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ORIGINAL PAPER

Two-year outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon: lessons from the bonus freeze protocol

Andreas Metzner[1] · Christian-Hendrik Heeger[1] · Peter Wohlmuth[1] · Bruno Reißmann[1] · Andreas Rillig[1] · Roland Richard Tilz[1] · Shibu Mathew[1] · Christine Lemes[1] · Sebastian Deiß[1] · Tilman Maurer[1] · Ardan Saguner[1] · Feifan Ouyang[1] · Karl-Heinz Kuck[1] · Erik Wißner[1]

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Abstract
Background Pulmonary vein isolation (PVI) using the second-generation cryoballoon (CB2) in patients with paroxysmal and persistent atrial fibrillation (AF) has demonstrated encouraging acute and mid-term results. Follow-up data on outcome beyond 1-year is lacking. The purpose of this analysis was to investigate the 2-year clinical outcome after CB2-based PVI.
Methods Sixty patients (age 62 ± 11 years) with paroxysmal [45/60 (75 %) patients] or short-standing persistent AF [15/60 (25 %) patients] underwent 28-mm CB2-based PVI. Freeze-cycle duration was 240 s. After successful PVI, a bonus freeze-cycle of the same duration was applied. Follow-up was based on outpatient clinic visits at 3, 6, 12, 18, and 24 months including 24 h Holter-ECGs and telephone interviews. Recurrence was defined as any symptomatic and/or documented atrial tachyarrhythmia (ATA) episode >30 s following a 3-month blanking period.
Results A total of 231 pulmonary veins (PV) were identified and 230/231 (99.6 %) PVs were successfully isolated. Phrenic nerve palsy occurred in 2/60 (3.3 %) patients. No other periprocedural complications occurred. Follow-up was available for 59/60 (98 %) patients with a mean duration of 838 ± 67 days. A total of 43/59 (73 %) patients remained in stable sinus rhythm. In 10/16 (63 %) patients with ATA recurrence, a repeat procedure was performed using radiofrequency energy. The overall success rate after a maximum of two ablation procedures and a follow-up period of 838 ± 67 days was 88 % (52/59) patients.
Conclusions Patients with paroxysmal or short-persistent AF undergoing PVI using the 28-mm CB2 demonstrated a 73 % 2-year single-procedure clinical success rate.

Keywords Atrial fibrillation · Pulmonary vein isolation · Cryoballoon · Long-term follow-up

Introduction

The second-generation cryoballoon (CB2, Arctic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) used for pulmonary vein isolation (PVI) has demonstrated high acute success rates and excellent 1-year clinical outcome data [1]. Applying different ablation protocols with and without a bonus freeze-cycle and different freeze-cycle durations in patients with paroxysmal atrial fibrillation (PAF), the 1-year clinical success rates after a single ablation procedure range from 80 to 84 % [2–6]. Furthermore, in patients with persistent atrial fibrillation (PersAF), 1-year clinical success rates up to 69 % have been reported [7–9]. The encouraging clinical outcome is based on a high rate of durable PVI in 91 % of PVs at 3.1 months and 77 % of PVs at 6 months, respectively [10, 11]. However, there is paucity of data on the clinical outcome beyond 1 year of follow-up. The current study reports the two-year clinical outcome following CB2-based PVI in patients with PAF and short-standing PersAF.

A. Metzner and C.-H. Heeger contributed equally.

✉ Andreas Metzner
AndreasMetzner1@web.de

[1] Department of Cardiology, Asklepios Klinik St. Georg, Lohmühlenstr. 5, 20099 Hamburg, Germany

Methods

Inclusion and exclusion criteria

Consecutive patients with documented (12-lead ECG, Holter monitoring, or pacemaker/ICD) symptomatic, drug-refractory PAF or short-standing PersAF (duration ≤3 months) were consented for CB2-based PVI. Exclusion criteria were prior left atrial (LA) ablation attempts, LA diameter >60 mm, severe valvular heart disease, or contraindications to postinterventional oral anticoagulation. Transesophageal echocardiography was performed prior to PVI to rule out intracardiac thrombi and to assess the LA diameter. No further pre-procedural imaging was performed. All patients gave written informed consent and all patient information was anonymized. All data were evaluated retrospectively. The study was approved by the local ethical review board.

Intraprocedural management

The intraprocedural management has previously been reported [2, 3]. In brief, the procedure was performed under deep sedation using midazolam, sufentanyl, and propofol. Prior to transseptal puncture, one diagnostic catheter was introduced via the right femoral vein and positioned within the coronary sinus (7F, Webster TM, Biosense Webster, Inc.). Single transseptal puncture was performed under fluoroscopic guidance using a modified Brockenbrough technique and an 8.5F transseptal sheath (SL1, St. Jude Medical, Inc., St. Paul, MN, USA). Subsequently, selective PV angiography was performed in all patients to identify the individual pulmonary vein (PV) ostia. The transseptal sheath was exchanged over a guidewire for a 12F steerable sheath (Flexcath Advance, Medtronic). After transseptal puncture, heparin boluses were administered targeting an activated clotting time of >300 s. A temperature probe (Sensitherm, St. Jude Medical) was placed within the esophagus at the level of the individual CB2 position to monitor esophageal temperatures during the freeze-cycle. The intraluminal esophageal temperature cut-off was set at 10 °C [12].

Pulmonary vein isolation using the 28-mm CB2

The 28-mm CB2 was advanced into the LA via the 12F steerable sheath using a spiral mapping catheter (20 mm diameter; Achieve™, Medtronic) for guidance. The balloon was inflated proximal to the PV ostium followed by gentle push aiming for complete sealing at the antral aspect of the target PV. Contrast injected through the central lumen was used to verify complete occlusion of the PV ostium. This was followed by at least one freeze-cycle of 240 s. After successful PVI, one additional bonus freeze-cycle of 240 s duration was applied [2]. The procedural endpoint was defined as persistent PVI verified by spiral mapping catheter recordings 30 min after the last CB2 application.

Phrenic nerve pacing

During energy delivery along the septal PVs, continuous PN pacing was performed using a diagnostic catheter positioned within the superior vena cava (7F, Webster TM, Biosense Webster, Inc.). Pacing was set at maximum output and pulse width (12 mA, 2.9 ms) and a cycle length of 1200 ms. PN capture was monitored by tactile feedback of diaphragmatic contraction. Energy delivery was stopped immediately in case of weakening or loss of diaphragmatic movement. In case of PN palsy, no further cryoenergy was delivered along the septal PVs [13, 14].

Postprocedural care

Following ablation, all patients underwent transthoracic echocardiography to rule out pericardial effusion. All patients were treated with proton-pump inhibitors (40 mg twice daily) for 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 achieved. The new oral anticoagulants were reinitiated 6 h post ablation. Anticoagulation was continued for at least 3 months and continued thereafter based on the individual CHA_2DS_2-VASc score. Previously, ineffective antiarrhythmic drugs were continued for 3 months [2, 3].

Repeat procedures

In patients admitted for a repeat procedure due to ATA recurrence, an electroanatomical LA map (Carto 3™, Biosense Webster, Inc., Diamond Bar, CA, USA) was generated and the PV ostia tagged on the map. Persistent PVI or electrical reconduction of previously isolated PVs was assessed by the presence or absence of electrical activity inside each PV using a spiral mapping catheter (Lasso™, Biosense-Webster). Identified gaps were closed by radiofrequency (RF) ablation using a 3.5-mm irrigated-tip catheter (Biosense Webster, NaviStar Thermocool). In patients demonstrating persistent isolation of all PVs admitted in sinus rhythm, fractionated ostial potentials along previously performed ablation lines were identified and ablated and/or linear lesion sets were applied. In patients admitted in AF and all PVs isolated, ostial potentials were identified and ablated followed by ablation of complex fractionated atrial electrograms (CFAE) and deployment of linear lesion sets if AF converted to an AT [15–17].

Follow-up

Following a blanking period of 3 months, patients completed outpatient clinic visits either at our hospital or at the referring physician at 3, 6, 12, 18, and 24 months including 24 h Holter-ECGs. In addition, regular telephone interviews were performed. Additional outpatient clinic visits were scheduled in case of symptoms suggestive of recurrent ATA [2, 3].

Endpoints

The primary endpoint was defined as recurrence of any symptomatic and documented ATA episode >30 s following a blanking period of 3 months. Secondary endpoints included procedure-related complications such as pericardial tamponade, PN palsy, stroke, or atrioesophageal fistula [2, 3].

Statistical analysis

Continuous data are shown as mean and standard deviation in case of normally distributed values and as median, interquartiles, minimum, and maximum otherwise. Categorical data were described with absolute and relative frequencies. Survival curves were generated with the Kaplan–Meier technique. Cox proportional-hazards models were applied to assess the effect of potential risk factors on ATA recurrence. Associations between the covariates and survival were described with hazard ratios and 95 % confidence intervals. All calculations were performed using SAS (version 9.3, SAS Institute, Inc., Cary, NC, USA) [3].

Results

Patient characteristics

A total of 60 patients [36 male (60 %), mean age 62 ± 11 years, mean LA diameter 43 ± 5 mm] with a history of PAF [45/60 (75 %) patients] or PersAF [15/60 (25 %) patients] underwent 28-mm CB2-based PVI. Baseline characteristics are presented in Table 1. Patient sub-cohorts of the current analysis were previously evaluated for their one-year clinical outcome after CB2-based ablation (2, 9).

Table 1 Baseline characteristics

Patients, *n*	60
Age (years)	62 ± 11
Male gender, *n* (%)	36 (60)
LA size (mm)	43 ± 5
Paroxysmal AF, *n* (%)	45 (75)
Short-term persistent AF, *n* (%)	15 (25)
Duration of AF (months)	38 ± 31
Left ventricular ejection fraction (%)	64 ± 4
Hypertension, *n* (%)	42 (70 %)
Coronary artery disease, *n* (%)	6 (10 %)
Diabetes mellitus, *n* (%)	8 (13)
Mean CHA_2DS_2-VASc score	2.0 ± 1.4

Values are mean ± SD or *n* (%) as appropriate

LA left atrium, *AF* atrial fibrillation

Acute ablation results

In 60 patients, 231 PVs were identified [60 right superior PVs (RSPV), 60 right inferior PVs (RIPV), 51 left superior PVs (LSPV), 51 left inferior PVs (LIPV), and 9 left common PVs (LCPV)]. A total of 230/231 (99.6 %) PVs were successfully isolated using the 28-mm CB2. Due to PN paralysis during energy application along the RSPV, 1/60 (1.7 %) ipsilateral RIPVs was not targeted. During the first CB-application, electrical PVI was achieved in 55/60 (92 %) RSPVs, 50/60 (83 %) RIPVs, 45/51 (88 %) LSPVs, 51/51 (100 %) LIPVs, and in 4/9 (44 %) LCPVs, respectively. The mean number of CB2 applications resulting in PVI was 1.1 ± 0.5, 1.3 ± 0.6, 1.1 ± 0.4, 1.0 ± 0, and 1.4 ± 0.5 for the RSPV, RIPV, LSPV, LIPV, and LCPV, respectively. A bonus freeze-cycle was applied after successful PVI. The mean total number of CB applications was 2.2 ± 0.6, 2.2 ± 0.7, 2.1 ± 0.4, 2.0 ± 0, and 2.4 ± 0.5 for the RSPV, RIPV, LSPV, LIPV, and LCPV, respectively (Table 2). Mean procedure duration was 138 ± 29 min including a waiting period of 30 min. The mean fluoroscopy time was 24 ± 8 min.

Peri- and postprocedural complications

PN palsy occurred in 2/60 (3.3 %) patients during energy delivery targeting the RSPV. In both instances, PN function recovered after up to 10 months during FU. No pericardial effusion, pericardial tamponade, symptomatic PV stenosis, stroke, or atrioesophageal fistula was observed.

Clinical follow-up

Clinical follow-up was obtained in 59/60 (98.3 %) patients, while 1/60 (1.7 %) patient was lost to follow-up. After a mean follow-up duration of 838 ± 67 days including a 3-month blanking period, 43/59 (73 %) patients [33/45 (73 %) patients with PAF, 10/14 (71 %) patients with

Table 2 Acute ablation results and periprocedural data

	RSPV	RIPV	LSPV	LIPV	LCPV
Number of PVs, *n*	60	60	51	51	9
Isolated PVs, *n* (%)	60/60 (100)	59/60 (98)	51/51 (100)	51/51 (100)	9/9 (100)
PVI during initial CB2-application, *n* (%)	55/60 (92)	50/60 (83)	45/51 (88)	51/51 (100)	4/9 (44)
Number of CB2-applications until PVI, *n*	1.1 ± 0.5	1.3 ± 0.6	1.1 ± 0.4	1.0 ± 0	1.4 ± 0.5
Total number of CB2- applications, *n*	2.2 ± 0.6	2.2 ± 0.7	2.1 ± 0.4	2.0 ± 0	2.4 ± 0.5
Mean minimal CB2- temperature, °C	−52.2 ± 6	−50.6 ± 6	−51.3 ± 6	−49.6 ± 7	−54.3 ± 8
Mean minimal eso temperature, °C	34.8 ± 2	31.2 ± 8	32.1 ± 6	25.8 ± 15	28.9 ± 9
Mean time to PVI, s	59.3 ± 40	57.5 ± 42	40.9 ± 14	37.3 ± 20	74.3 ± 39

Values are mean ± SD or *n* (%) as appropriate

PV pulmonary vein, *PVI* PV isolation, *CB2* second-generation cryoballoon, *eso* esophageal, *RSPV* right superior PV, *RIPV* right inferior PV, *LSPV* left superior PV, *LIPV* left inferior PV, *LCPV* left common PV

PersAF] remained in stable sinus rhythm (Fig. 1). An ATA recurrence was observed in 16/59 (27 %) patients [12/45 (27 %) patients with PAF, 4/14 (29 %) patients with PersAF]. Seven out of 16 (44 %) patients presented with PAF, 6/16 (38 %) patients with PersAF, and 3/16 (19 %) patients with AT. Following a 3-month blanking period, 18/59 (31 %) patients were still on ß-blockers, 8/59 (14 %) patients on flecainide, 1/59 (2 %) patients on dronedarone, and another 3/59 (5 %) patients on amiodarone. In total, 10/16 (63 %) patients with ATA recurrence were remained on antiarrhythmic drug treatment. Analyzing the patients' baseline characteristics (sex, age, LA size, diabetes mellitus, left ventricular ejection fraction, hypertension, coronary artery disease, duration of AF, PAF, PersAF), no statistically significant predictors for ATA recurrence were identified.

Findings during repeat procedures

A total of 10/16 (63 %) patients suffering from ATA recurrence [4/10 (40 %) PAF, 3/10 (30 %) PersAF, 3/10 (30 %) AT] underwent a repeat RF-based ablation procedure after a mean of 263 ± 164 days following the index procedure. Of 39 identified PVs, LA-to-PV reconduction was demonstrated in 14 PVs (36 %), while persistent PVI was documented in 25/39 (64 %) PVs. In 2/10 (20 %) patients, all PVs were still isolated. LA-to-PV reconduction of a single PV was noted in 2/10 (20 %) patients, whereas two recovered PVs were identified in 6/10 (60 %) patients. None of the patients demonstrated electrical reconduction of 3 or all PVs. LA-to-PV reconduction was demonstrated in 1/10 (10 %) RSPVs, 4/10 (40 %) RIPVs, 3/9 (33 %) LSPVs, 5/9

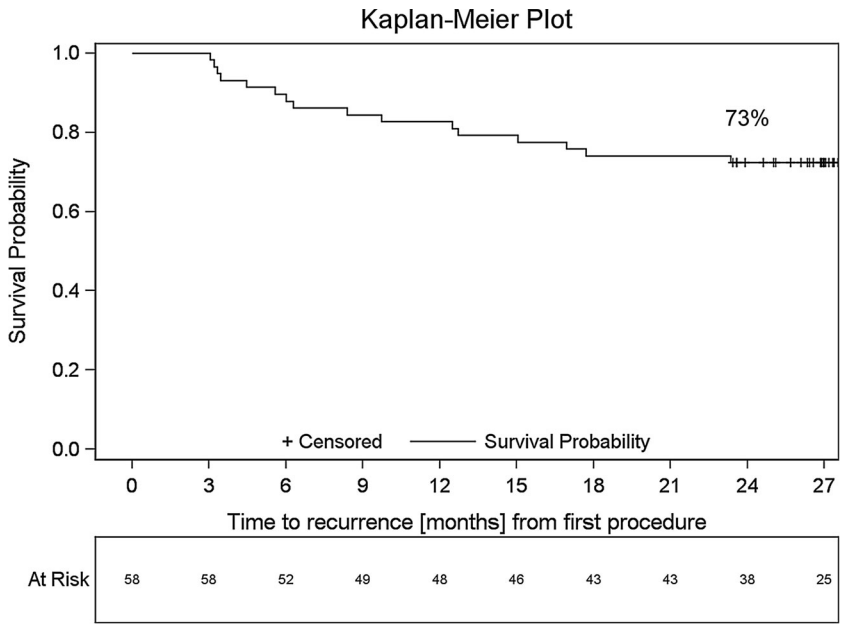

Fig. 1 Kaplan–Meier curve. Kaplan–Meier curve demonstrating the relative proportion of patients in stable sinus rhythm following initial pulmonary vein isolation using the 28-mm second-generation cryoballoon during a mean follow-up period of 838 ± 67 days including a 3-month blanking period

(56 %) LIPVs, and 1/1 (100 %) LCPVs. In 7/8 (88 %) patients with LA-to-PV reconduction, a detailed description of the location of each gap was provided, while in 1/8 (13 %) patient the exact location of the electrical gap was not assessed. In total, 14 reconduction gaps were identified in 7 patients and distributed as shown in Fig. 2. Re-isolation of all PVs was successfully performed in 8/8 (100 %) patients using RF energy. In addition, ablation of ostial potentials was performed in 2/8 (25 %) patients. Linear lesions were deployed in 3/8 (38 %) patients with AT (1 mitral isthmus line, 2 anterior lines, 1 roof line). No CFAE ablation was performed. In 2/10 (20 %) patients with persistent isolation of all PVs and admission in sinus rhythm, ostial potentials were targeted in both patients, while an additional anterior line was performed in 1 patient. Ablation of the right cavotricuspid isthmus was performed in 1/10 (10 %) patients due to documented typical cavotricuspid-dependent atrial flutter. Mean procedure and fluoroscopy time was 140 ± 56 and 19 ± 9 min, respectively. No complications occurred. After a mean follow-up of 567 ± 182 days following the repeat procedure, 9/10 patients (90 %) were in stable sinus rhythm. In summary, 52/59 (88 %) patients remained in stable sinus rhythm after a mean follow-up of 838 ± 67 days and a maximum of one repeat ablation procedure.

Discussion

The current study is the first to report 2-year clinical outcome in patients with PAF and/or short-standing PersAF undergoing CB2-based PVI. The present study found that the 2-year single-procedure clinical success rate was 73 % (73 % for PAF, 71 % for PersAF), while the overall success rate reached 88 % if including a single RF-based repeat procedure.

Clinical outcome after cryoballoon-based PVI

Previous studies utilizing the CB2 and a freeze-cycle duration of 240 s followed by a single bonus freeze reported a 1-year freedom from recurrent ATA of 82 and 84 % [2, 4]. Recently, two studies demonstrated that omitting the customary bonus freeze-cycle resulted in a 1-year success rate of 82 and 80 %, respectively [3, 6]. Of note, the latter study used a shortened freeze-cycle duration of 3 min. Encouraging results following PVI using the CB2 ablation in patients with PersAF were reported by Ciconte et al. and Lemes et al. with 60–69 % of patients in stable sinus rhythm after 1 year [7, 9]. Whether these encouraging 1-year success rates would translate into a high rate of stable sinus rhythm beyond 1 year had yet to be evaluated. In the present study, the 2-year single-procedure success

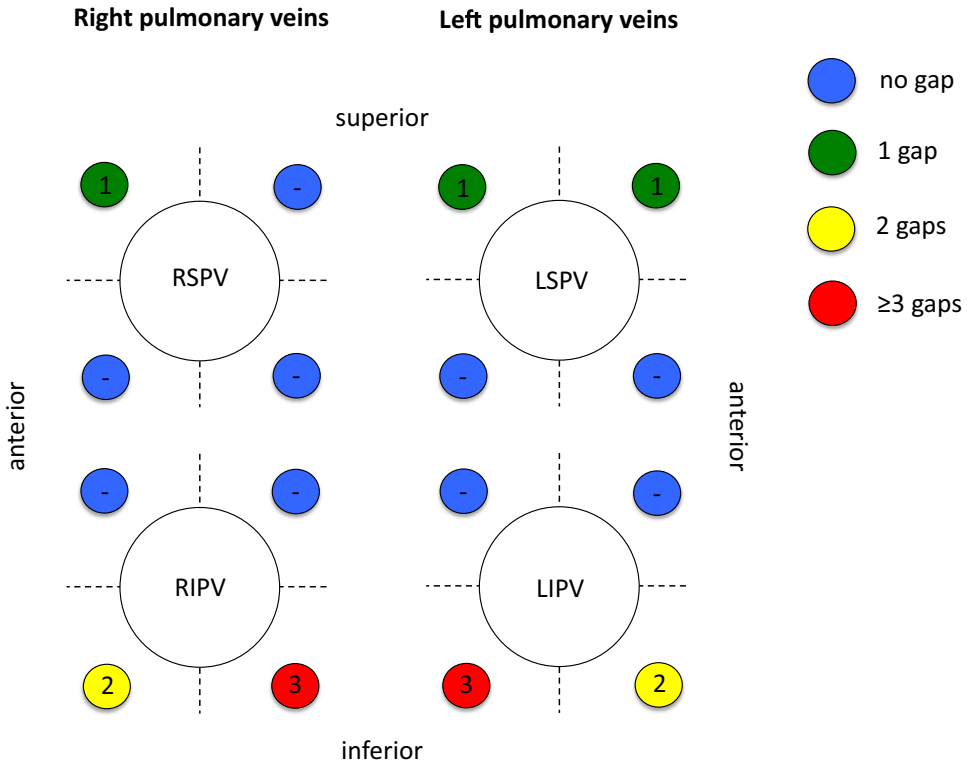

Fig. 2 Location of electrical reconduction gaps. Septal and lateral pulmonary vein ostia are divided into four segments (antero-superior, antero-inferior, postero-superior, postero-inferior). *Numbers* express the number of reconduction gaps found for each segment. No gaps were found along the carina between the ipsilateral pulmonary veins. Data for a single left common pulmonary vein ($n = 1$, with $n = 1$ posterior-superior gap) is not shown. *RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein, *LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein

rate was 73 % (73 % in patients with PAF and 71 % in patients with PersAF) underscoring the continued benefits of CB2-based PVI in patients followed more than 1 year.

Critical role of durable PVI

The CB2 uses a modified refrigerant injection system offering improved cooling characteristics over the first-generation device. The improved cooling characteristics directly translate into a higher rate of durable PVI as noted in two different studies. While in the first study all PVs were reassessed after a mean of 3.1 months irrespective of the clinical outcome [10], the latter study performed redo procedures only in patients with recurrent ATA after a mean follow-up period of 6 months [11]. In the former study, persistent isolation was noted in 91 % of previously isolated PVs, and in the latter study the rate was 77 %. The high rate of durable PVI may serve as one explanation for the convincing 1-, and 2-year clinical efficacy of the CB2. The present study supports the above-mentioned studies demonstrating a 64 % rate of persistent PVI during redo procedures.

Approach to redo procedures after CB2-based PVI

In patients admitted for a redo procedure due to ATA recurrence, the majority of PVs prove to be persistently isolated, while in 30 % of patients no electrical PV reconnection into any PV will be found. In non-isolated PVs, electrical conduction gaps are commonly identified at the superior aspect of the superior PVs and the inferior aspect of the inferior PVs. The predilection for these particular locations may be due to suboptimal CB2 contact and limited energy transfer to these regions during the index PVI. As noted in the present study, in most patients PV conduction gaps are easily targeted deploying a limited number of RF applications. However, the optimal ablative strategy in the setting of persistent isolation of all PVs and AF recurrence will need further evaluation in future studies.

Future perspective

The herein presented clinical 2-year outcome is based on an ablation protocol utilizing a 240-s freeze-cycle followed by a bonus freeze-cycle of the same duration once successful PVI is accomplished. By contrast, no long-term follow-up data are available for patients treated with a protocol applying a shorter freeze-cycle duration or foregoing the bonus freeze-cycle. Yet, a strategy aiming to reduce the overall energy delivery during CB2-based PVI may be particularly attractive if comparable acute and long-term outcome is maintained. Limiting ablation times may translate in shorter procedure duration, while improving the safety profile of the procedure. As known from previous studies, the endoluminal esophageal temperature is lowest towards the end of the freeze-cycle [12]. Limiting the freeze-cycle duration or reducing the number of freeze-cycles per PV may help to lower the incidence of esophageal thermal injury. Similarly, PN damage, a characteristic balloon-associated complication, is observed more frequently at the later stage of the freeze-cycle or during the bonus freeze [13]. Consequently, a shorter freeze-cycle duration may prove beneficial to further reduce the risk of PN palsy.

Limitations

The current study is a retrospective analysis based on a single-center experience enrolling a limited number of patients. Follow-up was based on 24 h Holter-ECGs at predefined intervals of 3, 6, 12, 18, and 24 months post PVI and may overestimate the success rate. Closer follow-up (e.g., via implantable loop recorders) may have detected a higher number of ATA recurrences.

Conclusions

The single-procedure 2-year success rate after PVI using the 28-mm CB2 was 73 %. Future studies will have to evaluate outcome beyond 1-year for protocols forgoing a bonus freeze-cycle or utilizing a shorter freeze-cycle.

Compliance with ethical standards

Conflict of interest A. Metzner received speaker's honoraria from Medtronic. E. Wissner received speaker's honoraria from Medtronic and is a member of Medtronic's advisory board. K.-H. Kuck received a Research Grant and speaker's honoraria from Medtronic. All other authors have no relevant disclosures.

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