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Efficacy and safety of cryoballoon ablation in the elderly: A multicenter study

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ABSTRACT

Background: The prevalence of atrial fibrillation (AF) increases with age. Second-generation cryoballoon (CB2)-based PVI has demonstrated encouraging clinical results in the treatment of paroxysmal (PAF) and persistent atrial fibrillation (PersAF). The objective of this study was to assess data on safety, efficacy and long-term clinical success of CB2-based pulmonary vein isolation (PVI) in patients ≥75 years of age.
Methods: CB2-based PVI was performed in 104 patients ≥75 years of age (elderly group) and symptomatic AF (PersAF: $n = 44$, 42.3%) in three highly experienced German EP centers. The data was compared to propensity score matched patients with age <75 years ($n = 104$, control group; PersAF: $n = 45$, 43.3%, $p = 0.956$).
Results: The median age of the elderly group was 77.5 [75, 80] years while it was 63 [52, 70] years of control group patients ($p = 0.0001$). The median procedure time was 92.5 [75, 120] minutes (elderly group) and 100 [75, 120] (control group), $p = 0.124$. Major complications were registered in 7/104 (6.7%) elderly patients and 7/104 (6.7%) control group patients ($p = 0.999$). Clinical success in terms of freedom from AF recurrence after one-year follow-up was 80% (95% CI: 72–88) and 82% (95% CI: 75–90) and after three-year follow-up 59% (95% CI: 47–74) and 49% (95% CI: 37 64) for the elderly group and the control group, respectively ($p = 0.7$).
Conclusions: CB2-based PVI in patients ≥75 years of age appears safe, is associated with low procedure times and shows promising clinical success rates equal to patients of the younger population.

1. Introduction

Atrial fibrillation (AF) affects approximately 1.5–2% of the general population in the developed world, and is associated with an increased rate of mortality, congestive heart failure, stroke and hospitalization [1,2]. The incidence of AF increases with age. Due to demographic changes of the population, the prevalence of AF will further increase in the future. Pulmonary vein isolation (PVI) forms the cornerstone of catheter ablation based AF treatment. Radiofrequency-based (RF) point-by-point ablation results in favorable clinical success rates, but its complexity demands a long learning curve and multiple procedures are oftentimes required to achieve durable PVI [3,4]. The second-generation cryoballoon (CB2, Arctic Front Advance, Medtronic Inc., Minneapolis, USA) for PVI has demonstrated high procedural success rates, high durability of PVI [5,6], and convincing short and long-term clinical success rates for patients with paroxysmal (PAF) and persistent atrial fibrillation (PersAF) [7–12]. The Fire and Ice trial proved non-inferiority

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of CB2- to RF-based PVI with regards to efficacy and safety for the treatment of patients with PAF [13]. In consequence, the latest AF guidelines state that PVI should be performed using either RF or CB ablation [14]. However, the Fire and Ice trial excluded patients with >75 years of age and only limited data is available concerning outcomes of CB2-based PVI in elderly patients [13,15–18].

2. Methods

2.1. Inclusion and exclusion criteria

All patients referred to three experienced EP centers in Germany (Asklepios Klinik St. Georg, Hamburg; Asklepios Klinik Harburg, Hamburg; University of Cologne, Cologne) were analyzed retrospectively. Patients with drug-refractory PAF or PersAF scheduled for CB2-based PVI and age of ≥75 years were included. Exclusion criteria were prior left atrial (LA) ablation, LA-diameter >60 mm, severe valvular heart disease or long-standing PersAF. Transesophageal echocardiography was performed prior to ablation to assess the LA-diameter and to rule out intracardiac thrombi. No additional preprocedural imaging was performed. Procedural data and clinical follow-up of patients with age ≥75 years that underwent CB2-based PVI (elderly group) were analyzed and compared to propensity score matched patients <75 years of age (control group). The patients for the control group were generated from the institutional databases. All patients gave written informed consent to the procedure. The study was approved by the local ethic's board (ethical review board number: WF-028/15 and 17–345) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2. Intraprocedural management

The intraprocedural management has been described in detail in previous studies [10,19,20]. In brief, in patients on vitamin K antagonists the procedure was performed under therapeutic INR values of 2–3. New oral anticoagulants were stopped the day before the procedure and continued 6 h 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 left subclavian vein and 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 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 pulmonary vein (PV) angiographies were then performed to identify the PV ostia.

2.3. Cryoballoon based PVI

Only the 28 mm CB2 was utilized in this population. The transseptal sheath was exchanged over a guidewire for a 12F steerable sheath (Flexcath Advance, Medtronic). The CB2 was then advanced into the LA via the 12F steerable sheath guided by the Achieve catheter (20 mm diameter, Medtronic).

A spiral-shaped temperature probe (Sensitherm, St. Jude Medical) was advanced into the esophagus to monitor luminal esophageal temperatures during each energy application. The intraluminal esophageal temperature cut-off was set at 15 °C [21]. During energy delivery along the septal PVs, continuous phrenic nerve (PN) pacing was performed using a diagnostic catheter introduced into the superior caval vein (7F, Webster, Biosense Webster Inc., Diamond Bar, USA). Pacing was set at maximum output and pulse width (12 mA, 2.9 ms) and a cycle length of 800–1200 ms. PN capture was monitored by tactile feedback of diaphragmatic contraction and assessment of the right diaphragmatic compound motor action potential (CMAP). Energy delivery was interrupted immediately if weakening or loss of diaphragmatic contraction was noted or a decrease of the CMAP amplitude of ≥30% was seen [22,23]. In case of persistent PN palsy (PNP), no further cryoenergy was delivered to the septal PVs.

The CB2 was inflated proximal to the PV ostium followed by gentle push aiming for complete PV sealing. Occlusion of the PV ostium was verified by contrast dye injections. Different ablation protocols were applied. The first 4 consecutive patients ($n = 6$ for the control group, $p = 0.517$) were treated by a "bonus-freeze" protocol (freeze-cycle duration of 240 s followed by one additional bonus-freeze-cycle of 240 s duration after PVI) [10]. Another 50 consecutive patients ($n = 47$ for the control group, $p = 0.677$) were treated with a "no-bonus-freeze" protocol (freeze-cycle duration of 180 or 240 s without an additional bonus-freeze-cycle following PVI) [19]. The last 50 consecutive patients ($n = 51$ for the control group, $p = 0.890$) were treated based on a "time-to-effect" guided ablation protocol (after real-time PVI another 120 s were applied without an additional freeze-cycle) [20,24].

2.4. Postprocedural care

Following ablation, all patients underwent transthoracic echocardiography to rule out pericardial effusion. 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. New oral anticoagulants were re-initiated 6 h post-ablation. Anticoagulation was recommended for at least 3 months and thereafter according to the individual CHA_2DS_2-VASc score. Previously ineffective antiarrhythmic drugs were continued for 3 months post-ablation [10,19]. All patients were treated with proton-pump inhibitors for 6 weeks.

2.5. Definition of complications

A complication was defined as peri-procedural when occurring during the ablation procedure, within hospital stay or during a period of 30 days after ablation as recommended in the consensus statement for catheter ablation of atrial fibrillation 2017 [25]. The term "major complication" was defined as a complication resulting in permanent injury or death, requiring intervention for treatment, or prolonging or requiring hospitalization for >48 h [25]. Bleeding was defined as a major complication if it required and/or was treated with transfusion or resulted in a 20% or greater fall in hematocrit [25]. Because early recurrences are to be expected following AF ablation, recurrent AF/atrial tachycardia (AT) of atrial flutter within 3 months that required or prolonged a patient's hospitalization were not considered to be a major complication [25].

2.6. Clinical follow-up and study endpoints

Following a blanking period of 3 months, patients completed outpatient clinic visits at 3, 6 and 12 months and in 6-month intervals thereafter including ECGs and 24 h-Holter ECGs. In addition, regular telephonic interviews were performed. Additional outpatient clinic visits were immediately initiated in case of symptoms suggestive of recurrent arrhythmia. The primary endpoint was defined as recurrence of any symptomatic or documented AF/AT episode >30 s following a blanking period of 3 months. Secondary endpoints were acute procedural data and procedure related complications such as bleeding, PNP, cerebral embolism, pericardial effusion/tamponade or atrioesophageal fistula.

2.7. Statistical analysis

Baseline and procedural data were summarized as means and standard deviations or medians and interquartile range for continuous data. Categorical data were presented as absolute frequencies and proportions.

The primary endpoint of this retrospective analysis was AF/AT recurrence-free survival of $n = 208$ patients after CB2-based PVI. $N = 104$ patients ≥75 years were matched to $n = 104$ patients <75 years. For the matched control-group propensity score matching was performed. It was based on a logistic regression model including gender, type of AF, hypertension, diabetes mellitus, LA size and congestive heart failure. A F-test of overall significance was performed to examine differences of the baseline variables between the groups. Differences in complications data between the groups were analyzed using the Chi-squared test. For **Kaplan-Meier plot** and patients at risk a log-rank test was used to compare AF recurrence-free survival between the groups. All p-values were two-sided and a p-value <0.05 was considered significant. All calculations were performed with the statistical analysis software R (R Core Team, 2018).

3. Results

3.1. Study population

Overall, 208 patients were analyzed, including 104 patients with AF and an age ≥ 75 years (elderly patients). The study population of the elderly patients consists of 44 patients with PersAF (42.3%) and 60 patients with PAF (57.7%). The median age of the elderly group was 77.5 [75, 80] years. The median age of control group patients was 63 [52, 70] years. The baseline characteristics of the study population are presented in Table 1. Except of age ($p < 0.0001$) and CHA_2DS_2-VASc

Table 1
Baseline characteristics.

Baseline characteristics	All	≥75 years	<75 years	p value
Patients	208	104	104	–
Age (years)	75 [63, 77]	77.5 [75, 80]	63 [52, 70]	<0.0001
LA diameter (mm)	44.6 (±5.6)	44.5 (±5.6)	44.5 (±5.6)	0.956
Female gender	102 (49.0%)	52 (50%)	50 (48.1%)	0.956
Persistent AF	89 (42.8%)	44 (42.3%)	45 (43.3%)	0.956
Arterial hypertension	163 (78.4%)	81 (77.9%)	82 (78.9%)	0.956
Congestive heart failure	22 (10.6%)	9 (8.7%)	13 (12.5%)	0.956
Diabetes mellitus type II	31 (14.9%)	16 (15.4%)	15 (14.4%)	0.956
Prior stroke	18 (8.7%)	11 (10.6%)	7 (6.7%)	0.324
CHA_2DS_2-VASc-score	2.9 ± 1.5	3.8 ± 1.1	2.1 ± 1.3	<0.0001

Continuous data are summarized as means ± standard deviations or as medians [25th and 75th percentiles]. Categorical data are presented as N (%). Test of no regression $p = 0.956$ based on gender, type of AF, hypertension, diabetes mellitus, LA size and congestive heart failure. AF = atrial fibrillation, LA = left atrium, CB2 = second-generation cryoballoon.

Table 2
Procedural data.

Characteristics	All	≥75 years (elderly group)	<75 years (control group)	p
Number of PVs	820	413	407	–
Number of isolated PVs	818/820 (99.8%)	413/413 (100%)	405/407 (99.5%)	0.999
Procedure time, min	95 [75, 125]	92.5 [75, 120]	100 [75, 120]	0.293
Fluoroscopy time, min	18.1 [13.8, 23.5]	17.8 [13, 23.5]	19.1 [14.2, 23.5]	0.286
Major complications	14 (6.7)	7 (6.7)	7 (6.7)	0.999
Major bleeding	1 (0.5)	0 (0)	1 (1)	0.124
Phrenic nerve palsy	8 (3.8)	4 (3.8)	4 (3.8)	0.999
Pericardial tamponade	2 (1)	1 (1)	1 (1)	0.999
Pneumothorax	0 (0)	0 (0)	0 (0)	0.999
Hematothorax	0 (0)	0 (0)	0 (0)	0.999
Stroke/TIA	1 (0.5)	0 (0)	1 (1)	0.124
Procedure related death	1 (0.5)	1 (1)	0 (0)	0.124
Myocardial infarction	1 (0.5)	1 (1)	0 (0)	0.124
Minor complications	8 (3.8)	4 (3.8)	4 (3.8)	0.999
Minor bleeding	7 (3.4)	4 (3.8)	3 (2.9)	0.701
Pericardial effusion	1 (0.5)	0 (0)	1 (1)	0.124

Values are expressed as mean and SD if data were normally distributed, median [25th and 75th percentiles] or *N* (%) as appropriate. CB2 = second-generation cryoballoon, SD = standard deviation, TIA = transient ischemic attack, PV = pulmonary vein.

score ($p < 0.0001$) no differences were identified between the two groups.

3.2. Procedural characteristics

Procedural parameters are depicted in Table 2. In the elderly patients 413 PVs have been identified and successfully isolated using the 28 mm CB2. No RF touch up ablation was necessary in any PV. In control group patients 407 PVs have been identified and 405 PVs were isolated utilizing the CB2; two right superior PVs were not targeted due to PNP during ablation at the right inferior PV. In 4/104 (3.8%) patients of the elderly group and in 3/104 (2.9%) patients of the control group an additional cavotricuspid isthmus-line was ablated due to documentation of typical atrial flutter ($p = 0.701$). No additional ablation strategies have been performed in any other patient.

3.3. Periprocedural complications

Table 2 summarizes the documented periprocedural complications. Major complications were registered in 7/104 (6.7%) patients of the elderly group and 7/104 (6.7%) patients of the control group ($p = 0.999$). PNP occurred in 4/104 (3.8%) patients of the elderly group ($n = 4$ RSPV) and in 4/104 3.8% patients of the control group, $n = 2$ right superior PV, $n = 2$ right inferior PV. All PNPs recovered within a maximum of 12 months. One periprocedural pericardial tamponade requiring pericardial puncture and drainage occurred in both groups ($p = 0.999$). One patient of the elderly group experienced periprocedural haemoptysis, developed pneumonia and died due to nosocomial pneumonia and respiratory failure 13 days following intensive care treatment after ablation. The patient was 92 years of age and suffered from highly symptomatic PAF and was biologically in a very good physical and mental condition so that decision to undergo an ablation attempt was made [26]. Furthermore, in one patient of the elderly group an air embolism with subsequent ST-elevation and myocardial infarction of the right coronary artery occurred. Postprocedural transthoracic echocardiography found no evidence of decreased LVEF. One patient of the control group experienced severe groin hematoma requiring blood transfusion. A further control group patient experienced periprocedural TIA. Both patients recovered without sequelae. No further major complications occurred in the elderly group or the control group.

A total of 4 (3.8%) patients per group experienced minor complications ($p = 0.999$). Four patients (3.8%) of the elderly group and 3 (2.9%) patients of the control group experienced groin complications with conservative treatment. In the control group one pericardial effusion not requiring epicardial puncture occurred. In both groups, no atrio-esophageal fistula and no PV stenosis were reported.

3.4. Follow-up and clinical success

The Kaplan–Meier plot (Fig. 1) demonstrates the relative proportion of patients in stable sinus rhythm following index PVI using the CB2. After one year of follow-up and a single CB2-based PVI procedure Kaplan-Meier estimates of patients in stable sinus rhythm were 80% (95% CI: 72–88, elderly group) and 82% (95% CI: 75–90, control group). Kaplan-Meier estimates for stable sinus rhythm after two years of follow-up were 70% (95% CI: 60–81, elderly group) and 58% (95% CI: 48–71, control group) while Kaplan-Meier estimates for stable sinus rhythm after three years of follow-up were 59% (95% CI: 47–74, elderly group) and 49% (95% CI: 37–64, control group). No significant differences were observed concerning the duration of follow-up (median time to event elderly group: 1.1 (0.4–2.0) years, median time to event control group: 1.2 (0.6–2.5) years, $p = 0.184$) and the comparison of AF recurrence of both groups ($p = 0.7$).

4. Discussion

To the best of our knowledge, this is the largest study to present periprocedural and outcome data of patients with ≥75 years of age with PAF or PersAF treated with the CB2. Data was compared to a propensity score matched control group of patients <75 years of age.

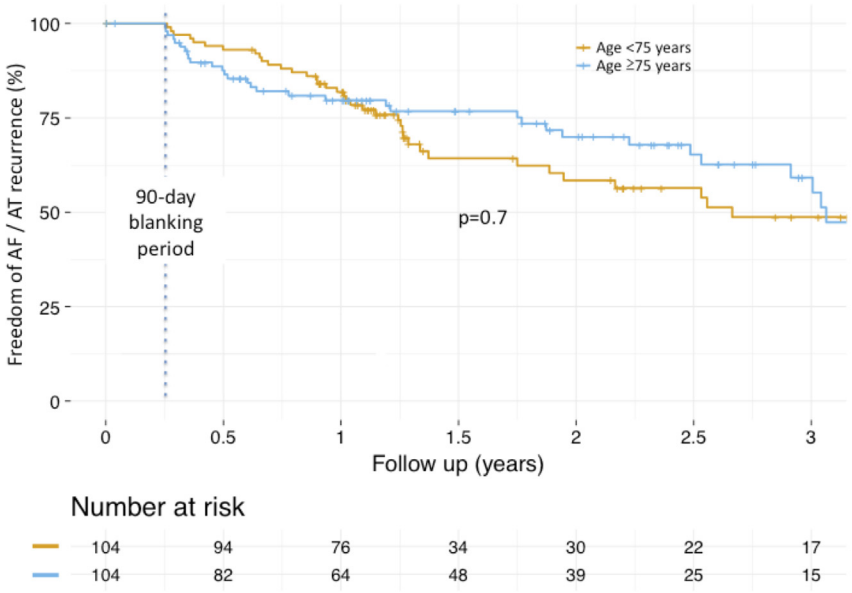
The main findings of this study are as follows:

(1) CB2 ablation is associated with relatively short procedure times and fluoroscopy times in elderly patients comparable to younger patients
(2) CB2 ablation in the elderly is associated with an incidence of procedure related major and minor complications similar to patients of the younger population
(3) The long-term clinical success rate in patients ≥75 years is comparable to patients <75 years when treated with CB2.

4.1. Efficacy of PVI in elderly patients using cryoballoon

The worldwide population is aging and therefore the elderly will become a more and more important patient group for AF treatment in the near future [27].

There is no uniform definition of elderly patients in cardiac interventions and the cutoff for analysis of elderly patients varies [28–30]. However, Chen et al. have shown, that about 30% of European electrophysiological centers are restrictive to perform AF ablation procedures in patients older than 75 years [31]. Regarding the success rates of CB2 ablation, the recently published fire and ice trial has demonstrated, that CB2 ablation is comparable to RF ablation in patients with paroxysmal AF with regards to complication rates and clinical success rate [13]. Importantly, patients aged older than 75 years were excluded from participation in this trial [18]. Thus, data comparing CB2 ablation in the elderly to younger patients in larger patient cohorts are lacking. To date, data about CB2 ablation in the elderly is only available for smaller patient cohorts from single-center analysis [16,32]. Therefore, this is the first study showing, that CB2 ablation in aged patients results in a similar clinical success rate as compared to younger patients in a larger multicenter-cohort. After a one-year follow-up period the clinical success rate in our study was 80% in the patient group ≥75 years and 82% in the younger patient



	≥75 years (elderly group)		<75 years (control group)	
	Point estimate (%)	95% confidence interval (%)	Point estimate (%)	95% confidence interval (%)
0.5 years	88	81 - 94	93	88 - 98
1 year	80	72 - 88	82	75 - 90
2 years	70	60 - 81	58	48 - 71
3 years	59	47 - 74	49	37 - 64

The Kaplan–Meier plot demonstrates the relative proportion of patients in stable sinus rhythm following index PVI using the second-generation 28mm cryoballoon. Log-rank test for AF recurrence-free survival between the groups found p = 0.7.

Fig. 1. Long-term clinical results. The Kaplan-Meier plot demonstrates the relative proportion of patients in stable sinus rhythm following index PVI using the second-generation 28 mm cryoballoon. Log-rank test for AF recurrence-free survival between the groups found $p = 0.7$.

group, which shows, that CB2 ablation is a highly effective ablation strategy even for aged patients with AF. It has to be considered, that >40% of the patients of the present study population were patients with persistent AF. Although data about patients with persistent AF treated with the CB2 are still sparse, similar results as compared to RF ablation procedures in persistent AF can be expected [8,33]. Thus, the present single-procedure success rate presents good results in particular in aged patients in this mixed AF cohort with PAF and persistent AF. However, these findings have to be confirmed in larger randomized trials.

4.2. Procedure times and fluoroscopy times

Noteworthy both, procedure times and fluoroscopy times were comparable between patients ≥75 years of age and younger patients in this study population. This further highlights that CB2 ablation is a straightforward procedure and easily and time-efficiently applicable also in older patients. Shorter procedure times might be of importance for older patients with regards of sedation times and complication rates.

4.3. Complication rates

Reports about complication rates in catheter ablation in the elderly are conflicting [15,28,30,32]. Studies using data from questionnaires or ICD10-codes as the basis for their analysis revealed in part a higher complication rate in the elderly during electrophysiological procedures [34,35]. Deshmukh et al. described an overall incidence of 7% for complications in patients between 65 and 79 years of age during AF ablation procedures [34]. These results were mainly driven by the results of RF based ablation procedures and are therefore only of limited value for a transfer to CB2-based ablation procedures in the elderly. However, the complication rate in both groups in the present study is in line with these data. Several smaller studies revealed no increased risk for periprocedural complications in aged patients for CB2-ablation [15,16,28–30,32]. The results of the present analysis support these data. In particular, the incidence of major complications was comparable between the elderly and the patient population <75 years of age. Furthermore, PNP or bronchial injury has been described for CB2 ablation [23,36,37]. The incidence of PNP was similar in older patients

when treated with the CB2 as compared to younger patients. Subgroup analysis of the recently presented CABANA trial found that younger patients (<65 years of age) might benefit from catheter ablation while elderly patients (>75 years of age) might no benefit [38]. Although the ablation technology (mainly RF) may explain these differences further studies focusing on this issue in CB2-based PVI are warrant.

4.4. Limitations

This study is of retrospective nature; however the analysis was performed using data of three high-volume centers and patient groups were matched according to baseline characteristics from a large database. Although propensity score matching may be an accepted method to obtain two similar groups it may be questionable, whether this statistical method leads to better comparability in this patient population. Since most diseases are age-dependent, patients that are equal in several conditions except age may not represent similar populations. Success rates were evaluated using 24 h Holter-ECGs. Thus, the clinical success rate might be overestimated and asymptomatic episodes of atrial tachyarrhythmia might have been missed.

5. Conclusion

In the elderly, acute success, periprocedural complications and long-term clinical success rates are comparable to patients of younger age when using CB2 ablation for the treatment of PAF or PersAF.

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