Cardiology Journal

VIA MEDICA

ORIGINAL ARTICLE

DOI: 10.5603/CJ.a2020.0147

ISSN 1897–5593
eISSN 1898–018X

Clinical outcomes of cryoballoon ablation for pulmonary vein isolation: Impact of intraprocedural heart rhythm

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Abstract

Background: *The current study sought to assess the impact of the intraprocedural heart rhythm (sinus rhythm [SR] vs. atrial fibrillation [AF]) on acute procedural characteristics, durability of pulmonary vein isolation (PVI) and long-term clinical outcomes of cryoballoon (CB) ablation.*

Methods: *A total of 195 patients with symptomatic paroxysmal (n = 136) or persistent AF (n = 59) underwent CB-based PVI. Ablation procedures were either performed in SR (SR group; n = 147) or during AF (AF group; n = 48). Persistent AF was more frequent in the AF group than in the SR group (62% vs. 20%). All other patient baseline characteristics did not differ between the two groups.*

Results: *The nadir temperature during the CB applications was significantly lower in the AF group than in patients in the SR group (–49 [interquartile range, –44; –54]°C vs. –47 [–42; –52]°C, p = 0.002). Median procedure and fluoroscopy times as well as the rate of real-time recordings were not different between the two groups. Repeat ablation for the treatment of atrial arrhythmia recurrence was performed in 60 patients (SR: 44 [30%] patients; AF: 16 [33%] patients), with a trend towards a lower rate of pulmonary vein reconnections in the AF group (p = 0.07). There was no difference in 3-year arrhythmia-free survival (p = 0.8).*

Conclusions: *Cryoballoon-based PVI during AF results in lower nadir balloon temperatures and a trend towards a higher durability of PVI as compared to procedures performed in SR. The rate of real-time PVI recordings was not affected by the intraprocedural heart rhythm.* (Cardiol J)

Key words: clinical outcomes, cryoballoon ablation, pulmonary vein isolation, intraprocedural heart rhythm

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Received: 28.09.2020 Accepted: 22.10.2020 Early publication date: 30.10.2020

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Introduction

Cryoballoon (CB) ablation has become an established treatment option for patients with atrial fibrillation (AF) [1–4]. The procedural endpoint is electrical isolation of the pulmonary veins (PV) [5]. Recent data indicate improved durability of pulmonary vein isolation (PVI) after CB ablation than after radiofrequency current (RFC) ablation [6]. Nevertheless, the number of patients requiring repeat ablation because of recurrences of AF — mainly driven by reconnected PV — remains high following either approach [7]. In contrast to point-by-point RFC ablation, the CB does not provide different energy levels, e.g., does not allow the use of higher energy settings at locations of poor tissue-catheter contact, such as the ridge between the left PV and the left atrial appendage. Once the CB has tissue contact at the antral aspect of the targeted PV, cryothermal energy is delivered via the entire distal hemisphere of the balloon. Durable, transmural lesion formation depends on the freeze cycle duration, and, more importantly, on the tissue contact of the CB. Since the latter cannot be measured directly, complete occlusion of the PV, duration of the temperature drop and nadir CB temperature serve as important surrogate parameters [8]. Theoretically, the reduced atrial contractility during AF might result in an enhanced stability of the balloon catheter and thereby, a more effective freeze cycle. However, to date, the impact of the intraprocedural rhythm (sinus rhythm [SR] vs. AF) during CB ablation has not yet been investigated.

The aim of the present study was to assess acute procedural characteristics, durability of PVI in patients with repeat ablation procedures and long-term clinical outcomes of CB ablation performed during AF or in SR.

Methods

Inclusion and exclusion criteria

Patients with symptomatic paroxysmal or persistent AF (as defined by 2016 ESC guidelines [5]) were included in the current study. Exclusion criteria were prior left atrial (LA) ablation procedures, a LA diameter > 60 mm, severe valvular heart disease or contraindications to post-interventional oral anticoagulation. Procedures were performed at two centers (Asklepios Klinik St. Georg, Hamburg, Germany, and German Heart Institute, Berlin, Germany).

The current study constitutes a retrospective analysis based oninstitutional databases. The study was approved by the local ethics boards and performed in accordance with the Declaration of Helsinki of 2013.

Preprocedural management

Transesophageal echocardiography was performed prior to PVI in all patients to rule out intracardiac thrombi and to assess LA diameter. No further pre-procedural imaging was performed.

Intraprocedural management

The intraprocedural management has been described in detail before [4, 9, 10]. In brief, in patients on vitamin K antagonists the procedure was performed under therapeutic international normalized ratio (INR) values of 2–3. Novel oral anticoagulants were stopped the day before the procedure and were later resumed 6 hours post ablation. All procedures were performed under deep sedation using midazolam, sufentanyl and propofol. One or two diagnostic catheters were introduced via the femoral vein and/or the left subclavian vein and were positioned within the coronary sinus and/or along the His bundle. A single transseptal puncture was performed via the femoral vein under fluoroscopic guidance, using a modified Brockenbrough technique and an 8.5 French (F) transseptal sheath (SL1, St. Jude Medical Inc., St. Paul, USA). After transseptal puncture, heparin boluses were administered in 30-minute intervals targeting an activated clotting time of ≥ 300 s. Selective angiographic visualization by dye injections or rotational angiography was performed to identify the individual PV ostia.

Cryoballoon-based PVI

The 28-mm second-generation CB was utilized exclusively in this study. The transseptal sheath was exchanged over a guidewire for a 12 F steerable sheath (FlexCath AdvanceTM, Medtronic, Inc.), through which the CB was advanced into the LA. Guiding of the CB to the target PV was performed over a 20-mm inner-lumen circular mapping catheter (Achieve™, Medtronic, Inc.) and complete occlusion of the PV ostium was verified by contrast injection through the central lumen of the inflated CB.

Patients were treated based on a "time-to--isolation" guided ablation protocol, i.e., after real-time verification of PVI, freezing was continued for an additional 120 s. In cases where the "time-to--isolation" could not be recorded, the freeze-cycle duration was set at 180 s; no additional bonusfreeze cycle was applied after successful PVI [9]. In patients undergoing CB ablation during AF, electrical

cardioversion was performed at the end of the procedure to restore SR.

An esophageal temperature probe (Sensitherm, St Jude Medical, Inc.; or Circa, Circa Scientific, Inc.) was inserted and positioned according to the individual CB position to provide esophageal temperature monitoring. The intraluminal esophageal temperature cut-off was set at 15°C [11].

During CB ablation along the septal PV, continuous phrenic nerve (PN) pacing was performed using a diagnostic catheter positioned in the superior vena cava (6 F, InquiryTM, St. Jude Medical, Inc.). PN capture was monitored by tactile feedback of diaphragmatic contraction by placing the operator's hand on the patient's abdomen. In addition, the continuous motor action potential was monitored and delivery of the refrigerant was stopped immediately if weakening or loss of diaphragmatic movement was noted or the amplitude of the continuous motor action potential decreased by 30% [12, 13].

Postprocedural care

Transthoracic echocardiography was performed in all patients to rule out a pericardial effusion. All patients were treated with proton-pump inhibitors for 4–6 weeks. Low molecular-weight heparin was administered in patients on vitamin K antagonists and an INR < 2.0 until a therapeutic INR of 2–3 was reached. Anticoagulation was continued for at least 3 months, and thereafter based on the individual CHA2DS2-VASc score. Previously ineffective antiarrhythmic drugs were continued for 3 months.

Follow-up

Following a blanking period of 3 months, patients completed outpatient clinical visits at 3, 6 and 12 months and in 6-month intervals thereafter according to our institutional standard; the clinical visits included electrocardiograms (ECGs) and 24 h-Holter ECGs. In patients with an implantable cardiac device with rhythm monitoring, regular device interrogations were additionally performed in order to detect arrhythmia recurrences. Moreover, regular telephone interviews were performed. In case of symptoms suggestive of recurrent arrhythmia, patients were advised to contact the outpatient clinic and subsequent clinical visits were immediately initiated.

Endpoints

The primary endpoints of this investigation were acute procedural characteristics, i.e., nadir balloon temperatures, procedure durations, fluoroscopy times, rate of real-time PVI recordings, and reconnection of initially isolated PV (assessed in patients with repeat ablation for recurrence of AF). Secondary endpoints were a documented recurrence of atrial arrhythmia with a duration of > 30 s outside the 3-month blanking period and complications, e.g., transient ischemic attack, stroke, pericardial tamponade, PN paralysis (PNP), and severe bleeding requiring blood transfusion.

Statistical analysis

All data were evaluated retrospectively. Continuous data are described as mean and standard deviation (SD) if normally distributed; otherwise the median and interquartile range [IQR, first quartile; third quartile] are reported. Categorical data are described with absolute and relative frequencies. Based on a logistic regression model (global test of no regression) baseline variables were simultaneously compared between the two groups.

Differences in procedural data were analyzed with a linear mixed model. Freedom from atrial arrhythmia recurrence was estimated with the Kaplan-Meier method. Differences in recurrence-free survival were analyzed with the log-rank test. All p-values were two-sided and a p-value < 0.05 was considered statistically significant. All calculations were performed with the statistical analysis software R (R Core Team, 2019).

Results

Patients

A total of 195 patients with symptomatic paroxysmal (n = 136) or persistent AF (n = 59) underwent PVI with the 28-mm second-generation CB. Ablation procedures were either performed in SR (n = 147) or during AF (n = 48). Persistent AF was more prevalent in the AF group than in the SR group (62% vs. 20%). All other baseline patient characteristics did not differ between the two groups (Table 1).

Procedural characteristics

In 193/195 patients, all PV were successfully isolated, while in 2 patients of the SR group both right inferior PV and one right superior PV were not isolated due to the occurrence of PNP. The nadir temperature during the freeze cycle applications was significantly lower in patients treated during AF than in patients treated in SR (–49 [IQR, –44; –54]°C vs. –47 [–42; –52]°C, p = 0.002). Median procedure and fluoroscopy times as well as the

Table 1. Baseline patient characteristics.

Characteristics	SR group (n = 147)	AF group (n = 48)
Age [years]	63 [54;70]	66 [55;71]
Male gender	92 (63)	33 (69)
Paroxysmal AF	118 (80)	18 (38)
Persistent AF	29 (20)	30 (62)
CHA_2DS_2-VASc score:		
0	28 (19)	8 (17)
1	37 (25)	8 (17)
2	37 (25)	14 (29)
3	32 (22)	11 (23)
4	8 (5)	5 (10)
5	5 (3)	2 (4)
BMI [kg/m^2]	28 ± 5	27 ± 4
LA diameter [mm]	42 ± 5	45 ± 5
LVEF < 50%	9 (6)	3 (6)
Coronary artery disease	17 (12)	6 (12)
Diabetes mellitus	17 (12)	5 (10)
COPD	9 (6)	2 (4)
Smoker	19 (13)	5 (10)
Arterial hypertension	91 (62)	29 (60)

Values are mean ± standard deviation, median [first quartile; third quartile], or number (%). Presence of persistent atrial fibrillation differ in the two groups. No difference was revealed considering the remaining characteristics (test of no regression: p = 0.713). AF — atrial fibrillation; BMI — body mass index; COPD — chronic obstructive pulmonary disease; LA — left atrium; LVEF — left ventricular ejection fraction; SR — sinus rhythm

rate of time-to-isolation recordings did not differ between the two cohorts. Procedural parameters are given in Table 2.

Periprocedural complications

Procedural complications were two cardiac tamponades requiring pericardiocentesis, an arteriovenous fistula and two groin hematomas with conservative treatment each. PNP occurred in 3 patients resulting in absence of PVI in two right inferior PV and one right superior PV as stated previously. In 1 patient all PV were successfully isolated at the time of PNP. No atrio-esophageal fistula, no symptomatic PV stenosis, no stroke and no procedure-related deaths were observed.

Repeat ablation procedures

Repeat ablation for the treatment of atrial arrhythmia recurrence following the index CB procedure was performed in 60 patients (SR group: 44 [30%] patients; AF group: 16 [33%] patients). Procedures were exclusively performed with the use of RFC guided by 3-dimensional mapping. All patients showed electrical reconnection of at least one initially isolated PV. All PV were successfully re-isolated. There was a trend towards a lower rate of PV reconnections in the AF group without being statistically significant (p = 0.07). Characteristics of PV reconnections during repeat ablation procedures are given in Table 2.

Clinical follow-up

In the SR and the AF group, 1-, 2- and 3-year estimated arrhythmia-free survival was 78% and 75%, 64% and 69%, and 57% and 57%, respectively. The log-rank test did not indicate a significant difference in arrhythmia-free survival between the groups (p = 0.8). Recurrence-free survival is bshown in Figure 1.

Discussion

Main findings

According to available research, the current study represents the first analysis investigating the impact of the intraprocedural heart rhythm during CB-based PVI on procedural characteristics and clinical outcomes. The main findings are: 1) significant lower nadir CB temperatures in patients undergoing PVI during AF than in patients being treated in SR; 2) a trend towards improved durability of PVI performed during AF; and 3) no influence of the basic rhythm on procedure and fluoroscopy times as well as the rate of time-to-isolation recordings during PVI. The 3-year arrhythmia-free survival did not differ between the two groups.

Key factors on efficacious CB ablation

Over the last decade, CB ablation aiming at PVI has become an established treatment for AF. During this time, several predictors of freedom from recurrence of AF and permanent PVI have been identified. As such, the time to PVI (confirmed by real-time recordings), the thaw time, and the nadir temperature of the CB impact PVI durability [8, 14–16]. Each of these parameters represents a surrogate of the balloon-tissue contact and energy transfer, which is still the most relevant aspect in creating durable, transmural cryolesions. The present study provides new insights into the impact of the intraprocedural heart rhythm on procedural parameters and clinical outcomes of CB ablation. One important result is the significantly lower nadir CB temperature in the AF group indicating that the reduced atrial contractility during AF is beneficial for balloon-tissue contact and en-

Table 2. Procedural data.

Characteristics	SR group (n = 147)	AF group (n = 48)	P
Total procedure time [min]	130 [110; 152]	135 [120; 145]	0.497
Fluoroscopy time [min]	18 [14; 25]	20 [16; 24]	0.364
Nadir balloon temperature [°C]:	–47 [–42; –52]	–49 [–44; –54]	0.002
RSPV	–50 [–44; –53]	–52 [–48; –55]	
RIPV	–46 [–41; –49]	–48 [–43; –54]	
LSPV	–47 [–42; –52]	–50 [–43; –56]	
LIPV	–44 [–41; –49]	–48 [–43; –52]	
LCPV	–55 [–47; –59]	–47 [–45; –51]	
Real-time PVI recording:	182 (31)	59 (30)	0.950
RSPV	48 (33)	18 (38)	
RIPV	40 (28)	10 (21)	
LSPV	48 (34)	16 (33)	
LIPV	41 (29)	14 (29)	
LCPV	5 (38)	1 (25)	
PV with electrical reconnection*:	100 (57)	26 (41)	0.070
RSPV	23 (52)	8 (50)	
RIPV	28 (64)	10 (62)	
LSPV	23 (55)	3 (19)	
LIPV	24 (57)	5 (31)	
LCPV	2 (100)	–	

Values are median [first quartile; third quartile], or number (%). *Reconnections of the pulmonary veins were assessed in the 60 patients who underwent repeat pulmonary vein isolation because of recurrent atrial arrhythmia. AF — atrial fibrillation; LCPV — left common pulmonary vein; LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; PV — pulmonary vein; PVI — pulmonary vein isolation; RIPV — right inferior pulmonary vein; RSPV — right superior pulmonary vein; SR — sinus rhythm

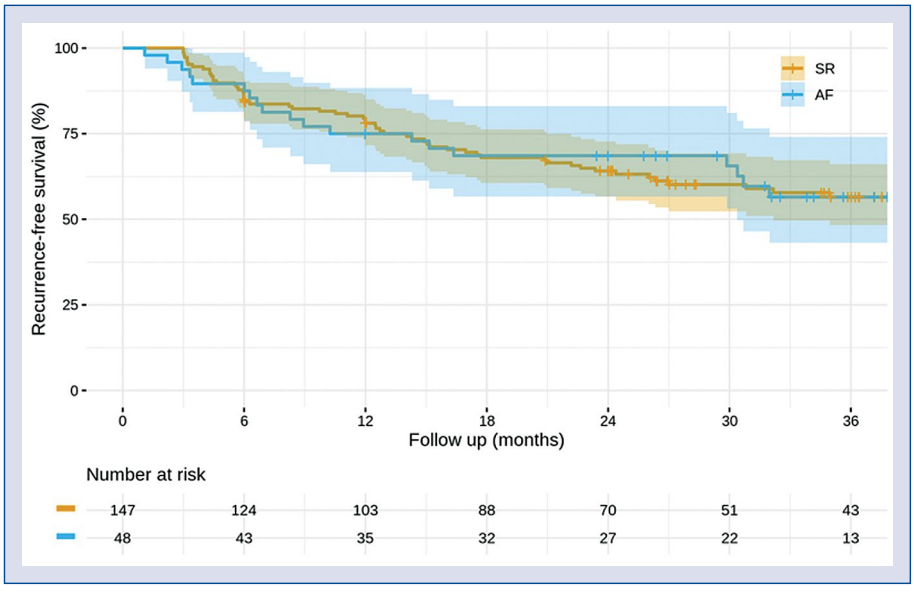

Figure 1. Freedom from atrial arrhythmia recurrence after cryoballoon ablation performed in sinus rhythm (SR; orange curve) or during atrial fibrillation (AF; blue curve). The log-rank test revealed no significant difference in arrhythmia-free survival between the groups (p = 0.8).

ergy transfer, respectively. The second-generation CB features a refrigerant injection system that provides homogeneous cooling of the entire distal hemisphere of the CB. Temperature monitoring of the CB is realized via a thermocouple located inside the balloon. Reduced atrial contractility during AF seems to enhance adherence of the CB to the atrial myocardium. As a result, the surrounding blood flow, which results in a competing warming of the balloon, is reduced. This allows for lower nadir CB temperatures and, thereby, for more effective CB applications. Accordingly, patients in the AF group appear to be at a lower risk for PV reconnection. Interestingly, data on the impact of the intraprocedural heart rhythm during point-by--point RFC ablation are inconsistent [17, 18]. It is conceivable that atrial contractility might play a greater role in "single-shot" CB ablation. During the first phase of the freeze cycle adherence of the balloon to the myocardium is essential for effective energy transfer to the tissue. The reduced atrial contractility during AF appears to support this process. Point-by-point RFC ablation is more complex and anatomic locations, e.g., the anterior or posterior aspect of the PV as well as individual anatomic variations, might pose a greater impact as compared to the relatively simple use of the CB.

Another relevant finding is that real-time recordings and proof of the occurrence of PVI is not hampered by performing CB ablation during AF. Real-time assessment of PVI is essential when applying time-to-isolation guided ablation protocols that pave the way for shorter procedure times without compromising procedural efficacy and safety [9, 19]. Aryana et al. [8] demonstrated that isolation of the PV within the first 60 s of the freeze-cycle is associated with a high durability of PVI. Therefore, the time to isolation provides one of the most powerful predictors of effective CB ablation [8].

Arrhythmia free-survival

In the current study, arrhythmia-free survival was not different between patients undergoing CB-based PVI during AF or in SR. A low nadir CB temperature is associated with a very high likelihood of durable PVI; however, our findings noted a significantly lower nadir CB temperature and a trend towards a higher durability of PVI in the AF group did not result in improved arrhythmia-free survival. The underlying causes might be multifactorial. First, a higher number of patients than provided in our analysis might be needed to demonstrate improved freedom from AF. Second, the prevalence of persistent AF was markedly higher in the AF group, and, as the experiences of previous studies have shown, results of catheter ablation for persistent AF are less successful than for paroxysmal AF [20–22]. Taking this into account, the similar arrhythmia-free survival in both groups is a positive result for the AF group.

Noteworthy, none of the 60 patients undergoing repeat ablation of AF showed permanent isolation of all PV underlining the impact of recovered PV conduction as one of the main drivers for recurrence of AF following PVI [23]. Yet, the rate of durable PVI was unexpected low at the time of repeat ablation, since previous studies reported on a proportion of patients with permanent isolation of all PV following CB ablation of 15% [6], 22% [24], and 53% [25]. However, even if these data were more convincing, durability of PVI is still not yet satisfactory. The implementation of the CB has led to greater availability of AF ablation, better reproducibility of clinical outcomes [26], and improved lesion characteristics as compared to RFC ablation [27], but the high proportion of reconnected PV demands further efforts ensuring permanent PVI following the index procedure. It also needs to be taken into consideration that only patients with symptomatic AF-recurrences were included in the study. It can be speculated that the proportion of durably isolated PVs is higher in patients without AF recurrences.

Limitations of the study

The current study is an observational, non--randomized analysis. The mode of the follow-up might have resulted in an overestimation of freedom from atrial arrhythmia recurrences. A sufficiently powered randomized comparison is mandatory before final conclusions can be drawn.

Conclusions

In this observational study, the performance of CB-based PVI during AF resulted in lower nadir CB temperatures and a trend towards higher durability of PVI when compared to procedures performed in SR. The rate of real-time PVI recording was not affected by the intraprocedural rhythm. In accordance to the present findings, in CB ablation, electrical cardioversion of AF should be performed once PVI has been obtained.

Conflict of interest: Andreas Metzner received speaker honoraria and travel grants from Medtronic. Andreas Rillig received travel grants from

Biosense Webster, Hansen Medical, Medtronic, EPSolutions and St. Jude Medical and lecture fees from St. Jude Medical, Medtronic and Boehringer Ingelheim, consultant fees from Medtronic and took part at the Boston Scientific EP fellowship. Bruno Reissmann and Christian-H. Heeger received travel grants from Medtronic. Karl-Heinz Kuck received research grants from Medtronic and speaker bureau's honoraria from Biosense Webster, Impulse Dynamics, and Biotronik. Doreen Schöppenthau received travel grants from St. Jude Medical, Bristol-Myers-Squibb and Biosense Webster, a research grant from Biosense Webster and took part in the Boston scientific EP fellowship program.

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