Clinical Research in Cardiology (2018) 107:570–577
https://doi.org/10.1007/s00392-018-1219-1

ORIGINAL PAPER

Safety and efficacy of persistent atrial fibrillation ablation using the second-generation cryoballoon

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Received: 17 December 2017 / Accepted: 19 February 2018 / Published online: 28 February 2018

Abstract
Background The second-generation cryoballoon (CB) is increasingly used for treatment of persistent atrial fibrillation (AF). Data regarding the clinical outcome and mechanism of arrhythmia recurrence following persistent AF ablation using CB is sparse. In this study, we aimed to assess the efficacy of CB and mechanisms of atrial tachyarrhythmia (ATA) recurrence in patients with persistent AF.
Methods and results A total of 133 patients (66 ± 10 years, 60% male) with symptomatic persistent AF, who were scheduled for PVI using the second-generation CB were enrolled. Follow-up included 24 h Holter recording at 3, 6 and 12 months. Any documented episode of ATA lasting more than 30 s was considered as a recurrent arrhythmic event. All targeted veins were isolated (100%). Phrenic nerve palsy with recovery during follow-up occurred in six patients (4.5%), no patient experienced tamponade or a cerebrovascular event. During 12.6 ± 5.4 months of follow-up, 89/133 (67%) patients were free of ATA recurrences. Multivariable analysis revealed recurrence in the blanking period (HR 11.46, 0.95 CI 3.92–33.49, $p < 0.001$), presence of cardiomyopathy (HR 2.75, 0.95 CI 1.09–6.96, $p = 0.032$) and PV abnormality (HR 3.56, 0.95 CI 1.21–10.43, $p = 0.021$) as predictors for late recurrence.
Conclusion In patients with persistent AF, second-generation cryoballoon use is associated with an excellent safety profile and favorable outcomes. Arrhythmia recurrence during the blanking period, presence of cardiomyopathy and PV abnormality were independent predictors of long-term AF recurrence.

Keywords Persistent atrial fibrillation · Cryoballoon ablation

Abbreviations

ATA	Atrial tachyarrhythmia
AF	Atrial fibrillation
CB	Cryoballoon
CMP	Cardiomyopathy
CTI	Cavotricuspid isthmus
EHRA	European Heart Rhythm Association
ICD	Implantable cardioverter defibrillator
INR	International normalized ratio
LA	Left atrium
LCPV	Left common pulmonary vein
LIPV	Left inferior pulmonary vein
LSPV	Left superior pulmonary vein
LVEF	Left ventricular ejection fraction
PM	Pacemaker
PNP	Phrenic nerve palsy
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RIPV	Right inferior pulmonary vein
RMPV	Right middle pulmonary vein
RSPV	Right superior pulmonary vein
RF	Radiofrequency
SR	Sinus rhythm

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Introduction

Atrial fibrillation (AF) is the most common sustained chronic arrhythmia. Catheter ablation of symptomatic patients by targeting the pulmonary veins (PV) is widely used as recommended by current guidelines [1]. In recent years, cryoballoon (CB) based isolation of the PVs has an increasing trend with successful outcome especially in patients with paroxysmal AF patients [2, 3]. In patients with persistent AF, the substrate is more complex resulting in heterogeneous ablation strategies such as PV isolation as the sole ablative strategy, substrate-based ablation strategies and novel strategies such as rotor guided strategies [4–7]. PV isolation (PVI) as the sole ablative strategy using radiofrequency (RF) energy has been demonstrated to be non-inferior to more extensive ablation in persistent AF [8].

The second-generation CB (Arctic Front Advance, Medtronic) has been released with technical developments resulting in a larger and more homogeneous zone of freezing on the balloon surface, translating into significant improvements in procedural and clinical outcomes as compared with its predecessor [9, 10]. Although an increasing interest has already developed regarding the efficacy of AF ablation in patients with persistent AF, follow-up data in those patients using novel CB is limited [11–13]. In this study, we aimed to assess the efficacy of second-generation CB in patients with persistent AF and to analyze predictors of arrhythmia recurrence.

Methods

Between July 2015 and March 2017, 133 patients underwent second-generation cryoballoon ablation at the University Heart Center Luebeck for the treatment of symptomatic persistent AF. Persistent AF was defined as, continuous AF lasting for more than 7 days but less than 1 year [1]. Patients with left atrial (LA) thrombus, uncontrolled thyroid dysfunction, contraindication to anticoagulation, pregnancy, and previous AF ablation, severe valvular disease and a LA size > 60 mm were excluded. Severity of symptoms was recorded according to European Heart Rhythm Association (EHRA) score. Informed consent was taken from each patient before the procedure. The study was in compliance with the principals outlined in the Declaration of Helsinki and approved by the local Ethics Committee.

Preprocedural management

Transesophageal echocardiography was performed in all patients prior to the procedure. Apart from echocardiography, no additional preprocedural imaging was performed. In patients on vitamin K antagonists, anticoagulation was continued throughout the procedure aiming at an INR of 2–3. In patients treated with novel oral anticoagulants (NOACs), the drug was discontinued ≥ 24 h prior to the procedure and and re-initiated 6 h post-ablation at half the regular dose, and at full dose the following day.

Procedural management

All procedures were performed under deep sedation using midazolam, fentanyl, and propofol. Cryoballoon ablation procedure was performed as previously described [3]. Cavo-tricuspid isthmus ablation (CTI) using an open irrigated RF catheter (Celsius ThermoCool or ThermoCool SF, Biosense Webster Inc.) was solely performed in patients with documented or induced common type atrial flutter.

Postprocedural management

Following ablation, all patients underwent transthoracic echocardiography to rule out a pericardial effusion. All patients were treated with proton-pump inhibitors twice daily for 6 weeks. Anticoagulation was continued for at least 3 months and thereafter based on the individual CHA_2DS_2-VASC score. To prevent early recurrence, an antiarrhythmic drug was administered throughout the three months blanking period. Discontinuation of the antiarrhythmic drug was strongly recommended thereafter. Follow-up was performed either by the outpatient clinic or the referring cardiologist at 3, 6, and 12 months as well as in case of symptoms suggestive of arrhythmia recurrence and included a ≥ 24 h Holter recording and interrogations of implanted devices, if present. Symptoms suggestive of recurrent atrial tachyarrhythmia (ATA) prompted additional outpatient clinic visits. Any documented episode of ATA lasting more than 30 s were considered as recurrent arrhythmic event. Repeat ablation was offered to the patients in case of symptomatic ATA recurrence after the blanking period or symptomatic drug refractory recurrent ATA within the blanking period that could not be managed without intervention.

The primary endpoint of this study was ATA recurrence including common type flutter after a 3 months blanking period or triggering a redo ablation within the blanking period.

Secondary endpoints were complications related to the procedure, such as pericardial effusion/tamponade, PNP, cerebrovascular events, and groin complications.

Statistical analysis

Continuous data are presented as mean ± standard deviation, skewed continuous parameters were expressed as median (interquartile range defined as Q1–Q3). Categorical data were summarized as frequencies and percentages and were compared using χ^2 test. Comparisons between baseline characteristics were performed by independent Student's *t* test, Mann–Whitney rank-sum, Fisher exact, or χ^2 tests where appropriate. To analyze the association between baseline and procedural parameters on AF recurrence, binary logistic regression analysis was used. Parameters that were found to be univariately associated with the outcome and those that show a slight association with the outcome with $p<0.20$ are included in the multivariable analysis. Kaplan–Meyer and Cox regression analysis was performed to describe ATA free survival. Statistical analyses were performed using SPSS statistical software (version 22.0; SPSS Inc., Chicago, IL, USA). A 2-tailed $p<0.05$ was considered statistically significant.

Results

A total of 133 patients (66 ± 10 years, 60% male) with persistent AF including 14 patients (10.5%) with concomitant documented typical atrial flutter were included in this study. Baseline characteristics are summarized in Table 1. Cardiomyopathy (CMP) was diagnosed in 34 patients [25.6%, (23/34 nonischemic CMP, 9/34 ischemic CMP, 2/34 hypertrophic CMP)] and 19 patients (14.3%) had an implanted electrical cardiac device including pacemaker (PM, $n=9$) or implantable cardioverter defibrillator ($n=10$).

All targeted veins were isolated. Mean number of CB applications per PV and mean temperature during the procedure per PV as well as procedural characteristics are presented in Table 1. PV abnormality was observed in 21 patients (15.7%) with a left common ostium in 13 patients (9.7%) and a right middle PV in 9 patients (6.8%). Total procedural and fluoroscopy time were 107.5 ± 22.3 and 22.8 ± 10.1 min, respectively. In 14 (10.5%) patients, cryoballoon application converted atrial fibrillation to sinus rhythm and 70 (52.6%) patients required DC cardioversion.

Adverse events

Complications requiring intervention occurred in 2 (1.5%) patients (arterioveneous fistula requiring surgery).

PNP occurred in 6 (4.5%) patients during the ablation of the right sided veins. PNP resolved in 4/6 (66.6%) during the procedure, 2 days later in 1/6 (16.6%) and 12 months later in remaining 1/6 (16.6%) patient.

Other minor adverse events with spontaneous sequel occurred in four (3.0%) patients and included hematoma ($n=3$) and pericardial effusion ($n=1$) without hemodynamic compromise. No other adverse events such as significant pericardial effusion, pericardial tamponade, symptomatic PV stenosis, cerebral embolism, or atrioesophageal fistula were noted.

Clinical follow-up

Twenty-five (19%) patients had early recurrence of ATA within the first 3 months after index CB ablation. After a mean follow-up period of 12.6 ± 5.4 months, single procedure success rate including a 3 months blanking period was 67% (Fig. 1). Our institutional approach strongly recommends discontinuation of AAD after blanking period. After blanking period, in 125/133 (93.9%) patients, AAD was discontinued. 3/44 (6.8%) patients in the ATA recurrence group and 5/89 (5.6%) patients with no ATA recurrence continued to take AAD, due to either patient's preference or referring physician's preference ($p=0.78$). Freedom of AAD at 12th month follow-up was 111/133 (83.4%). 29/44 (65.9%) of patients with ATA recurrence and 82/89 (92.1%) of patients without recurrence ($p=0.001$) were free of AAD at 12-month visit.

Univariate analysis demonstrated that in patients with ATA recurrence, the LA diameter was larger (44.6 ± 5.7 vs 41.2 ± 6.5 mm, $p=0.004$), LVEF was lower (48.6 ± 10.0 vs 51.8 ± 7.7, $p=0.04$), LIPV diameter was larger (14.6 ± 2.6 vs 13.6 ± 2.7 mm, $p=0.04$) as compared to the remaining patients. Also, presence of cardiomyopathy (17/44 vs 17/89, $p=0.02$), PV abnormality (11/44 vs 10/89, $p=0.047$) and arrhythmia recurrence during blanking period (19/44 vs 6/89, $p<0.001$) were more common in patients with ATA recurrence (Table 1). After multivariate analysis, presence of early recurrence within the blanking period (HR 11.46, 0.95 CI 3.92–33.49, $p<0.001$), presence of cardiomyopathy (HR 2.75, 0.95 CI 1.09–6.96, $p=0.032$) and PV abnormality (HR 3.56, 0.95 CI 1.21–10.43, $p=0.021$) solely remained as independent predictors of late recurrence (Fig. 2, Supplement).

A total 29 of 44 (66%) patients underwent redo ablation for recurrent ATA. In 8 (27%) patients, the repeat procedure was performed during the blanking period due to need for multiple and/or failure of electrical CV despite antiarrhythmic drug therapy. PV re-connection was found in 18/29 (62.0%) patients and included one vein ($n=12$), two veins ($n=3$) or four veins ($n=3$). The reconnected PVs were the LSPV ($n=9$), LIPV ($n=5$), RSPV ($n=7$) or the RIPV ($n=9$). After PV re-isolation, 15 patients received additional ablation lines. Sites of additional lesions were roof line in three, anterior line in five, CTI line in seven and ostial potential ablation in three individuals. In 11/29 (37.9%) patients with recurrence despite isolated PVs, ostial potential ablation was performed in six, anterior line in six, roof line in four, posterior line in two and CTI line were ablated in four patients, respectively.

Table 1 Comparison of patients with and without late ATA recurrence

Parameter	All patients ($n=133$)	Recurrence− ($n=89$)	Recurrence+ ($n=44$)	p value
Age (years)	66 ± 10	67 ± 10	65 ± 9	0.42
Male gender (*n*)	80 (60)	52 (58)	29 (66)	0.58
Height (cm)	176 ± 11	176 ± 11	176 ± 10	0.95
Weight (kg)	90 ± 20	92 ± 20	86 ± 19	0.12
Hypertension	104 (71)	68 (76)	36 (82)	0.51
Diabetes mellitus	27 (20)	16 (18)	11 (25)	0.36
Dyslipidemia	55 (41)	36 (40)	19 (43)	0.85
LA diameter (mm)	42 ± 6	41.2 ± 6.5	44.6 ± 5.7	0.004
LVEF (%)	51 ± 8	51.8 ± 7.7	48.6 ± 9.9	0.04
CHA2DS2VASc	3 (1–6)	3 (2–5)	3 (2–5)	0.96
EHRA	3 (2–4)	2 (1–3)	2 (1–3)	0.92
HASBLED	2 (1–3)	2 (1–3)	2 (1–3)	0.80
Previous MI	16 (12)	10 (11)	6 (13)	0.78
Previous PCI	35 (26)	22 (24)	13 (29)	0.67
CABG operation	6 (4)	2 (2)	4 (9)	0.09
Cardiomyopathy	34 (26)	17 (19)	17 (38)	0.02
PM/ICD	9 (7)	8 (9)	1 (2)	0.27
ICD	10 (8)	4 (4)	6 (13)	0.08
Pneumopathy	18 (14)	14 (15)	4 (9)	0.42
Mean duration of AF (months)	26.1 ± 38.4	28.1 ± 41.9	21.9 ± 30.1	0.38
Additional CTI during the procedure	14 (10)	10 (11)	4 (9)	0.70
PV abnormality (n)	21 (15)	10 (11)	11 (25)	0.04
LCPV (*n*)	13 (10)	7 (7)	6 (13)	0.34
RMPV (*n*)	9 (6)	4 (4)	5 (11.3)	0.15
Total procedure time (min)	107.5 ± 22.3	109.1 ± 23.2	104.2 ± 20.3	0.23
Fluoroscopy time (min)	22.8 ± 10.1	23.3 ± 10.2	21.7 ± 10	0.38
Freezes in LSPV (times)	1.4 ± 0.6	1.4 ± 0.6	1.5 ± 0.7	0.68
Freezes in LIPV (times)	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	0.48
Freezes in RSPV (times)	1.3 ± 0.5	1.3 ± 0.6	1.2 ± 0.5	0.48
Freezes in RIPV (times)	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.6	0.79
LSPV freeze duration (seconds)	301 ± 142	300 ± 142	302 ± 146	0.94
LIPV freeze duration (s)	298 ± 125	305 ± 131	284 ± 114	0.36
RSPV freeze duration (s)	207 ± 132	265 ± 137	237 ± 120	0.25
RIPV freeze duration (s)	240 ± 138	191 ± 137	197 ± 143	0.81
Minimum temperature in LSPV (°C)	−48.0 °C ± 5.7	48.2 ± 5.4	47.6 ± 6.3	0.57
Minimum temperature in LIPV (°C)	−45.4 °C ± 6.1	45.4 ± 5.8	45.3 ± 6.9	0.91
Minimum temperature in RSPV (°C)	−46.0 °C ± 6.5	47.7 ± 7.6	50.0 ± 6.3	0.08
Minimum temperature in RIPV (°C)	−46.9 °C ± 7.5	45.8 ± 6.6	46.3 ± 6.4	0.68
Initial sinus rhythm (*n*)	49 (37)	35 (39)	14 (32)	0.45
Cardioversion during procedure (*n*)	70 (52)	47 (53)	23 (52)	0.95
Recurrence in Blanking period	25 (18)	6 (6)	19 (36)	< 0.001

LA left atrium, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary bypass grafting operation, *CMP* cardiomyopathy, *PM* pacemaker, *ICD* implantable cardioverter/defibrillator, *AF* atrial fibrillation, *CTI* cavotricuspid isthmus, *LCPV* left common pulmonary vein, *RMPV* right middle pulmonary vein, *LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein, *RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein

Discussion

The main findings of the study are, (I) the use of second-generation 28 mm CB in persistent AF patients results in 100% isolation of targeted veins, with 1-year clinical success rate of 67%. (II) Recurrence during blanking period, presence of cardiomyopathy and PV abnormality were independent predictors of recurrence after CB PVI. (III) In addition, in

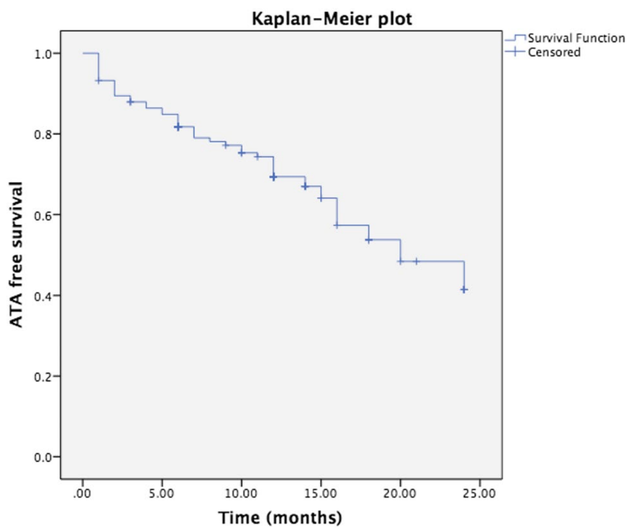

Fig. 1 Freedom from ATA during follow-up period after second-generation cryoballoon

the majority of patients undergoing repeat ablation PV reconnection was observed.

Currently, the best ablative strategy to treat patients with persistent AF is controversial, due to complex substrate. Besides PVI, different ablative strategies such as ablation of complex fractionated atrial electrograms, rotors or low voltage areas or linear ablation are performed aiming at improved outcomes [5–7, 14].

Results from the STAR-AF II study suggest that outcome after PVI only in patients with persistent AF, using RF ablation in conjunction with a 3D mapping-system, is not inferior to more extensive ablation strategies such as ablation of complex fractionated atrial electrograms (CFAE) or placement of linear lesions in addition to PVI [8]. These results re-emphasize the importance of durable PVI even in patients with persistent AF.

PVI is still the primary ablative approach for AF, especially in paroxysmal and persistent AF [2, 3, 11]. The randomized "fire and ice" trial proved non-inferiority of ablation with the second-generation CB compared to RF-based PVI with regard to efficacy and safety for the treatment of patients with PAF [2]. After this study, the number of CB-based PVI procedures increased. Although previously published data suggests lower recurrences with second-generation CB in paroxysmal AF patients, there is limited data in persistent AF concerning success rates. Aytemir et al. [15] reported 50% success rate with first-generation CB in patients with persistent AF at a median 18 (6–27) months follow-up. However, second-generation CB was found to have better outcomes compared with first-generation CB among patients with both paroxysmal and persistent AF [9, 16]. Freedom from ATA following persistent AF ablation with RF and second-generation CB was comparable at 1-year follow-up after a single procedure [11]. Guhl et al. [17]. analyzed the results of 69 s generation CB procedures for persistent AF and ATA recurrence-free rate at 1-year was 58.5%. Koektuerk et al. [12] evaluated 1-year outcome after second-generation CB for persistent AF patients. After mean follow-up of 10.6 ± 6.3 months, 67 of 100 patients were in sinus rhythm. Recurrence during blanking period was the only independent predictor of late recurrence. In a study by Lemes et al. [13], 69% of persistent AF patients were recurrence free after a follow-up of 416 + 178 (range 188–744) days. In a recent meta-analysis [18], after a mean follow-up of 16.7 ± 3.0 months, 68.9% were free from recurrences.

In our study, the freedom from ATA recurrence at a mean follow-up period of 12.6 ± 5.4 months was comparable to previous studies. Similar to the study by Koektuerk et al. [12], recurrence during the blanking period was an independent predictor of late recurrence.

Due to failure of AADs or need for multiple cardioversions, eight patients (27.5%) underwent a redo ablation during the blanking period. This amount is higher than previously described, e.g., in the STOP-AF [19] trial, in which 19% of patients underwent repeat ablation during the blanking period. However, this study included only paroxysmal AF patients with a suggested less complex arrhythmic substrates compared to our cohort with persistent AF and a considerable amount of patients with cardiomyopathy.

In our study, presence of cardiomyopathy and PV abnormality also emerged as independent predictors of late recurrence. This might be attributed to the characteristics of the study population enrolled in our analysis. Patients with cardiomyopathy have a more diseased atrium that may

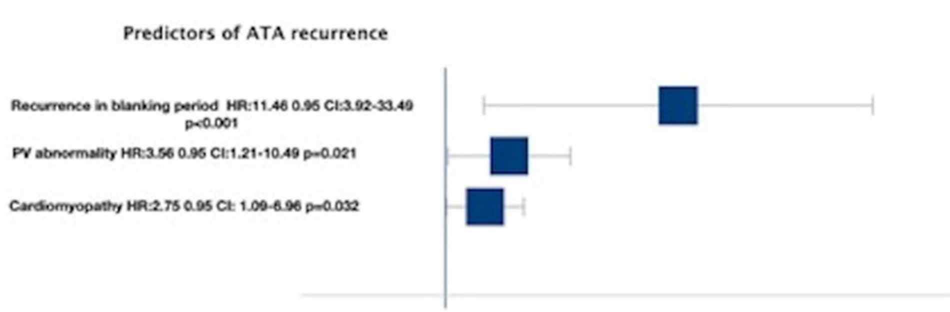

Fig. 2 Predictors of ATA recurrence after multivariable analysis. *ATA* atrial tachyarrhythmia, *HR* hazard ratio, *PV* pulmonary vein

predispose to develop AF. There are several explanations for the higher recurrence rate in patients with anatomical variants of the PVs. The anatomical variant may pose technical challenges during the procedures, thus potentially compromising effective lesion formation. However, the authors believe, that the most likely mechanism of the higher recurrence rate is the more distal PV isolation in common PV ostia which results in a smaller substrate modification of the LA and PV antrum. Variant PV- anatomy as assessed by preprocedural evaluation via a multi-detector computed tomography was found to be a predictor of AF recurrence after PVI by remote magnetic navigation [20]. Heeger et al. [21] reported high acute success rates and procedural safety for the treatment of left common pulmonary veins (LCPV). Freedom from ATA recurrence was 64% after 2 years of follow-up with no statistical difference compared to patients of the control group with normal PV anatomy (66%). On the contrary, Shigeta et al. [22]. found that, presence of LCPV was associated with poor clinical outcome of AF ablation in patients undergoing second-generation CB-based PVI. We used PV angiography to assess PV anatomy and in our study, while the presence of right middle PV, and/or LCPV was linked to ATA recurrence.

Furthermore, CTI ablation was performed during index cryoballoon ablation, if atrial flutter was documented or induced. This additional ablation approach might have an impact on the recurrence of ATA during follow-up. However, in our cohort, none of the patients undergoing CTI ablation during redo ablation had previous CTI ablation and performance of CTI in patients with and without ATA recurrence was equally distributed. Furthermore, one has to acknowledge that atrial flutter and atrial fibrillation frequently coexist. Correspondingly, 4.5% of paroxysmal AF patients in the FIRE and ICE study underwent CTI ablation due to coexisting CTI dependent atrial flutter. We therefore think, that our results are comparable to other studies and results should not be biased by the fact that CTI ablation was performed [2].

Several significant improvements became evident in clinical practice with the use of second-generation CBs, including better acute and chronic success rate and decreased fluoroscopy time [2, 3]. Besides ostial PV isolation, application of second-generation CB results in large atrial lesion formation causing substrate modification, especially in the posterior LA wall. The spherical shape of second-generation CBs may cause a mismatch between the balloon and PV ostia during optimal contact causing additional atrial wall ablation that may eliminate components responsible for persistent AF such as CFAEs [23], rotors [24], and vagal ganglia [25] as well. Despite technological improvements, recurrences still occur in around one-third of patients and etiology of recurrences are supposed to relate to (1) lack of durable pulmonary vein isolation and (2) need for addressing non-pulmonary vein triggers. In our study patients, analysis of redo procedures revealed re-connection of the PVs in 62% of patients with recurrence, suggesting the importance of electrical linkage of the LA with the PVs. Moreover, in 6 of 11 patients with isolated PVs and ATA recurrence ostial potential ablation was performed due to distal PV isolation. Future techniques aiming at durable PV isolation and larger ostial atrial lesions might probably increase the success rates.

Our study findings with 67% clinical success rate have some important clinical implications. First, our results are in line with recently published studies with a higher rate of freedom from ATA. Moreover, our study expands the literature in terms of a larger patient population included. The complication rate was also low without any pericardial tamponade or cerebrovascular events and with only two femoral arteriovenous fistula necessitating surgery. PNP was observed in only 4% of the patients, which was also comparable with other studies using cryoballoon [26, 27]. Early recurrence in blanking period, presence of cardiomyopathy and PV abnormality can be used to identify patients at risk for recurrence. PV re-connection was observed in nearly 2/3 of patients with ATA recurrence, highlighting the importance of durable PVI in the treatment of persistent AF.

Limitations

This study has some limitations. First, this is a single centre, retrospective, nonrandomized study evaluating the efficacy and safety of primarily second-generation CB ablation in persistent AF patients without preprocedural cardiac imaging. Due to our institutional standard is cryoballoon for initial ablation approach of AF, our study has no control group. Because some of the patients were scheduled for cryoballoon ablation after cardioversion, more than one-third of patients were in sinus rhythm during the procedure, despite having persistent AF. Although our study has the highest patient group reported, large-scale randomized studies are needed both to confirm and expand our findings. Second, our follow-up did not include routine continuous monitoring with implanted devices or 7 day-Holter recording. Nevertheless, follow-up included 24 h Holter monitoring, and/or device interrogations (if present), at 3, 6 and 12 months.

No systematic oesophagoscopy was performed in this study. Therefore, no data about the incidence of esophageal injury is available.

Conclusion

In patients with persistent AF, second-generation cryoballoon use is associated with an excellent safety profile and favorable outcomes. Arrhythmia recurrence during the blanking period, presence of cardiomyopathy and PV abnormality were independent predictors of long-term AF recurrence.

Acknowledgements K. Yalin recieved research and educational grant from Turkish Society of Cardiology. E. Lyan received travel grants and Speaker's Bureau Honoraria from Biosense Webster, Medtronic, Boston Scientific. R. Tilz received travel grants from St. Jude Medical, Topera, Biosense Webster, Daiichi Sankyo, Sentrheart and Speaker's Bureau Honoraria from Biosense Webster, Biotronik, Pfizer, Topera, Bristol-Myers Squibb; Bayer, Sanofi Aventis.

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