mentioned that electrical isolation could be obtained in all veins without the need of focal tip catheter touch-up irrespective of the anatomical variations in the PV drainage pattern. This finding underlines once more the technological improvements with respect to the first-generation balloon but might also question the utility of a pre-procedural CT scan prior to CB-Adv ablation.

In our study, a bonus freeze strategy did not ameliorate clinical outcome if compared with a single 3 min freeze per vein approach. Two other groups recently compared a single vs. bonus freeze approach using the CB-Adv, and both concluded that results did not differ between both strategies.[17,18] However, although these findings are very promising, these studies were conducted on a relatively smaller number of patients. Furthermore, the authors all used 4 min duration freezing cycles. Our findings report the largest population having undergone CB-Adv ablation with a single freeze approach with a reduced duration to 3 min cryoenergy application times. In fact, in our total cohort of patients, up to 80% (313) were treated with a single 3 min strategy. Despite confirming the enhanced efficacy of the CB-Adv, reducing the freeze duration might bare additional advantages. As cryoenergy reaches deeper tissue layers as the application goes on, a reduced dosing strategy might hypothetically lead to reduced damage of extracardiac structures, such as the oesophagus or the lung tissue. However, this is a currently a mere hypothesis, and larger, randomized studies are needed to confirm it.

Patients with persAF and individuals with documented early recurrence of atrial arrhythmias during the BP were significantly more likely to experience AF on the long term. Persistent AF is sought to be a more advanced stage on the disease and is usually characterized by diffuse electroanatomical modifications in the atria, such as fibrosis, if compared with the paroxysmal variant of AF. Therefore, PVI might not be sufficient to treat patients with persAF. The recently published STAR-AF2 trial[19] surprisingly showed that adjunctive ablation strategies such as CAFE ablation or the creation linear ablation lines on top of PVI did not decrease the rate of AF recurrence in patients affected by persAF compared with 'PVI-only' strategy. This probably underlines the current poor understanding of the mechanisms causing and maintaining persAF. Interestingly, the latter showed that PVI only was able to achieve freedom from AF in 60% of individuals in this subset of patients. Our findings are similar. In fact, 61.3% of patients pertaining to the persistent group were free of AF on a 12-month follow-up period. Therefore, the cryoballoon might be a valuable alternative to traditional point-by-point ablation with RF in these patients.[20]

Early recurrence also predicted failure at final follow-up in our study. This is in line with a recently published article by Andrade *et al.*[21] that showed that early recurrence was significantly related to late arrhythmia relapse after cryoballoon ablation. Although *in vitro* studies seem to indicate that cryoenergy is associated to a minimal inflammatory reaction[22] if compared with RF, studies in humans seem to show that both energy sources result in a comparable rise of markers of cell damage, platelet activation, and inflammatory response.[23] Therefore, similarly to RF, early recurrence in the BP might be an indicator of late relapse of AF. This might question the real need of considering a BP, and operators might be prone to propose a repeat procedure earlier in the follow-up if AF recurs shortly after the index procedure.[24]

Limitations

Although conducted on a large cohort of patients, this study bears the limitations of being single-centre and non-randomized study. Patients were followed up by clinical consultations and 24 h Holter monitoring. Inner loop recorders might have shown a higher rate

of recurrence. We did not use a thermal oesophageal probe. Therefore, a certain amount of oesophageal lesions might have gone unnoticed. We did not perform compound motor action potential during right PN pacing. The incidence of PNP might have been lower. Finally, the most important limitation consists in the fact that 16% of patients presenting with persAF might not represent the mean population that is referred for AF ablation in a tertiary centre and results should not be generalized. Although during our initial experience we mostly treated patients affected by PAF with the CB-Adv, recently published articles seem to indicate that the second-generation device is equally effective to RF in treating persAF.[20,21]

Conclusions

Freedom from any ATa can be achieved in 81.9% of patients after a single CB-Adv procedure in a large cohort of patients. A bonus freeze does not influence the clinical outcome, and reducing the duration of the cryoapplication to 3 min offers excellent clinical outcome. Persistent AF and arrhythmia recurrence during the BP are strong recurrence predictors of AF on a 12-month follow-up period.

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