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Atrial fibrillation ablation with the second generation cryoballoon: Multicenter propensity score matched comparison between freezing strategies☆

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ABSTRACT

Background: Second generation cryoballoon (CB-A) ablation is highly effective in achieving pulmonary vein (PV) isolation and freedom from atrial fibrillation (AF). However, the ideal freezing strategy is still under debate. Our objective was to investigate the efficacy and outcome between different freezing strategies used with the CB-A in a multicenter, matched population.

Methods: From a total cohort of 1018 patients having undergone CB-A ablation for drug-refractory AF, 673 patients with follow-up ≥6 months were included and stratified according to the applied freezing strategy: bonus freeze (BF) versus single freeze (SF). Final population of 256 BF patients was compared with 256 propensity-score matched SF patients.

Results: BF strategy consisted of 3 different protocols: 3 cycles of 180 s; 2 cycles of 240 s; and cycles of 240 s followed by 180 s in 99/256 (39%); 42/256 (16%); and 115/256 (45%) patients, respectively. SF approach included cycles of 240 s in 23/256 (9%), and 180 s in 233/256 (91%) patients. Electrical isolation could be achieved in all PVs by both protocols, with shorter procedure and fluoroscopy times in the SF group (mean 106 vs 65 min, and 18 vs 14 min, respectively, $P < 0.001$). Phrenic nerve palsy persisted after discharge in a total of 11 patients (2.1%): 4 (1.6%) in the BF group vs 7 (2.7%) in the SF group, $P = 0.5$. AF-free survival was similar between the 2 groups during follow-up (mean 18 ± 10 months) (log rank, $P = 0.6$).

Conclusions: CB-A ablation showed equal efficacy and outcome between SF and BF strategy.

1. Introduction

Pulmonary vein isolation (PVI) is currently an established treatment for drug-resistant atrial fibrillation (AF) [1–2]. In recent years, cryoballoon (CB) ablation has emerged as a valid alternative to traditional point-by-point radiofrequency ablation [3–4]. The second generation CB (CB-A; Arctic Front Advance, Medtronic) offers a larger and more homogeneous freezing zone on the balloon surface, resulting in significantly better procedural and clinical outcome compared to its predecessor [5–6]. Although the optimal number of the freeze cycles still needs to be determined, recent studies showed high effectiveness of a single freeze (SF) strategy per vein in terms of achieving acute PVI and mid-term clinical outcome [7–8]. Moreover, there is an increasing use of shorter freeze cycle durations per vein. Studied at a preclinical level in canine models, there was no difference in acute PVI rate or mature transmural lesions (30 days) between 2- versus 4-min applications, however, 4-min freezes were associated with strictures of the PV due to neointimal proliferations [9]. In terms of clinical outcome, a single 3-min freeze strategy seems to have a comparable AF-free survival compared to a double 4-min bonus freeze (BF) approach in patients with paroxysmal AF [10]. Hypothetically, using SF applications and/or reduced freeze cycle durations, shorter procedure and fluoroscopy times might be obtained with an associated lower risk of procedural complications related to longer LA dwelling times [11]. In the present study, we sought to investigate the acute performance, procedural complications, and post-procedural clinical outcome between different freezing strategies used with the CB-A.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Study population

Between June 2012 and June 2016, all consecutive patients with drug-resistant AF who underwent CB-A ablation were considered, but included only when a clinical follow up ≥6 months was available. Data was collected from two high-volume AF ablation centers: Heart Rhythm Management Centre, Universitair Ziekenhuis Brussel (Belgium), and Electrophysiology Unit, ZNA Middelheim Antwerp (Belgium). The study was carried out in accordance with the ethical principles for medical research involving human subjects established by the Helsinki Declaration. The study was approved by the local ethics committee.

2.2. Pre-procedural management

All patients provided written informed consent for the ablation procedure. A transthoracic echocardiogram was performed within 1 week prior to ablation enabling assessment of the left ventricular ejection fraction, intracavitary dimensions and to rule out any structural and/or valvular disease. To exclude the presence of thrombi, trans-esophageal echocardiography was performed the day before the procedure. Additionally, all patients underwent a pre-procedural CT-scan as standard practice to assess left atrial (LA) and PV anatomy.

2.3. Cryoballoon ablation procedure

All procedures were performed as previously reported [12]. Briefly, after gaining access to the LA (echo-guided), cryoenergy applications were performed at each vein with the 28 mm CB-A. Right sided phrenic nerve (PN) function was monitored by diaphragmatic stimulation as previously described [13]. Isolation of PVs was confirmed by using the inner lumen mapping catheter (Achieve). In the BF group, cryoablation consisted of a double or triple application (either 240 or 180 min), and this on top off the first application were successful PVI was achieved. In the SF group, all procedures were performed with the intention to deliver a single application per vein (either 240 or 180 min). In the latter setting, a second cryoapplication was only delivered if the temperature values could not reach −40 °C within 1 min, or if either absence of PV isolation or early spontaneous PV reconnection after the first cycle occurred. At the end of procedure, all pulmonary veins were revisited to confirm the isolation.

2.4. Post-ablation management and follow-up

Patients were discharged the day following ablation if the clinical status was stable. Previously ineffective antiarrhythmic drug (AAD) treatment was discontinued 3 months post ablation if no recurrence. The decision to restart AADs after the blanking period was taken in case of a first episode of arrhythmia recurrence. Patients were scheduled for follow-up visits at 1, 3, and 6 months, and every 6 months thereafter. Symptom-driven consultations were planned in case of symptoms outside the scheduled follow-up, to record a 12 lead ECG recording, interrogate the implanted device or if needed, plan additional 24 h holter or event recorders in case of recurrent symptoms. All reports of holter monitoring or ECG recording having been performed in referring centers were sent to our center for diagnosis confirmation. All documented episodes of AF and left atrial tachyarrhythmias (LAT) >30 s after the index procedure were considered as a recurrence. A blanking period of 3 months was applied.

2.5. Diagnosis and follow-up of patients with phrenic nerve injury

Phrenic nerve (PN) injury was graded as impending, transient, and persistent. Impending PN injury was a progressive weakening and reduced motility of palpable diaphragmatic palpation during intra-procedural high-output pacing. Transient PN injury was characterized by a hemi-diaphragm paresis or paralysis detected by fluoroscopy during the procedure that completely resolved before the end of the procedure. Persistent PN palsy was defined as an elevated hemi-diaphragm noted on post-procedural radiography, CT scan, or sniff test, which persisted after the procedure. Once the diagnosis of persistent PN palsy was established, the patient was closely monitored in the clinic with repeated tests, usually every 3 months. Complete recovery of PN function was diagnosed in case of normalization of the position of the diaphragm in the X-ray images both at rest and during sniff tests as compared to the pre-procedural chest images.

2.6. Statistical analysis

Continuous variables are expressed as mean ± SD and significant differences were analyzed by Student's *t*-test. Categorical data are expressed as number and percentages, and compared with χ^2 test or Fischer's exact test, when appropriate. Propensity-score matching was performed in order to compare the outcome between the BF versus the SF group. Patients were matched in a 1:1 ratio based on propensity scores, calculated for each patient using multivariable logistic regression based upon the covariates: age, gender, body mass index (BMI), type of atrial fibrillation (paroxysmal vs persistent), and follow-up duration (calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score). Survival curves were calculated by using the Kaplan–Meier method and compared by using the Log Rank test. Univariate and multivariate Cox proportional hazards regression analysis was applied on candidate variables to predict the dichotomous outcome. A 2-tailed probability value of <0.05 was deemed significant. Statistical analyses were conducted using the SPSS software (SPSS version 24, Armonk, NY, USA) and PS Match 3.04 R extension for SPSS.

3. Results

3.1. Baseline characteristics

A total of 1018 consecutive patients underwent CB-A during the study period. We included 673 patients with a follow up ≥6 months in the matching process. Of that cohort, 256 patients with a BF strategy and 256 with a SF strategy, were matched in a 1:1 ratio based on propensity scores, which resulted in two balanced groups of 256 patients each. Table 1 shows baseline characteristics of the matched patients (BF versus SF approach). Mean follow-up period was 18 ± 10 months after the procedure. All patients had failed treatment with ≥1 class I or III AAD drug, or needed to stop these drugs due to poor tolerability. Clinical follow-up with arrhythmia detection could be obtained in these patients, either by recordings from implanted medical devices in 14% of patients or the scheduled 24 h ECG recordings in the other patients.

3.2. Procedural characteristics

The BF strategy consisted of 3 different protocols: 3 cycles of 180 s; 2 cycles of 240 s; and cycles of 240 s followed by 180 s in 99/256 (39%); 42/256 (16%); and 115/256 (45%) patients, respectively. The SF approach included cycles of 240 s in 23/256 (9%), and 180 s in 233/256 (91%) patients. All procedures were performed using the Achieve as circular mapping catheter. Significant differences were found in procedure and fluoroscopy times between the 2 groups (Table 1). Mean nadir temperature achieved per vein were equal in both groups. Acute PVI could be achieved during the procedure in all veins using the large 28-mm CB-A without the need of a different

Table 1
Baseline and procedural characteristics of matched patients.

	Bonus freeze	Single freeze	*P*-value
No. of patients, *n*	256	256	
Gender, male, *n* (%)	171 (67%)	159 (62%)	0.3
Age, years (mean ± SD)	60 ± 11	59 ± 12	0.12
BMI, kg/m^2 (mean ± SD)	26 ± 4	26 ± 4	1
Diabetes, *n* (%)	15 (6%)	15 (6%)	1
Paroxysmal AF, *n* (%)	201 (79%)	211 (82%)	0.3
CHADS vasc score			
0, *n* (%)	69 (27%)	67 (26%)	1
1, *n* (%)	64 (25%)	51 (20%)	0.2
≥2, *n* (%)	123 (48%)	138 (54%)	0.3
LVEF, % (mean ± SD)	57 ± 4	56 ± 5	0.1
LA diameter AP, mm (mean ± SD)	42 ± 6	43 ± 10	0.2
Follow-up duration (months ±SD)	18 ± 11	18 ± 9	0.9
Procedure time, min (mean ± SD)	106 ± 25	65 ± 19	<0.001
Fluoroscopy time, min (mean ± SD)	18 ± 8	14 ± 8	<0.001
LSPV			
Mean no of freeze, *n* (mean ± SD)	2.4 ± 0.5	1.2 ± 0.4	<0.001
Min temperature, °C (mean ± SD)	−51 ± 5	−50 ± 6	0.1
LIPV			
Mean no of freeze, *n* (mean ± SD)	2.4 ± 0.5	1.1 ± 0.3	<0.001
Min temperature, °C (mean ± SD)	−47 ± 4	−47 ± 6	0.4
RSPV			
Mean no of freeze, *n* (mean ± SD)	2.3 ± 0.6	1.1 ± 0.4	<0.001
Min temperature, °C (mean ± SD)	−52 ± 5	−51 ± 6	0.2
RIPV			
Mean no of freeze, *n* (mean ± SD)	2.3 ± 0.5	1.2 ± 0.4	<0.001
Min temperature, °C (mean ± SD)	−48 ± 7	−48 ± 6	0.2

BMI, body mass index; AF, atrial fibrillation; LVEF, left ventricle ejection fraction; LA, left atrium; AP, anteroposterior; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein, RIPV, right inferior pulmonary vein; SD, standard deviation.

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