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Pulmonary Vein Isolation with the Second-generation Cryoballoon in Paroxysmal and Persistent Atrial Fibrillation

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München, 29.03.2018 Stefan Maximilian Hartl

Table of Contents

Abbreviations & Acronyms

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
AT	Atrial tachycardia
AV	Atrioventricular
BP	Blanking period
CA	Catheter ablation
CB	Cryoballoon
CBG2	Second-generation CB
CHA_2DS_2-VASc	**C**ongestive heart failure/left ventricular dysfunction, **h**ypertension, **a**ge ≥75 years, **d**iabetes, **s**troke, **v**ascular disease, **a**ge 65–74, female **s**ex
CS	Coronary sinus
CT	Computed tomography
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
HAS-BLED	**H**ypertension, **a**bnormal renal / liver function, history of **s**troke / **b**leeding, **l**abile INR, **e**lderly, **d**rugs or alcohol
ICE	Intracardiac echocardiography
LA	Left atrium
MRI	Magnetic resonance imaging
PNP	Phrenic nerve palsy
PV	Pulmonary vein
PVI	PV isolation
RF	Radiofrequency
SVC	Superior vena cava
TIA	Transient ischemic attack
TTI	Time to isolation

List of Publications

Two manuscripts are part of this cumulative dissertation and were both published in the *Journal of Cardiology*, a renowned, peer-reviewed international cardiology journal (Impact Factor 2015: 2.405). The studies investigate cryoablation with the second-generation cryoballoon in patients with paroxysmal (1) or persistent atrial fibrillation (2).

Publication I

Lessons from individualized cryoballoon sizing. Is there a role for the small balloon?

Stefan Hartl, Uwe Dorwarth, Benedikt Bunz, Michael Wankerl, Ullrich Ebersberger, Ellen Hoffmann, Florian Straube. J Cardiol (2017); DOI: http://dx.doi.org/10.1016/j.jjcc.2016.12.016

Publication II

Cryoballoon ablation for persistent atrial fibrillation - Large single-center experience. Florian Straube#, **Stefan Hartl**#, Uwe Dorwarth, Michael Wankerl, Benedikt Bunz, Ullrich Ebersberger, Ellen Hoffmann. J Cardiol (2016); DOI: http://dx.doi.org/10.1016/j.jjcc.2016.02.007

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S. Hartl prepared both manuscripts with all text tables, figures and references and was responsible for data acquisition, statistical analyses and interpretation of data. In publication II, the first authorship is shared with F. Straube, who prepared the manuscript text in equal measure and was responsible for the study design. All contributing co-authors gave their written informed consent to this dissertation.

Introduction

Atrial Fibrillation

With a prevalence of approximately three percent of the general population, atrial fibrillation (AF) is the most common cardiac arrhythmia (3-5). In general, AF is a non-lethal supraventricular tachycardia diagnosed by ECG documentation (6). Chaotic electric activity of the atria generates an atrial heart rate of at least 300 beats per minute followed by an irregular response of the ventricles due to AV node modulation (6). And although often asymptomatic (7), typical symptoms may occur including palpitations, chest discomfort and dizziness, dyspnea or reduction in exercise capability leading to a decrease of life quality (3, 6). AF impairs atrial contractility and, according to the Virchow triad (blood stasis, endothelial dysfunction, hypercoagulability), facilitates thrombus formation and therefore increases the risk of stroke and other thromboembolic events in AF patients (8, 9). Furthermore, AF may cause cardiac dysfunction and can decrease pre-existing cardiovascular disease to severe heart failure, consequentially, leading to an increase in morbidity and mortality (6, 10). AF is a dynamic disease and in the majority of cases the arrhythmia develops from paroxysmal AF in the beginning to persistent and permanent AF over time (6, 10). Several possible mechanisms (pulmonary vein sleeves merging into the left atrium, triggered activity, reentry, focal drivers, rotors, atrial fibrosis and more) (11-15) have been described for the initiation, transition and maintenance of AF (16). Individual characteristics such as arterial hypertension, structural heart disease, age, obesity, genetic predisposition influence above pathophysiological mechanisms (17). Therefore, the management of AF is complex and requires an individual approach. In general, there are three therapeutic goals: (a) the prevention of thromboembolic complications using oral anticoagulation whose indication depends on a risk-benefit assessment. The CHA_2DS_2-VASc score (**C**ongestive heart failure/left ventricular dysfunction, **H**ypertension, **A**ge

≥75 years, **D**iabetes, **S**troke, **V**ascular disease, **A**ge 65–74, and **S**ex **c**ategory female) can estimate the thromboembolic stroke risk and the HAS-BLED score can estimate the bleeding risk for each patient (3, 10, 18, 19). Furthermore, a rate control therapy (b) that slows down the ventricular rate in AF, or, a rhythm control therapy (c) that aims to restore or maintain sinus rhythmus through electrical cardioversion, the use of antiarrhythmic drugs (AAD) or catheter ablation (CA) are available to reduce AF symptoms (3, 6, 10). Rhythm control can be achieved with interventional catheter ablation and is reserved for symptomatic patients with paroxysmal or persistent AF (3). It targets the pulmonary veins as arrhythmogenic PV triggers have been found in more than 90% of patients with paroxysmal and persistent AF (11, 20). Therefore, electrical pulmonary vein isolation (PVI) is the major goal in the catheter treatment of AF (21, 22). Today, radiofrequency (RF) energy is the dominant energy source in use to perform PVI (10, 23) but the novel cryoablation technique using a cryoballoon for PVI has attracted worldwide interest due to favorable results that were non-inferior to RF ablation (24, 25). In addition, the cryoballoon technique convinces with a faster operator learning curve, a high reproducibility of the results across various centers, a short total procedure time, higher catheter stability through cryoadhesion to the tissue and others (10, 23, 25-28). Nevertheless, outcome data for the second-generation of the cryoballoon (CBG2) are still limited and the preferred technique for the initial ablation procedure when PVI is the procedural endpoint has not yet been determined. In this cumulative dissertation, the main focus lies on PVI using the CBG2. Two studies investigating the clinical outcome and safety after initial CBG2-PVI in patients with paroxysmal or persistent AF have been published. The following sections provide more detailed information about AF types, the management and mechanisms of AF and will then focus on catheter ablation strategies and present results of both prospective single center observational studies.

Types of Atrial Fibrillation

AF often evolves from rare and short events to more frequent and longer episodes. Next to the first diagnosis of AF, four main AF types are distinguished due to the clinical presentation of the arrhythmia (6, 22). “Paroxysmal AF” is defined as spontaneous conversion into sinus rhythm or the use of medical or electrical cardioversion within seven days. “Persistent AF” considers AF episodes that last longer than 7 days. In “longstanding persistent AF” a decision for rhythm control has been made after at least one year AF duration. When AF is accepted by both patient and the treating physician and no rhythm control strategies are pursued, the condition is classified as “permanent AF”. All AF types are summarized in **Table 1**.

Table 1: AF types, definition and indications for catheter ablation. Based on the 2012 Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society expert consensus statement on catheter and surgical ablation of atrial fibrillation (22), and the 2016 ESC Guidelines for the management of atrial fibrillation (3)

AF type	Definition	Indications for Catheter Ablation
first diagnosed	Any AF first documented by ECG recording irrespective of the duration or symptoms	_
paroxysmal	Recurrent AF that terminates spontaneously usually within 48 hours but may continue up to 7 days. Episodes of AF ≤ 7 days’ duration that are terminated with electrical or pharmacological cardioversion should be considered as paroxysmal	Class I / Level A • CA is recommended* Class IIa / Level B • primary CA therapy with-out prior AAD treatment

persistent	Continuous AF that is sustained beyond 7 days.	Class IIa / Level B • CA is reasonable*
longstanding persistent	Continuous AF ≥ 12 months' duration	Class IIb / Level B • CA could be considered*
permanent	A decision has been made to not restore or maintain sinus rhythm	_

Class indicates recommendation, level indicates evidence. AF, atrial fibrillation; CA, catheter ablation; *) valid for symptomatic AF patients who were refractory or intolerant to at least one class 1 or 3 antiarrhythmic drug

Management of Atrial Fibrillation

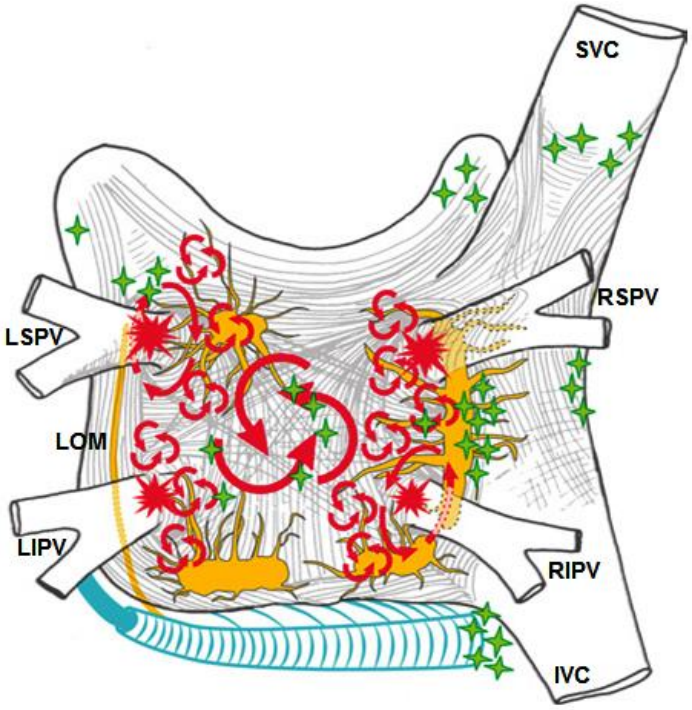
The management of AF is complex and requires an individual approach mainly depending on AF burden, AF type, symptom score (EHRA I-IV) and patient's preference, underlying heart disease, LA diameter, age and other comorbidities (6). Next to a diversity of treatment modalities the personalized therapy needs continuous reevaluation as AF is a progressive disease and the clinical course changes over time (29). Main strategies for the management of AF are aiming at oral anticoagulation to prevent thromboembolic events and a rate control and/or rhythm control therapy to reduce AF symptoms (6). The indication for oral anticoagulation is based on the CHA_2DS_2-VASc score that predicts the thromboembolic stroke risk in percent per year in AF patients. The score adds up two points for age ≥75 years or a history of stroke/TIA, and one point for age 65–74 years, arterial hypertension, diabetes mellitus, congestive heart failure, vascular disease and female sex. Antithrombotic therapy is recommended for all patients with valvular AF and patients with non-valvular AF who have ≥1 stroke risk factor. It is not recommended for patients with lone AF who are 64 years or younger

(including females) (3, 10, 18, 19). To achieve rate control, pharmacological therapy that slows down the ventricular rate in AF is necessary to reduce symptoms and prevent tachycardia-induced heart failure (29). Furthermore, AV node ablation including pacemaker implantation ("ablate and pace") is another possibility for a small group of patients, e.g. in permanent AF with tachyarrhythmia despite optimal medical treatment (3, 6, 10). The goal of rhythm control, however, is to restore or maintain sinus rhythm by electrical cardioversion, the use of antiarrhythmic drugs (AAD), and catheter ablation (CA), or, at times, AF surgery (3, 6, 10).

Catheter Ablation ─ Based on Mechanisms of Atrial Fibrillation

Indications for CA are reserved for symptomatic, usually drug-refractory paroxysmal and persistent AF patients (**Table 1**) (3, 22). The primary goal of CA therapy is to ablate either the trigger that induces AF and/or to modify the substrate that leads to the maintenance of AF (22). Therefore, the understanding of pathophysiological mechanisms that initiate, maintain and lead to AF progression is important. Haïssaguerre et al. first described that the pulmonary veins (PV) as the source of ectopic beats are responsible for the initiation of paroxysmal AF (11). Others, for example further non-PV trigger sites (e.g. coronary sinus, crista terminalis, SVC, left atrial appendage) (30-33) or conduction disturbances, such as focal drivers (12) have also been named for initiating AF. Nevertheless, PVI ─ with the goal to electrically isolate the PV from the left atrium ─ has prevailed and has become the cornerstone in the catheter treatment of paroxysmal AF. The mechanisms underlying persistent AF are more complex and less understood. Next to pulmonary vein foci, other mechanisms that form an arrhythmogenic substrate are responsible for transitioning and maintaining the arrhythmia and can thus be target of ablation therapy. Examples are atrial fibrosis that causes reentry (13, 15), autonomic sources, rotors and focal mechanisms (14). **Figure 1** summarizes the variety of different anatomic and pathophysiological mechanisms of AF and illustrates the diversity of possible therapeutic interactions.

Figure 1: Mechanisms of Atrial Fibrillation – drawing focusing the left atrium from posterior. Based on and adapted from Europace (22), Circulation (34), Am J Cardiol (35), Tex Heart Inst J (36).



Yellow: ganglionic plexi and axons including Ligament of Marshall (LOM); Blue: coronary sinus (enveloped by muscle fibers with connections to the atrium); Red circuits: large and small reentrant wavelets; Red stars: common locations of pulmonary veins (PV); Green: common origins of non-PV triggers. LSVP indicates left superior PV; LIPV, left inferior PV; RSPV, right superior PV; LSPV, left inferior PV; SVC, superior vena cava; IVC, inferior vena cava.

Energy sources for atrial fibrillation ablation

With radiofrequency- (RF) and cryothermal energy, two main energy sources are established to perform CA for PVI. RF energy is still the dominant energy form in use (10, 23) since the first RF ablation for AF in 1994 (37). The newer cryothermal energy was first approved for AF ablation

using an over-the-wire cryoballoon technique in 2005 and seems to offer certain advantages over RF energy:

1) Sharply demarked tissue destruction without or minimal endothelial damage leading to a 5.6-fold lower risk of thrombus formation (27)
2) Minimal tissue contraction with healing after re-warming results in fewer major complications such as PV stenosis and esophageal injuries (26, 28)
3) Broad, wide antral circumferential ablation lesion leading to a durable PVI (38)
4) Real time PV-potential recordings during the application allows to determine the “time-to-PV-isolation” (TTI), an unique intraprocedural predictor for durable PVI (39)
5) Higher catheter stability through cryoadhesion of the CB to the target tissue whereas RF-catheters are prone to be instable (“free floating”) during the application. This might result in a more continuous circumferential lesion and in less injuries of surrounding anatomic areas (28, 40).
6) In cryoablation there is no risk of steam pops which can occur in RF ablation from overheating. These are the main contributors for pericardial tamponades in RF ablation (41)
7) Pain-free ablation that is well tolerated by the sedated patient (42-44)
8) Continuous circumferential lesion sets through homogenous refrigerant distribution within the balloon compared to focal point-by-point lesions with RF and the possibility of a “single-shot” PVI making the CB procedure less complex and less operator dependent resulting in a shorter overall procedure time (23, 26, 27)
9) Similar overall complication rate with fewer major complications (26); asymptomatic phrenic nerve palsy with a recovery rate of 99% is the main cryospecific complication (26)
10) Less re-do ablation procedures, electrical cardioversions and re-hospitalizations during follow-up in paroxysmal AF (45)

Considerable disadvantages of cryoballoon ablation in comparison to RF ablation are a higher radiation exposure due to PV angiographies (46), no supportive 3D-mapping system that allows a reconstruction of the left atrium for anatomic non-fluoroscopic guidance of the ablation or AF substrate characterization (no voltage mapping) (46), and a less flexible catheter application without the possibility of potential substrate modification (47).

Catheter Ablation Strategies

Regarding the mechanisms of AF, various ablation strategies have been developed. For paroxysmal AF, PVI is the goal in the catheter treatment (21, 48). PVI can be achieved using RF-energy by the conventional point-by-point RF-ablation, or cryoballoon based ablation which allows a single-shot PVI. Due to more complex mechanisms in persistent AF, several empirical strategies using RF energy have been investigated (e.g. PVI plus trigger based ablation, linear ablations, ablation targeting complex fractionated atrial electrograms, stepwise ablation approach, etc.). The results have shown limited success rates and multiple procedures were often necessary (49-59). Furthermore, the STAR AF II trial has recently demonstrated that PVI alone was non-inferior to strategies with additional substrate modification. The authors even mentioned that more extensive ablation may induce new arrhythmogenic substrate (60). Hence, the preferred strategy for the treatment of persistent AF is still unclear and it is reasonable to obtain PVI alone with either RF- or cryoenergy even in persistent AF in the initial ablation procedure.

As a result, cryoballoon based ablation has attracted increasing worldwide interest. Particularly since 2012, as the technically improved second-generation cryoballoon (CBG2) was released and impressed with an increase in refrigerant flow and a broader freezing zone (complete distal hemisphere of the balloon) leading to a more potent ablation in an equally safe procedure as compared to its predecessor (61-63). However, data were limited to smaller single-center

cohorts and the preferred cryoablation protocol for optimal lesion generation has not yet been determined. In this cumulative dissertation, CBG2-PVI was performed in two large patient populations with either paroxysmal or persistent AF. The following section will give information about the objectives and general approach of the research, the cryoablation procedure protocol and main findings.

Scientific Questions and Objectives

The main goals were

- To assess baseline characteristics, procedural data and periprocedural adverse event rates after PVI using the CBG2 in patients with symptomatic paroxysmal or persistent AF
- To investigate the clinical outcome ≥12 months (freedom from AF, atrial tachycardia, AF-related symptoms) excluding a 3-month blanking period
- To provide additional data and to evaluate, whether cryoablation is a safe and effective treatment option and thus can be a first choice ablation strategy for the initial ablation procedure
- To investigate the role of both balloon sizes: the small 23-mm CB and the large 28-mm-CB

Own Contribution:

Catheter Ablation with the Second-generation Cryoballoon

Two large cohorts of consecutive patients with symptomatic drug-refractory paroxysmal or persistent AF were investigated and underwent initial CBG2-PVI from May 2012 to February 2014. Baseline characteristics and periprocedural data were collected prospectively. Follow-up was performed at the institution immediately after ablation and at 1, 3, 6, 9, 12 and 18 months (ECG, Holter monitoring, symptoms) by referring physicians, outpatient clinics, structured telephone interviews and questionnaires. Data were processed using Excel 2010 (Microsoft Corp., Redmond, WA) and SPSS 20.0 (IBM Corp., Armonk, NY) (1, 2).

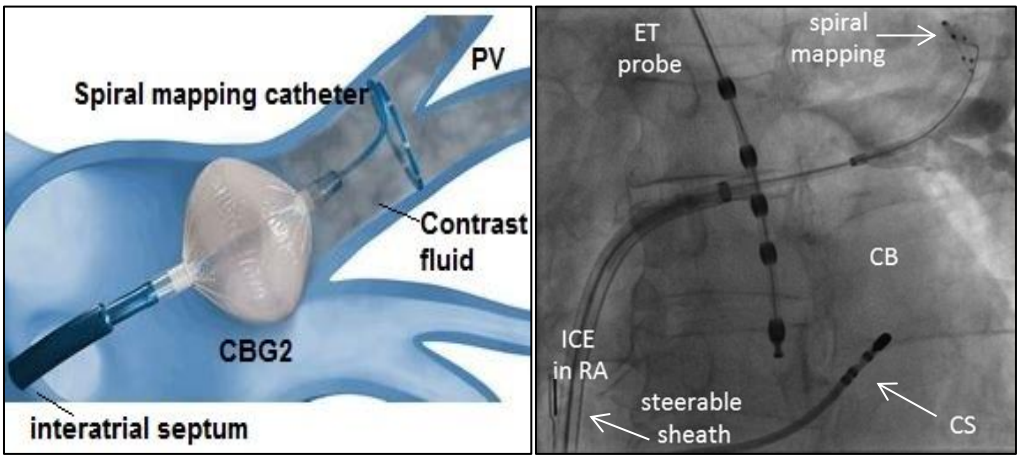
CB procedure was performed based on an individual approach with respect to PV anatomy measured prior to ablation via CT or MRI scans. Two CB sizes were available. The 28-mm CB was used as the primary catheter if any PV diameter was >21mm. The smaller 23-mm CB was applied if all PV diameters were exclusively small (≤ 21mm). The insertion of a second CB size was allowed if PVI could not be achieved with the primary balloon. However, the use of the 23-mm CB in larger PV (e.g. >21mm) was generally excluded (64). In this case, the CB could develop distal into the PV lumen which is suspected to bear a higher complication rate, e.g. PV stenosis or phrenic nerve palsy (64). For this reason, most centers follow a single-big balloon strategy for PVI. Our background of using both balloon sizes lies in our positive experience with the double balloon strategy with the first generation CB in persistent AF (65). Additionally, individual PV anatomies leave legitimate doubts whether all PV can be sufficiently isolated in all patients with a standardized balloon size.

To deploy the CB in the left atrium, transseptal puncture was performed guided by fluoroscopy and intracardiac ultrasound (Vivid I, GE Healthcare EUROPE, GE Ultraschall Deutschland GmbH, Solingen, Germany). Then, the balloon was inflated and positioned at the PV ostium

using the Achieve™ spiral mapping catheter (8-pole) as a guide wire and for real-time PV potential recordings. After optimal balloon positioning was confirmed through PV angiography and intracardiac echocardiography (ICE), refrigerant supply was started and thus circumferential lesions were created in tissue-balloon contact zones leading to PVI (**Figure 2,** not shown in publications). The Achieve™ catheter was pulled back to the proximal part of the vein to record the PV potentials during the freeze. The time to PV isolation (TTI) was determined if feasible. At least two freeze-thaw-freeze cycles per vein were applied including a bonus application after acute PVI was achieved. PV potentials were mapped before and after each freeze cycle and at the end of the procedure. Additional RF touch-up applications were allowed if necessary to achieve electrical isolation of the vein. Phrenic nerve pacing at the right subclavian vein or the superior vena cava (SVC) was performed with manual palpation of the diaphragmatic motion to screen for phrenic nerve palsy, which is one of the main complications of CB ablation. In case of difficulties to feel the diaphragmatic motion, ICE was placed at the level of the right diaphragm and the liver to visualize the phrenic nerve function during the pacing maneuver. Furthermore, an endoluminal esophageal temperature probe (SensiTherm^{TM}, St. Jude Medical, Saint Paul, Minnesota, US) with three thermocouples was applied to detect lowest esophageal temperature during the applications. Standard application times per freeze were ≤ 240 and ≥ 180 seconds. Recent data demonstrated that 180 seconds are equally effective (66). Premature termination of the freeze was performed under the following circumstances: 1) phrenic nerve impairment, 2) low esophageal temperatures (≤+15°C), 3) low balloon temperatures when ablating the right sided veins (<-55°C), and 4) inefficacy of the freeze, e.g. very long TTI or high balloon temperatures (1, 2).

The following part summarizes the background of the studies and the main findings.

Figure 2: Cryoablation procedure using the second-generation cryoballoon. Left: graphic viewed from the inside of the left atrium. Right: PV angiography



Left: PV, pulmonary vein; CBG2, second-generation cryoballoon. Based on and modified from Medtronic: http://www.medtronic.com/for-healthcare-professionals/products-therapies/cardiac-rhythm/ablation-products-for-atrial-fibrillation/arctic-front/index.htm#tab2

Right: ET, esophageal temperature; ICE, intracardiac echocardiography; RA, right atrium, LSVP: left superior pulmonary vein; CB: cryoballoon and CS, coronary sinus. With kind permission of the Department of Cardiology and Internal Intensive Care Medicine, Municipal Hospital Munich-Bogenhausen

Cryoablation in Paroxysmal Atrial Fibrillation

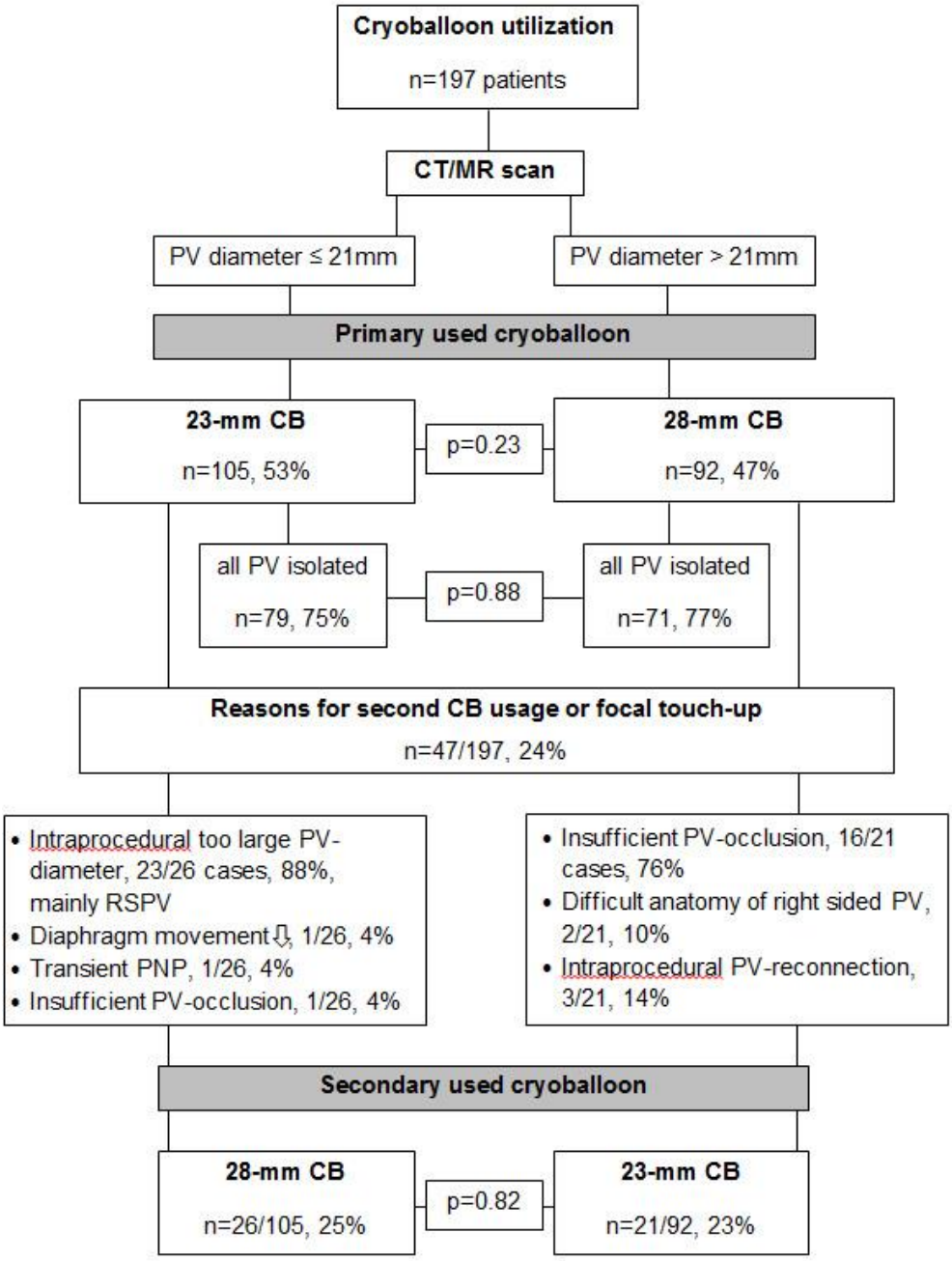
In **publication I** (page 39ff, (1)) we investigated the overall safety and efficacy of CBG2-PVI in patients with paroxysmal AF as well as their differences after an individualized cryoballoon sizing (23-mm CB, 28-mm CB, both CB) depending on PV diameter. Thereby, another main goal was to show whether – and under which conditions – even the 23-mm CB can be a reasonable ablation tool, although a higher complication rate is generally suspected.

One hundred and ninety-seven patients with symptomatic drug-refractory paroxysmal AF (64±11 years, 36% female) were investigated. Cryoballoon size selection was based on pre-procedural CT/MRI measurements (**Figure 3**). The 28-mm CB was the primary catheter in 47% (92/197 patients), the 23-mm CB in 53% (105/197, p=0.23), respectively. Significantly more females, patients with shorter LA diameters (each $p<0.01$) and smaller patients ($p=0.04$) were in the 23-mm CB group in comparison to the 28-mm CB group. Both CB sizes were necessary in 25% (21/92 patients) after beginning the procedure with the 28-mm CB and in 23% (26/105 patients, p=0.82) after beginning with the 23-mm CB, respectively. The main reason for a transition from the 28-mm CB to the 23-mm CB as a second catheter was an insufficient PV occlusion as a result of difficult PV anatomy. The main reason for a transition from the 23-mm CB to the 28-mm CB was a discordant, too large PV diameter compared to pre-procedural imaging results (**Figure 3**), which unnecessarily increased material costs. Acute PVI was accomplished in 99.9% of PV with cryoenergy only. Therefore, one additional focal touch-up ablation with RF-tip catheter was necessary to achieve PVI in one vein. Mean left atrial procedure time was 104±35 minutes. Mean total procedural and fluoroscopy times were 142±42 minutes and 25±9 minutes, respectively. Further baseline characteristics and procedural data are shown in **Table 3 and 4**. The study reveals an arrhythmia- and symptom free survival of 86% at 12 months and, at 18 months, 71% of patients were still in stable sinus rhythm irrespectively of the cryoballoon sizes used (**Figure 4**). At baseline, 41% of patients were on

AAD. After 12 and 18 months of follow-up, 6% of patients still received AAD treatment. There were no predictors for AF recurrence (**Table 5**). Periprocedural complication rates were low (4%, 8 of 197 patients; **Table 6**). One transient amaurosis fugax occurred as the only major complication (0.5%). Notably one phrenic nerve palsy (0.5%) resolved until discharge. No major adverse cardiac or cerebrovascular events and no PV stenosis or atrioesophageal fistula occurred during follow up.

Our study shows that cryoballoon based PVI can sometimes be challenging. The 28-mm CB should be the primary ablation catheter in all patients. If PVI is difficult with the 28-mm CB, the 23-mm CB is an equivalent alternative in small veins with a favorable outcome result in a safe procedure. Whether the 23-mm CB can be beneficial as the primary catheter in females with small body height and short LA diameters needs to be further investigated.

Figure 3: Cryoballoon utilization in patients with paroxysmal atrial fibrillation. The graphic shows our individualized cryoballoon size selection and the reasons for additional cryoballoon insertion



PV, pulmonary vein; CB, cryoballoon; RSPV, right superior PV and PNP, phrenic nerve palsy. One focal touch-up with RF energy was performed in 1 PV (not shown) on the operator's discretion (1).

Table 2: Baseline characteristics of patients with paroxysmal atrial fibrillation

Data are presented as mean ± SD, median (IQR) or % of patients. Pairs of † and ‡ indicate significant differences.

	Overall	23-mm CB	28-mm CB	both CB	P-value
Number of patients	197	79 (40)†	71 (36)†	47 (24)‡	<0.01
Age, years	64 ± 11	63 ± 11	65 ± 10	63 ± 11	0.65
Female gender	71 (36)	37 (47)†	15 (21)‡	19 (40)‡	<0.01
Ejection fraction, %	58 ± 4	58 ± 4	58 ± 4	57 ± 5	0.95
LA diameter, mm	42 ± 6	40 ± 5†	45 ± 6‡	41 ± 6†	<0.01
Arterial hypertension	124 (63)	51 (65)	50 (70)	23 (49)	0.09
Hypertensive heart disease	33 (17)	10 (13)	14 (20)	9 (19)	0.61
Structural heart disease	28 (14)	10 (13)	13 (18)	5 (11)	0.62
Coronary artery disease	22 (11)	8 (10)	10 (14)	4 (9)	0.79
Mitral Valve Insufficiency °II	1 (1)	1 (1)	0 (0)	0 (0)	0.83
Cardiomyopathy	5 (3)	1 (1)	3 (4)	1 (2)	0.78
Creatinine, mg/dl	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.1	0.99
Height, cm	176 ± 0.1	174 ± 0.1†	178 ± 0.1‡	176 ± 0.1	0.04
BMI, kg/m²	26.6 ± 4	26.4 ± 5	26.7 ± 4	26.7 ± 5	0.92
History of AF, months	50 (19 - 103)	46 (22 - 90)	57 (23 - 108)	67 (10 - 112)	0.72
AAD treatment at baseline	83 (42)	35 (44)	24 (34)	24 (51)	0.23

LA, left atrium; BMI, body mass index; AF, atrial fibrillation; PVI, pulmonary vein isolation; and AAD, antiarrhythmic drug (1)

Table 3: Procedural data of patients with paroxysmal atrial fibrillation

Data are presented as mean ± SD, median (IQR) or % of pulmonary veins and patients, respectively. Pairs of † and ‡ indicate significant differences.

	Overall (n=197)	**23-mm CB**	**28-mm CB**	**both CB**	***P*-value**
Total procedure time, min	146 ± 42	137 ± 45†	141 ± 34†	172 ± 38‡	<0.01
LA time, min	104 ± 35	97± 35†	97 ± 29†	129 ± 32‡	<0.01
Fluoroscopy time, min	25 ± 9	22 ± 8†	25 ± 9†	31 ±9‡	<0.01
Dose area product, cGy*cm²	2481 (1586 – 3810)	2224† (1408 – 3138)	2304† (1342 – 3783)	2866‡ (2008 – 4046)	0.01
Acute PVI with cryoenergy only	778/779 (99.9)	432/432 (100.0)	346/347 (99.7)	–	0.91
Focal touch-ups per vein	1/779 (0.1)	0/432 (0.0)	1/347 (0.3)	–	0.91
Ablation duration per application,s	194 ± 37	194± 41	195± 31	–	0.61
Ablation duration per patient, s	826 ± 151	862 ± 135†	789 ± 167‡	822 ± 134	<0.01
Applications per patient	12.1 ± 2.60	11.9 ± 2.43†	11.8 ± 2.57†	14.8 ± 2.42‡	<0.01
Number of applications until PVI	1.24 ± 0.60	1.18 ± 0.49†	1.21 ± 0.52†	1.57 ± 0.97‡	<0.01
Single Shot PVI, % of PV	82.7	82.9	82.4	–	0.98
Applications per PV	2.98 ± 1.18	2.70 ± 0.96†	2.86 ± 1.25†	3.98 ± 1.17‡	<0.01
Time to isolation determined	376/779 (48)	226/432 (52)	150/347 (43)	–	0.01
Time to isolation, s	39 ± 25	35 ± 24	46 ± 28	–	<0.01

LA, left atrium; PVI, pulmonary vein isolation; CB, cryoballoon; and PV, pulmonary vein (1)

Table 4: Intraprocedural differences and premature freezing-termination during 23-mm or 28-mm cryoballoon application in patients with paroxysmal atrial fibrillation

Data are presented as mean ± SD, single value or % of pulmonary veins

Pulmonary veins (n= 779)	**23-mm CB**	**28-mm CB**	***P*-value**
Nadir CB-temperature, °C	- 56 ± 7	- 51 ± 6	<0.01
Lowest CB-temperature, °C	-78	-69	–
Premature termination of the application for low CB-temperature	41/434 PV (9%)	18/345 PV (5%)	0.04
Nadir esophageal-temperature, °C	+33 ± 5	+33 ± 14	0.58
Lowest esophageal-temperature, °C	+6.8	+7.1	–
Premature termination of the application for low esophageal- temperature	12/434 PV (3%)	15/345 PV (4%)	0.33

CB indicates cryoballoon, and PV, pulmonary vein (1)

Table 5: Univariate and multivariate analyses indicating predictors for AF recurrence after cryoablation for paroxysmal atrial fibrillation

Variable	β coefficient	Hazard ratio (95% confidence interval)	*P*-value
Univariate analysis			
Age (years)	-0.016	0.98 (0.96 - 1.01)	0.22
Female gender	-0.25	0.78 (0.44 - 1.37)	0.39
Ejection fraction (%)	-0.04	0.97 (0.91 - 1.02)	0.24
Hypertension	-0.02	0.98 (0.55 - 1.73)	0.94
LA diameter (mm)	0.01	1.01 (0.97 - 1.05)	0.71
History of AF (months)	0.001	1.00 (1.00 - 1.00)	0.22
Cryoballoon size			
23-mm	—	—	0.21
28-mm	-0.61	0.55 (0.27 – 1.09)	0.86
both	-0.44	0.65 (0.32 – 1.30)	0.22
Relapses in BP	-0.43	1.54 (0.83 – 2.87)	0.17
Multivariate analysis			
Relapses in BP	0.62	1.86 (0.93 – 3.75)	0.08
LA diameter (mm)	0.02	1.02 (0.98 - 1.07)	0.35
Arterial hypertension	0.16	1.17 (0.63 - 2.20)	0.42
Ejection fraction (%)	-0.24	0.98 (0.92 – 1.04)	0.46

LA, left atrium; AF, atrial fibrillation; and BP, blanking period (1)

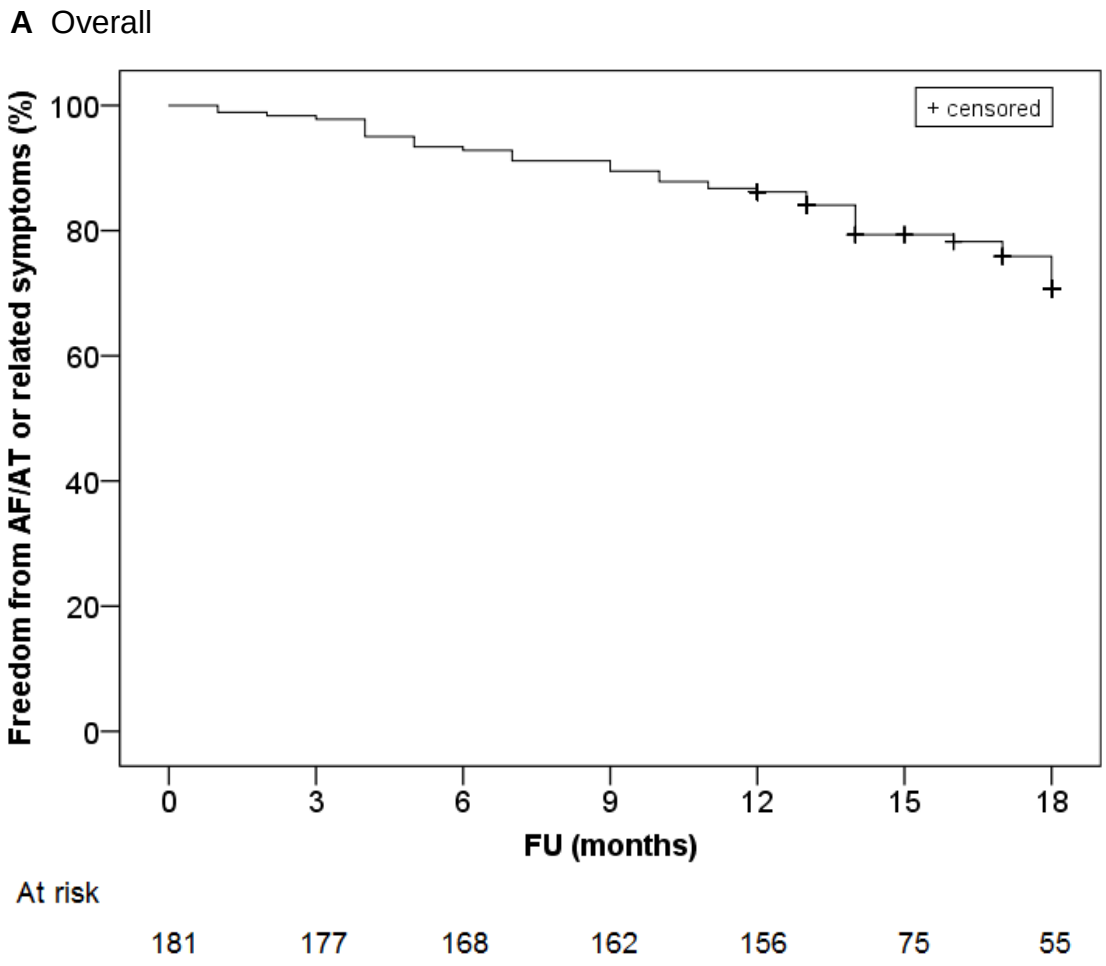
Table 6: Periprocedural adverse event rates in patients with paroxysmal atrial fibrillation

Type of complication	**Cryoballoon**				**Rate** (%)
	23-mm (n=79)	**28-mm** (n=71)	**both** (n=47)	**total** (n=197)	
Major adverse events				**1**	**0.5**
Death, MI, TIA/stroke, PV stenosis				0	0.0
Transient amaurosis fugax	1			1	0.5
Tamponade				0	0.0
Minor adverse events				**7**	**3.5**
PNP recovered at discharge		1		1	0.5
Inflammatory pericardial effusion	1	2		3	1.5
Groin complication			1	1	0.5
Febrile airway infection		1		1	0.5
Urinary tract infection			1	1	0.5
Overall adverse events	**2**	**4**	**2**	**8**	**4.0**
	p=0.63				

MI, myocardial infarction; TIA, transient ischemic attack; PV, pulmonary vein, and PNP, phrenic nerve palsy (1).

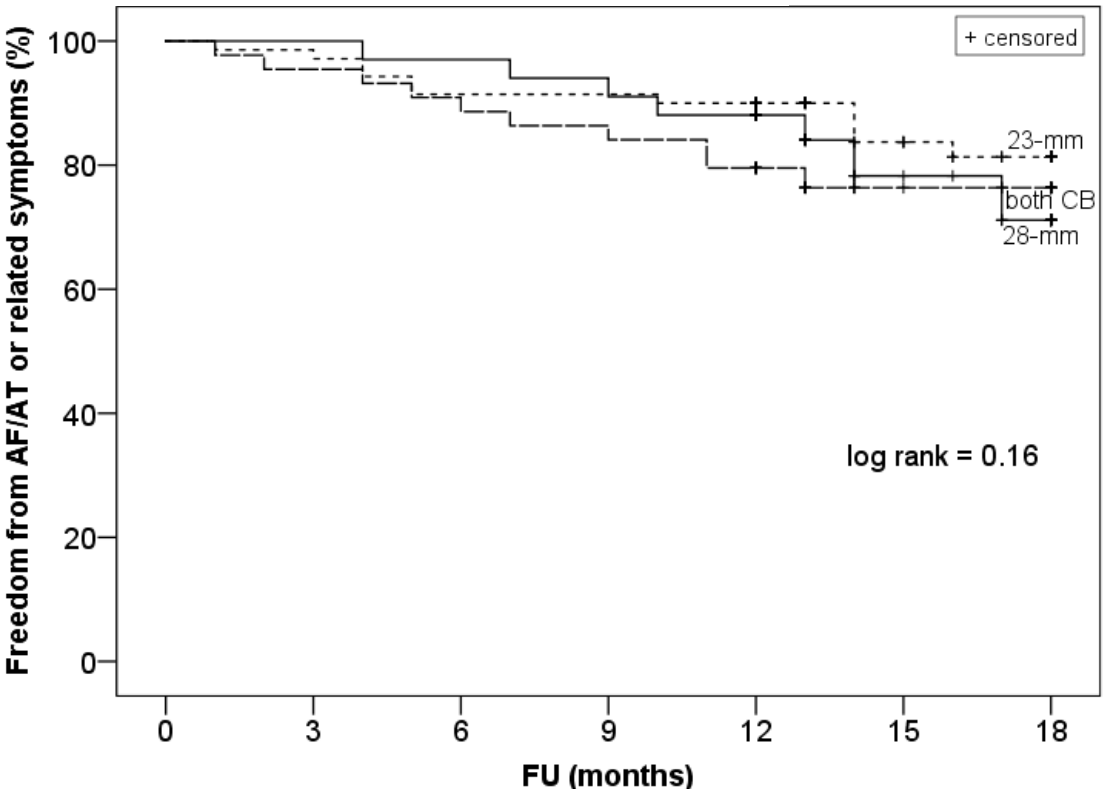
Figure 4: Primary composite endpoint after a single procedure for patients with paroxysmal atrial fibrillation: Freedom from AF/AT or AF symptoms

Kaplan–Meier estimates of freedom from AF/AT or related symptoms, with or without the use of antiarrhythmic drugs (**A**). There was no significant difference regarding the outcome of different balloon sizes or the usage of two balloons (**B**). A 3-months blanking period was considered. Four patients received re-ablation during the blanking period and were calculated as failure. Median follow-up was 13 months.



AF indicates atrial fibrillation; AT, atrial tachycardia and FU, follow up (1)

B Depending on different cryoballoon usage



At risk

23-mm:	70	68	64	64	63	38	28
28-mm:	67	67	65	61	59	23	16
both CB:	44	42	39	37	34	14	11

AF indicates atrial fibrillation; AT, atrial tachycardia and FU, follow up (1)

Cryoablation in Persistent Atrial Fibrillation

Different ablation strategies have been proposed for the treatment of patients with persistent AF. At study entry, outcome data using the second generation cryoballoon for PVI in persistent AF patients were sparse and the method (e.g. PVI only) has been controversially discussed as the mechanisms to maintain persistent AF are more complex. In **publication II** (page 47ff, (2)), we investigated whether the CBG2 can be an option as a first line ablation strategy in persistent AF. One hundred seventy-three patients (64±10 years, 29% female) with symptomatic drug-refractory persistent AF were identified. Twenty-seven percent of patients presented with a relevant structural heart disease (coronary artery disease, cardiomyopathy or mitral valve insufficiency ≥ °II). One hundred fifty-seven patients (91%) completed the follow-up ≥ 12 months and were enrolled for the analysis of the primary endpoint. Median follow-up was 14 months (IQR 12-19). Acute PVI was achieved in 100% of PV. Mean left atrial time was 112 ± 30 minutes. Mean procedure time was 155±37 minutes and the mean fluoroscopy time was 27±11 minutes. Baseline characteristics and procedural data are shown in **Table 7 and 8**. At 12 months, freedom from AF, atrial tachycardia or symptoms was achieved in 82% of patients. At 18 months, 59% of patients were still in stable sinus rhythm (**Figure 5**). At baseline, 66% of patients were on AAD. Seventeen percent of patients at 12 months and 6% at 18 months of follow-up were still on AAD treatment. A relapse during the blanking period was an independent predictor for AF recurrence in uni- and multivariate analyses (**Table 9**). The complication rate was low (4%). Major complications occurred in 1.7% including two phrenic nerve palsies which resolved until discharge and one inflammatory pericardial effusion requiring pericardial drainage (**Table 10**). No major adverse cardiac or cerebrovascular events and no PV stenosis or atrioesophageal fistula occurred during follow up.

The study shows, that PVI with the CBG2 is a safe and effective treatment option for patients with persistent AF and can be used as an initial ablation approach in persistent AF ablation.

Table 7: Baseline characteristics of patients with persistent atrial fibrillation

Data are presented as mean ± SD, median (IQR) or % of patients.

Number of patients	173	157 (follow up)	
Age, years	64 ± 10	**Basal rhythm at study entry**	
Female sex	50 (29)	Sinus rhythm, n (%)	122 (78)
Ejection fraction, %	54 ± 8	Atrial fibrillation, n (%)	35 (22)
LA diameter, mm	46 ± 7		
LA volume, ml	145 ± 39		
LA volume index, ml/m^2	47 ± 13	**Medical treatment at baseline**, n (%)	139 (89)
Arterial hypertension	123 (71)	AAD treatment, n (%)	103 (66)
Hypertensive heart disease	41 (24)	Amiodarone, n (%)	68 (43)
Structural heart disease	46 (27)	Dronedarone, n (%)	17 (11)
Coronary artery disease	23 (13)	Flecainide, n (%)	11 (7)
Mitral Valve Insufficiency ≥ °II	12 (7)	Propafenone, n (%)	2 (1)
Cardiomyopathy	11 (6)	Sotalol, n (%)	5 (3)
Creatinine, mg/dl	0.98 ± 0.07	Beta-receptor blockers, n (%)	36 (23)
BMI, kg/m^2	27.3 ± 5	None, n (%)	18 (11)
History of AF, months	29 (12 - 67)		
Number of cardioversions	2.4 ± 1.6		

LA, left atrium; BMI, body mass index; AF, atrial fibrillation; PVI, pulmonary vein isolation; and AAD, antiarrhythmic drug (2)

Table 8: Procedural data of patients with persistent atrial fibrillation

Data are presented as mean ± SD, median (IQR) or % of pulmonary veins and patients, respectively.

	Overall (n=173 patients)
Total procedure time, min	155 ± 37
LA time, min	112 ± 30
Fluoroscopy time, min	27 ± 11
Dose area product, cGy*cm²	3230 (1870 - 5297)
Acute PVI with CB only	673/673 (100)
Focal touch-ups per vein	0/673 (0)
Cryoballoon usage	
23-mm CB only	32/173 (19)
28-mm CB only	97/173 (56)
28-mm + 23-mm CB	44/173 (25)
Ablation duration per PV, s	198 ± 40
Ablation duration per patient, s	808 ± 166
Applications per patient	12.39 ± 2.78
Applications per PV	3.02 ± 1.19
Number of applications until PVI	1.26 ± 0.62
Time to isolation, s	44 ± 37
Feasibility to determine the TTI (veins, %)	292/673 (43)
Single Shot PVI (% of veins)	82

LA, left atrium; PVI, pulmonary vein isolation; CB, cryoballoon; PV, pulmonary vein; and TTI, time to isolation (2)

Table 9: Univariate and multivariate analyses indicating predictors for AF recurrence after cryoablation for persistent atrial fibrillation

Variable	β coefficient	Hazard ratio (95% confidence interval)	*P*-value
Univariate analysis			
Age (years)	-0.05	0.96 (0.97 - 1.02)	0.70
Female sex	-0.23	0.80 (0.47 - 1.35)	0.40
Ejection fraction (%)	-0.32	1.00 (0.97 - 1.04)	0.84
Hypertension	-0.04	1.00 (0.59 - 1.67)	0.99
LA diameter (mm)	0.01	1.01 (0.98 - 1.05)	0.49
Number of cardioversions	-0.28	0.76 (0.54 - 1.05)	0.10
History of AF (months)	0.001	1.00 (1.00 - 1.01)	0.59
Cryoballoon size			
23-mm	—	—	0.93
28-mm	0.07	1.07 (0.48 - 2.40)	0.86
28-mm + 23-mm	0.12	1.13 (0.59 - 2.16)	0.71
Relapses in BP	0.81	2.26 (1.38 - 3.70)	**<0.01**
Multivariate analysis			
Relapses in BP	0.84	2.31 (1.31 - 4.09)	**<0.01**
LA diameter (mm)	0.04	1.00 (0.96 - 1.05)	0.86
Number of cardioversions	-0.32	0.74 (0.51 - 1.06)	0.10
History of AF (months)	<0.01	1.00 (0.99 - 1.00)	0.70

LA, left atrium; AF, atrial fibrillation; and BP, blanking period (2)

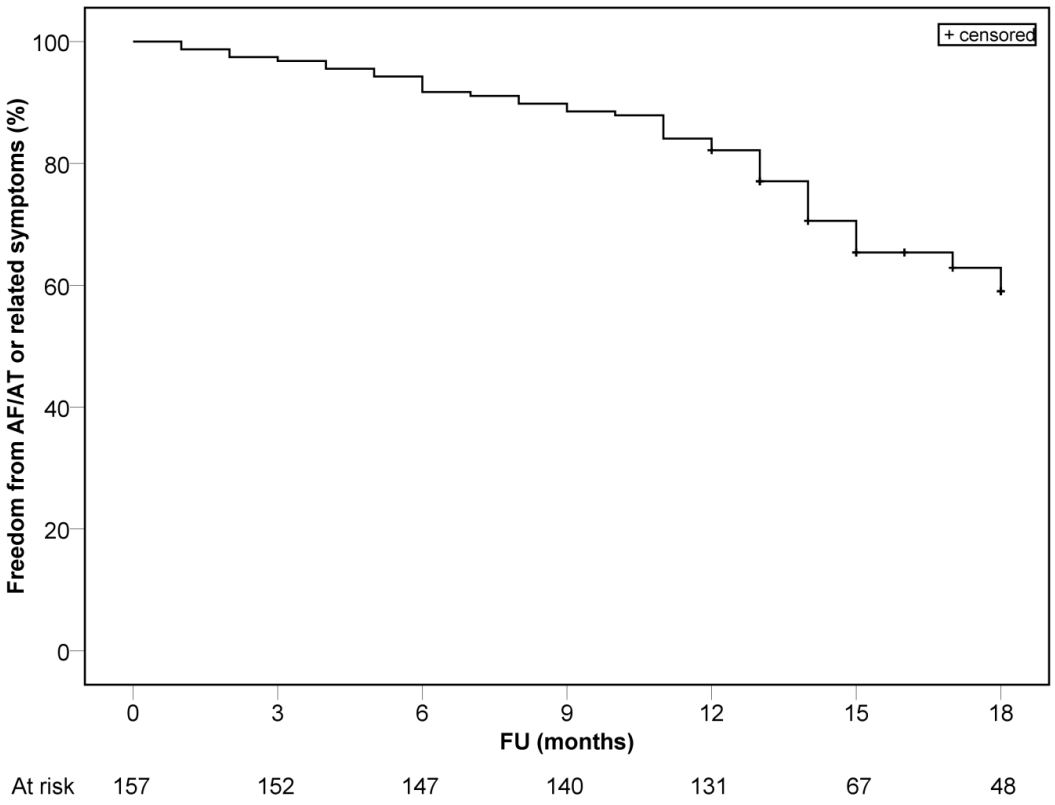
Table 10: Adverse event rates after cryoablation for persistent atrial fibrillation

Type of Complication	No. of patients (n=173)	Rate, %
Total major adverse events	3	1.73
Death, MI, TIA/stroke	0	0.00
PV stenosis	0	0.00
Persistent PNP until discharge	2	1.15
Pericardial effusion incl. drainage	1	0.57
Total minor adverse events	4	2.31
Groin complication	2	1.15
Febrile airway infection	2	1.15
Total adverse events	7	4.05

MI, myocardial infarction; PV, pulmonary vein; TIA, transient ischemic attack; and PNP, phrenic nerve palsy (2)

Figure 5: Primary composite endpoint after a single procedure for patients with persistent atrial fibrillation: Freedom from AF/AT or AF symptoms

The graph shows Kaplan–Meier estimates of freedom from arrhythmia with or without the use of antiarrhythmic medications. A 3-months blanking period was considered. Five patients were re-ablated during the blanking period and therefore calculated as failure. Median follow-up was 14 months.



AF, atrial fibrillation; AT, atrial tachycardia and FU, follow-up (2)

Discussion

The present research results validate that PVI using the CBG2 is a safe and effective treatment option for the index procedure of symptomatic paroxysmal (1) and also persistent AF ablation (2), although the method (e.g. PVI only) has been controversially discussed as the mechanisms in the maintenance of persistent AF are more complex. Acute PVI was achieved with the cryoballoon technique in 99.9% (paroxysmal AF group) and 100% (persistent AF group), respectively. Furthermore, the results demonstrate that PVI using the exclusive single-big balloon technique can be challenging in case of difficult PV anatomy, especially in small veins. As the single-big balloon technique is widely performed because of a suspected higher complication rate of the small CB, the physician needs to consider additional tools to achieve PVI if the big balloon fails to isolate all veins. Most physicians would switch to RF energy and point-by-point RF ablation to close remaining gaps after the ablation with the 28-mm CB. If 28-mm CB PVI was difficult in the present study, the 23-mm CB was applied in small PV only (≤21-mm) to minimize the risk of potential complications (PV stenosis, phrenic nerve palsy). Following this, analyses showed similar results in terms of safety and efficacy as compared to the big balloon.

Freedom from atrial arrhythmia after a single cryoablation procedure was 86% at 12 months for patients who underwent paroxysmal AF ablation (6% on AAD), which is in range with the current literature on cryoablation for paroxysmal AF (67-70). Interestingly, significantly more females, patients with shorter LA diameters and small body height were in the 23-mm CB group. For the persistent AF cohort, the success rate was 82% at 12 months of follow up in our study, while 17% of patients were still treated with antiarrhythmic drugs (59% at 18 months, 6% on AAD). The total adverse event rates were low in both of our study groups (4% each) with very few major adverse events. No death, stroke, myocardial infarction, PV stenosis or atrioesophageal fistula occurred during follow up.

Whether cryo- or radiofrequency ablation is the optimal approach in the initial ablation strategy has not yet been clarified. The randomized FIRE AND ICE trial (24) revealed non-inferiority of first *and* second generation cryoballoon versus RF ablation in terms of safety and efficacy for paroxysmal AF patients (event rate at 365 days off AAD treatment: 34.6% vs. 35.9%, $p<0.001$ for non-inferiority; adverse events: 10.2% vs. 12.8%, $p=0.24$). Our outcome data seem to be superior. This can be explained by the exclusive use of the CBG2 that was technically improved in comparison to the first generation CB (62, 63) and might be biased by a co-treatment with AAD. Furthermore, our data of the persistent AF group compare well with recent findings of the STAR AF II trial. Here, radiofrequency PVI without additional substrate modification revealed freedom from arrhythmia in 59% at 18 months (60). However, Squara et al. published a comparative work of CBG2 and contact force RF ablation and recognized a higher rate of severe non-lethal complications in the RF arm (2.5% vs. none, $p=0.03$) (71).

Reconnection of PV is a main predictor for AF recurrence following catheter ablation. Accordingly, durable PVI should come with a positive impact on clinical outcome. In our cohorts, 81% (paroxysmal AF group) and 72% (persistent AF group) of veins of those patients who required second ablation procedure due to arrhythmia recurrence were still isolated (1, 2). In contrast, the EFFICAS I and II trial showed that the rate of durable PVI increased from 35 to 63% of patients using contact-force guided RF ablation (72, 73), which is still substantially lower compared to the findings with CB.

According to the results of our studies (1, 2) and in respect of current literature of cryo- or RF ablation as described above, the cryoballoon seems to be a favorable ablation tool and the cryoballoon technique convinces with a faster operator learning curve, a high reproducibility of the results across various centers and a short total procedure time (10, 23, 26, 27). Furthermore, insights of the FIRE AND ICE trial demonstrated significantly fewer rates of re-do procedures, re-hospitalizations and electrical cardioversions during follow up after cryoablation

in comparison to RF ablation (45). The improvement in secondary outcome measured with the CBG2 might lead to substantially lower healthcare system costs. Meanwhile, the novel guidelines on atrial fibrillation recommend RF- or cryoablation in equal measure (3, 74).

Conclusions

The results of the present manuscripts state that PVI using the CBG2 is a safe and highly effective treatment option for symptomatic paroxysmal and even persistent AF and can be applied in the initial ablation procedure. The 28-mm CB should be the primary ablation tool in all patients, but the 23-mm CB can be an alternative in small veins, if acute PVI is not achievable with the big balloon. Whether the 23-mm CB could play a role as the primary catheter in females with small body height and short LA diameter needs to be further investigated. Ongoing investigations for CB and RF ablation in large patient populations (FREEZE Cohort Study (75), NCT01360008) will give more answers to the question of the preferred technique to perform a safe and effective AF ablation.

Summary

Pulmonary vein isolation (PVI) is the cornerstone in the catheter ablation treatment of atrial fibrillation (AF). Meanwhile, radiofrequency (RF) energy is the dominant energy source in use to perform PVI. However, the novel cryoballoon technique using cryothermal energy for PVI has shown promising results but outcome data are still limited and the preferred technique for the initial ablation has not yet been determined. The goal of this dissertation was to investigate baseline characteristics, procedural data, periprocedural adverse event rates and the clinical outcome ≥12 months (freedom from AF/atrial tachycardia/ AF-related symptoms) after PVI using the second-generation cryoballoon (CBG2) in two large groups of consecutive patients with symptomatic drug-refractory paroxysmal (197 patients, 64±11 years, 36% female) or persistent AF (173 patients, 64±10 years, 29% female). Two cryoballoon sizes were available and applied following an individualized anatomic approach using prior CT/MRI measurements of the PV diameter (all PV≤21mm: 23-mm CB as the primary catheter; one PV>21mm: 28-mm CB). If acute PVI was difficult with the primary balloon, the second CB size was allowed. We experienced that 28-mm CB PVI – most centers perform a “one size fits all” strategy – can be challenging because of difficult PV morphologies. In these cases, the 23-mm CB was an equivalent alternative to achieve PVI in small veins. Nevertheless, the 28-mm CB should be the primary catheter in all patients since PV diameter is not known prior to ablation in most centers. This might lead to a usage of the small CB in too large veins and increase the risk of complications (PV stenosis, phrenic nerve palsy). Furthermore, PV diameter appeared often larger than initially measured, which required a change to the big CB and lead to extended material costs.

Acute PVI with the cryoballoon was achieved in 99.9% (paroxysmal AF) and 100% (persistent AF). Therefore, one additional RF focal touch-up for one PV was necessary. Total procedure

time was 142±42 minutes in the paroxysmal AF group and 155±37 minutes in the persistent AF group. At 12 months of follow-up, arrhythmia and symptom-free survival was achieved in 86% of patients with paroxysmal AF (6% on antiarrhythmic drugs, AAD) and in 82% of patients with persistent AF (17% on AAD) irrespectively of whether the 23-mm, the 28-mm or both CB sizes were used. A recurrence in the blanking period was the only predictor for AF recurrence (found in the persistent AF group). The complication rate was very low in both cohorts.

The results state that PVI using the CBG2 is a time-saving, highly effective and safe treatment option for the catheter ablation of paroxysmal and even persistent AF. Until recently, PVI only has been controversially discussed for the ablation of persistent AF because its mechanisms are more complex. The actual data, however, provided an important contribution to the current guideline recommendations (3, 74) that meanwhile support cryoablation even in persistent AF as an initial ablation strategy. To the best of our knowledge, we were the first to report that 23-mm CBG2 usage is equally safe in small pulmonary veins which can improve outcome results in veins that are difficult to occlude with the preferred 28-mm cryoballoon. Nevertheless, more long term data and comparative data of cryo- and RF-ablation are necessary to define the optimal initial ablation strategy.

Zusammenfassung

Die Pulmonalvenenisolation (PVI) ist der Eckpfeiler der Katheterablation von Vorhofflimmern (VHF). Derzeit ist Radiofrequenzenergie (RF) die führende Energiequelle, welche für die PVI verwendet wird. Die neue Kälteballontechnologie hingegen basiert auf Kryoenergie und hat bislang vielversprechende Ergebnisse gezeigt. Dennoch ist die Studienlage limitiert und eine Empfehlung zur bevorzugten Energieform für die Erstablation von VHF konnte noch nicht gegeben werden. In der vorliegenden Dissertation wurde die PVI mit dem Kryoballon der zweiten Generation (CBG2) in zwei großen Gruppen konsekutiver Patienten mit symptomatischem, medikamentös-therapierefraktärem, paroxysmalen (197 Patienten, 64±11 Jahre, 36 % weiblich) oder persistierenden VHF (173 Patienten, 64±10 Jahre, 29 % weiblich) durchgeführt. Das Ziel bestand darin, prozedurale Daten und Komplikationen zu erfassen sowie den klinischen Erfolg nach ≥12 Monaten (Freiheit von VHF/Atriale Tachykardie/VHF-typische Symptome) zu untersuchen. Zwei Cryoballongrößen waren verfügbar und wurden entsprechend individueller PV-Durchmesser eingesetzt. Diese wurden vorab mittels CT/MRT Untersuchungen vermessen. Waren alle PV-Durchmesser ≤21mm wurde der 23-mm CB als primärer Ablationskatheter verwendet, zeigte sich ein PV-Durchmesser >21mm, der 28-mm CB. Falls der Eingriff mit dem primären Ablationskatheter schwierig war, kam die zweite Ballongröße zum Einsatz. Wir konnten zeigen, dass die PVI mit dem 28-mm CB – die meisten Zentren verfolgen eine „One size fits all“ Strategie – aufgrund verschiedener PV-Morphologien eine Herausforderung sein kann. In diesen Fällen erwies sich der 23-mm CB als eine gleichwertige Alternative für kleine Venen. Nichtsdestotrotz sollte der 28-mm Ballonkatheter stets die erste Wahl sein, da der PV-Durchmesser in den meisten Zentren vor der Behandlung nicht bekannt ist. Ansonsten könnte der 23-mm CB an zu großen PV verwendet werden und ggf. Komplikationen wie eine PV-Stenose oder Phrenikusparese verursachen. Zusätzlich erwies sich

der PV-Diameter während der Prozedur häufig als größer als zuvor bestimmt, was einen Katheterwechsel auf den 28-mm CB notwendig machte und die Materialkosten steigern kann.

Eine akute PVI mit der Cryoballonmethode wurde in 99.9 % (Patienten mit paroxysmalem VHF) und 100% (Patienten mit persistierendem VHF) erreicht. Folglich wurde eine fokale RF touch-up Ablation nur einer einzigen PV notwendig. Die Eingriffszeit lag in der Gruppe der paroxysmalen VHF Patienten bei 142±42 Minuten und in der Gruppe der Patienten mit persistierendem VHF bei 155±37 Minuten. Nach 12-monatigem Follow-Up konnte eine Erfolgsrate von 86 % bei Patieten mit paroxysmalem VHF (6 % unter antiarrhythmischer Therapie) und von 82 % bei Patienten mit persistierendem VHF (17 % unter antiarrhythmischer Therapie) verzeichnet werden. Dabei war es unerheblich, ob der Eingriff mit dem 23-mm CB, dem 28-mm CB oder beiden Ballons durchgeführt wurde. Der einzige statistisch signifikante Vorhersagewert für ein VHF-Rezidiv wurde in der persistierenden VHF Gruppe gefunden: Rezidive von Vorhofflimmern in der dreimonatigen Blanking Periode nach der Ablation waren ein Prädiktor für weitere Rezidive im Verlauf. Die Komplikationsrate war in beiden Kohorten niedrig.

Zusammengefasst zeigen die Ergebnisse, dass die CBG2-PVI eine zeitsparende, hocheffektive und komplikationsarme Option in der Behandlung von paroxysmalem und persistierendem VHF darstellt. Bislang wurde eine alleinige PVI bei persisterendem VHF aufgrund der komplexeren Mechanismen kritisch gesehen. Die erhobenen Daten lieferten jedoch einen wichtigen Beitrag zu den aktuellen Leitlinienempfehlungen (3, 74), welche die Kryoablation nun selbst zur Behandlung von persistierendem VHF als Erstablation unterstützen. Anhand der uns bekannten Studienlage konnten wir erstmals zeigen, dass die Verwendung des 23-mm CBG2 bei kleinen Pulmonalvenen eine gleichwertige Alternative ist und die Erfolgsrate bei Venen, die mit dem favorisierten 28-mm Ballon schwierig zu okkludieren sind, steigern kann. Nichtsdestotrotz werden zusätzliche Langzeit- und Vergleichsdaten von Kryo- und RF-Ablation benötigt um die überlegene Energieform für die Erstablation von VHF zu bestimmen.

Appendix

Publication I

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Original article

Lessons from individualized cryoballoon sizing. Is there a role for the small balloon?

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ABSTRACT

Background: Cryoablation for paroxysmal atrial fibrillation (PAF) is well established. The single-big-balloon strategy has been preferred for pulmonary vein isolation (PVI) using the second generation cryoballoon (CBG2). Individual PV-morphologies raise the question if an individualized anatomic approach using the 23-mm or 28-mm CB is reasonable.
Methods: Consecutive patients were prospectively enrolled in the non-randomized single-center study. Patients were treated with the 28-mm CB, if any PV was >21 mm, the 23-mm CB, if all PV were ≤21 mm, or both sizes, if PVI was difficult. The primary endpoint was arrhythmia-free survival. The secondary endpoint considered procedural results and complications.
Results: Overall, 197 patients with symptomatic PAF (64 ± 11 years, 36% female) were included. Acute PVI was achieved in 99.9% of PV. Based on preprocedural imaging, the 28-mm CB was applied as the primary catheter in 47% (92/197 patients), the 23-mm CB in 53% (105/197, $p = 0.23$). The 23-mm CB group included more females, patients with short left atrial (LA)-diameters (each $p < 0.01$), and smaller patients ($p = 0.04$). Both CB-sizes were used in 24% (47/197). Additional 23-mm CB usage was necessary in 23% (21/92) of patients, mainly because of insufficient PV-occlusion with the 28-mm CB. Additional 28-mm CB usage was necessary in 25% (26/105, $p = 0.82$), mainly because PV diameters were larger than initially measured. Both CB-sizes were equally safe and effective with a low complication rate and an overall success rate of 86% at 12 and 71% at 18 months (6% on antiarrhythmic drugs). No predictors for AF-recurrence were identified.
Conclusion: CB ablation can sometimes be challenging. The 28-mm CB is the preferred catheter in all patients. If balloon positioning is difficult, the 23-mm CB is an option to achieve PVI in small veins. Further studies need to investigate if the 23-mm CB could be beneficial as the primary CB in females with small body height and short LA diameter.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with a reduced quality of life, increased morbidity and mortality [1]. According to the current guidelines, catheter ablation for pulmonary vein isolation (PVI) is recognized as a class I/A indication for the treatment of symptomatic drug-refractory paroxysmal (P)AF [1,2]. The second-generation cryoballoon (CBG2, Arctic Front Advance; Medtronic Inc, Minneapolis, MN, USA) has attracted worldwide interest as an effective and safe ablation tool. Consistent results regarding safety, procedural efficacy [3,4], and clinical outcome were published by different groups using a single-big balloon approach (28-mm CBG2 only) and freedom from arrhythmia was seen in 80% and more after one year [5–8]. However, in some patients the ablation with the big cryoballoon only can be challenging because of the variety of different PV morphologies and especially in small and inferior veins. We evaluated the safety and efficacy of CBG2-PVI based on an individualized anatomic approach using the 28-mm, the 23-mm, or both balloons for a large group of consecutive patients with symptomatic PAF undergoing AF ablation as an index procedure.

Methods

Objectives

The purpose of the study was: (1) to evaluate the clinical outcome ≥12 months after primary cryoballoon ablation and individual CB

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size selection in a large consecutive group of patients with PAF, (2) to analyze procedural data and periprocedural adverse events.

Study population

Consecutive patients with PAF who underwent PVI with CBG2 as an index procedure and who were eligible for a follow-up ≥ 12 months were prospectively enrolled in our non-randomized, single-center observational registry study. PAF was defined as classified in the current guidelines [1]. Patients were diagnosed with symptomatic drug-refractory PAF or had contraindications for antiarrhythmic drug (AAD) treatment. According to the guidelines, the wish of selected patients was considered in the decision for PVI as the primary AF therapy (class II a/B recommendation) [1]. Exclusion criteria were persistent AF, prior AF ablation therapy, intracardiac thrombi, and severe valvular disease. All patients provided written informed consent for participating in the study prior to ablation therapy. The study was approved by the institutional review committee and complies with the declaration of Helsinki.

Ablation procedure protocol

A detailed summary of our standardized ablation procedure has been previously described [3,9]. Cardiac computed tomography (CT) or magnetic resonance imaging (MRI) scanning was performed in all patients prior to ablation to build a 3D reconstruction of the left atrial (LA)/PV-anatomy, and to rule out significant coronary heart disease if the coronary status was not evaluated before [10]. Intracardiac thrombi were ruled out using transesophageal echocardiography. PVI was performed with the 28-mm and/or the 23-mm cryoballoon (CBG2) as necessary to isolate all PVs sufficiently. After advancing the balloon into the left atrium through a single intracardiac echocardiography (ICE)-guided transseptal puncture (Vivid I, GE Healthcare EUROPE, GE Ultraschall Deutschland GmbH, Solingen, Germany) in an over-the wire technique the balloon was inflated and positioned at the PV ostium. The 8-pole spiral mapping catheter (15 or 20 mm Achieve™, Medtronic Inc.) was used for balloon positioning, mapping, and real-time-PV potential recording. The degree of vessel occlusion was assessed by PV angiography immediately prior to ablation. Then, refrigerant supply was started and PVI was performed with at least two freeze-thaw-freeze cycles per vein including one bonus application after acute electrical isolation. The standard freezing time was ≥180 and ≤240 seconds. The temperature limit was set minus 55 °C CB-temperature for right-sided PVs. ICE was used in all cases to verify optimal antral balloon positioning at the PV ostium and vessel occlusion (Doppler imaging) during ablation. PV-potentials were mapped before and after each freeze cycle and 15 minutes after the last freeze. One bonus application was applied after acute PVI was achieved. Time to isolation was determined if PV potentials were visible during the cryoapplication. The use of the second balloon size or touch-up applications (RF- or cryotip-catheters) was allowed to obtain PVI. RF ablation was only used if PVI was not achievable using cryoenergy. During the entire procedure, intravenous heparin was administered to maintain an activated clotting time between 300 and 400 seconds. Before sheath removal, protamine was given to reduce the risk of bleeding. One hour after sheath removal, we continuously administered intravenous unfractionated heparin with a target partial thromboplastin time of 50 to 70 seconds and oral anticoagulation was resumed on the day after ablation.

Cryoballoon size selection

Patients were primarily treated with the 28-mm CB, if any PV was >21 mm. The 23-mm CB was used as the primary catheter, if all PV were exclusively small (≤21 mm). If PVI could not be achieved with the first balloon, e.g. because of insufficient occlusion with the 28-mm CB, or, when the 23-mm CB was too small for one of the veins (intraprocedural guidance using angiography or ICE to ensure antral balloon positioning), the other CB size (23-mm or 28-mm CB) was applied as a second catheter. However, the 23-mm CB was only allowed in those veins with a PV diameter ≤21 mm to prevent too distal balloon deployment within the PV [11].

Phrenic nerve monitoring

For the early recognition of possible phrenic nerve palsy (PNP), continuous phrenic nerve pacing with a cycle length of 1200 ms was performed after achieving −20 °C or 20 seconds of freezing time using a 4-pole deflectable catheter placed near the junction of the superior vena cava (SVC) and the right subclavian vein or the anterolateral portion of the SVC, near the atrial-SVC junction, and continuous palpation of the diaphragm was performed. Cryoenergy was immediately interrupted if weakening or loss of diaphragmatic contractions were noticed.

Esophageal temperature probe

An esophageal temperature probe (SensiTherm™, 3 thermocouples, St. Jude Medical, Saint Paul, MN, USA) was used in all patients to detect the lowest esophageal temperature. Cryoenergy was immediately terminated if the intraluminal esophageal temperature reached ≤+15 °C. This cut-off value is based on recent findings demonstrating that an esophageal temperature ≤+12 °C induced esophageal lesions with 100% sensitivity and 92% specificity [12], and our own observation that there is always a further temperature drop after the termination of the freeze.

Follow-up

Electrocardiography (ECG) and Holter studies were performed for the first 24 to 48 hours post ablation and up to 7 days in patients with AF symptoms. Transthoracic echocardiography was performed in all patients to rule out pericardial effusion. All complications were registered prospectively. Routine outpatient follow-up was performed at 1, 3, 6, 12, and 18 months (Holter, ECG, symptoms). We collaborated with referring centers to confirm the diagnosis if any recurrence was suspected based on outpatient follow-up results.

Statistical analysis

Continuous data are given as mean with standard deviation (SD) or as the median with interquartile range (IQR), if data were non-normally distributed in accordance to the Kolmogorov–Smirnov test. Continuous data were compared using the Student's *t*-test, or, in case of more than two groups, using ANOVA test (analysis of variance) or Kruskal Wallis test, if appropriate. Categorical data are shown as numbers and percentages and were compared using the chi-square test. In case of more than two groups, further closed testing procedure was performed. Event rates were plotted over time using Kaplan–Meier method. Univariate and multivariate analyses were performed to ascertain potential predictors for AF recurrence using the Cox-regression model. A two tailed p-value < 0.05 was considered significant. Data processing and analysis was performed using Excel 2010 (Microsoft Corp., Redmond, WA, USA) and SPSS 20.0 (IBM Corp., Armonk, NY, USA).

Results

From May 2012 to February 2014, 197 patients with symptomatic PAF underwent cryoballoon ablation. One hundred eighty one (92%) completed the follow-up ≥ 12 months and were enrolled for the analysis of the primary endpoint. Median follow-up was 13 months (IQR 12–19). Sixteen of 197 patients (8%) were lost to follow-up.

Baseline characteristics

The mean age was 64 ± 11 years and 36% (71 of 197 patients) were female. Median history of AF until PVI was 50 months (IQR 19–103). Patients were refractory to ≥1 class I or class III AAD, had a contraindication for AAD treatment, or preferred first-line ablation therapy. Eighty-three patients (42%) were treated with AAD at baseline. The mean LA diameter was 42 ± 6 mm. A relevant structural heart disease (coronary artery disease, cardiomyopathy, or mitral valve insufficiency °II) was present in 28 of 197 patients (14%). The 23-mm CB group included significantly more females, patients with small LA-diameters (each $p < 0.01$), and smaller patients ($p < 0.04$) in comparison to the 28-mm CB group. Additional baseline characteristics are listed in Table 1.

Procedural data and acute success rates

In total, 779 pulmonary veins (PV) were ablated and acute PVI was accomplished in 99.9% (778/779). After a single cryoapplication 83% of veins were isolated (single-shot success). One additional focal touch-up ablation with RF-tip catheter was performed to isolate one right middle PV (0.1%, 1/779 PV). Mean total procedural and fluoroscopy times were 146 ± 42 minutes and 25 ± 9 minutes, respectively. Mean LA procedure time was 104 ± 35 minutes. Comparing cryoapplications with either the 23-mm or 28-mm CB, results showed a significantly lower nadir CB temperature and higher rates of premature freezing-termination for the 23-mm CB (−56 ± 7 vs. − 51 ± 6 °C, $p < 0.01$).

The 28-mm CB was applied as the primary catheter in 47% (92/197 patients) and the 23-mm CB in 53% (105/197, $p = 0.23$). Both CB sizes were used in 24% of procedures (47/197 patients). In these cases, procedure times were significantly longer compared to the 23-mm CB or 28-mm CB group ($p < 0.01$), radiation exposure was significantly higher ($p = 0.01$), and more cryoapplications were applied ($p < 0.01$).

After beginning with the 28-mm CB, further 23-mm CB insertion as a second catheter was necessary in 23% (21/92 patients) for successful PVI. The main reason was an insufficient PV-occlusion with the 28-mm CB in 16 of 21 cases (76%; correlating with 19 PV: left superior PV: 6, right inferior PV: 6, left inferior PV: 4, common ostium: 2, right superior PV: 1). Other reasons were a difficult anatomy of right-sided PV (10%, 2/21 cases) and intraprocedural PV-reconnection (14%, 3/21 cases). Oppositely, after beginning with the 23-mm CB, further 28-mm CB insertion was required in 25% (26/105 patients, $p = 0.82$). The main reason was that PV diameters appeared larger than initially measured in CT/MRI-scan in 23 of 26 patients (88%; correlating with 23 PV: right superior PV: 17, right inferior PV: 3, left superior PV: 2, common ostium: 1). Other reasons were a reduction in diaphragmatic movement, transient phrenic nerve palsy and insufficient PV occlusion (each 4%, 1/26 patients). A detailed graphic of our cryoballoon utilization can be seen in Fig. 1, other procedural details are summarized in Tables 2 and 3.

Periprocedural adverse event rates

Overall, 8 of 197 patients (4%) experienced procedure-related complications. All recovered during follow up. There was no significant difference between the balloons. As the only major complication, one transient amaurosis fugax (0.5%, 1 of 197 patients) occurred. Minor complications were seen in 3.5% (7 of 197 patients) including one persistent PNP that recovered until discharge (0.5%) and three inflammatory pericardial effusions (1.5%) that were treated conservatively. No PV stenosis or atrioesophageal fistula occurred. A complete list of all periprocedural adverse events is given in Table 4.

Outcome results

Fig. 2 demonstrates the clinical outcome of the total study population over time and depending on the CB-sizes used. At 12 months of follow-up, overall rate of freedom from AF, atrial tachycardia, or related symptoms was 156 of 181 patients (86%). At 18 months, the probability for arrhythmia-free survival was estimated to be 71%. Six percent of patients were still treated with AAD at 12 and 18 months. When comparing the primary outcome of those patients treated with the single 23-mm CB or the single 28-mm CB compared to those with a more challenging PV anatomy who received both balloon sizes, no difference was found.

Table 1
Baseline characteristics.

	Overall	23-mm CB	28-mm CB	Both CB	*P*-value
Number of patients	197	79 (40)†	71 (36)†	47 (24)‡	<0.01
Age, years	64 ± 11	63 ± 11	65 ± 10	63 ± 11	0.65
Female gender	71 (36)	37 (47)†	15 (21)‡	19 (40)‡	<0.01
Ejection fraction, %	58 ± 4	58 ± 4	58 ± 4	57 ± 5	0.95
LA diameter*, mm	42 ± 6	40 ± 5†	45 ± 6†	41 ± 6†	<0.01
Arterial hypertension	124 (63)	51 (65)	50 (70)	23 (49)	0.09
Hypertensive heart disease	33 (17)	10 (13)	14 (20)	9 (19)	0.61
Structural heart disease	28 (14)	10 (13)	13 (18)	5 (11)	0.62
Coronary artery disease	22 (11)	8 (10)	10 (14)	4 (9)	0.79
Mitral Valve Insufficiency °II	1 (1)	1 (1)	0 (0)	0 (0)	0.83
Cardiomyopathy	5 (3)	1 (1)	3 (4)	1 (2)	0.78
Creatinine, mg/dl	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.1	0.99
Height, cm	176 ± 0.1	174 ± 0.1†	178 ± 0.1‡	176 ± 0.1	0.04
BMI, kg/m²	26.6 ± 4	26.4 ± 5	26.7 ± 4	26.7 ± 5	0.92
History of AF, months	50 (19–103)	46 (22–90)	57 (23–108)	67 (10–112)	0.72
AAD treatment at baseline	83 (42)	35 (44)	24 (34)	24 (51)	0.23

Data are presented as mean ± SD, median (IQR) or % of patients. Pairs of † and ‡ indicate significant differences.
LA, left atrium; BMI, body mass index; AF, atrial fibrillation; AAD, antiarrhythmic drug; CB, cryoballoon.
* Measured by transthoracic echocardiography (anterior/posterior orientation).

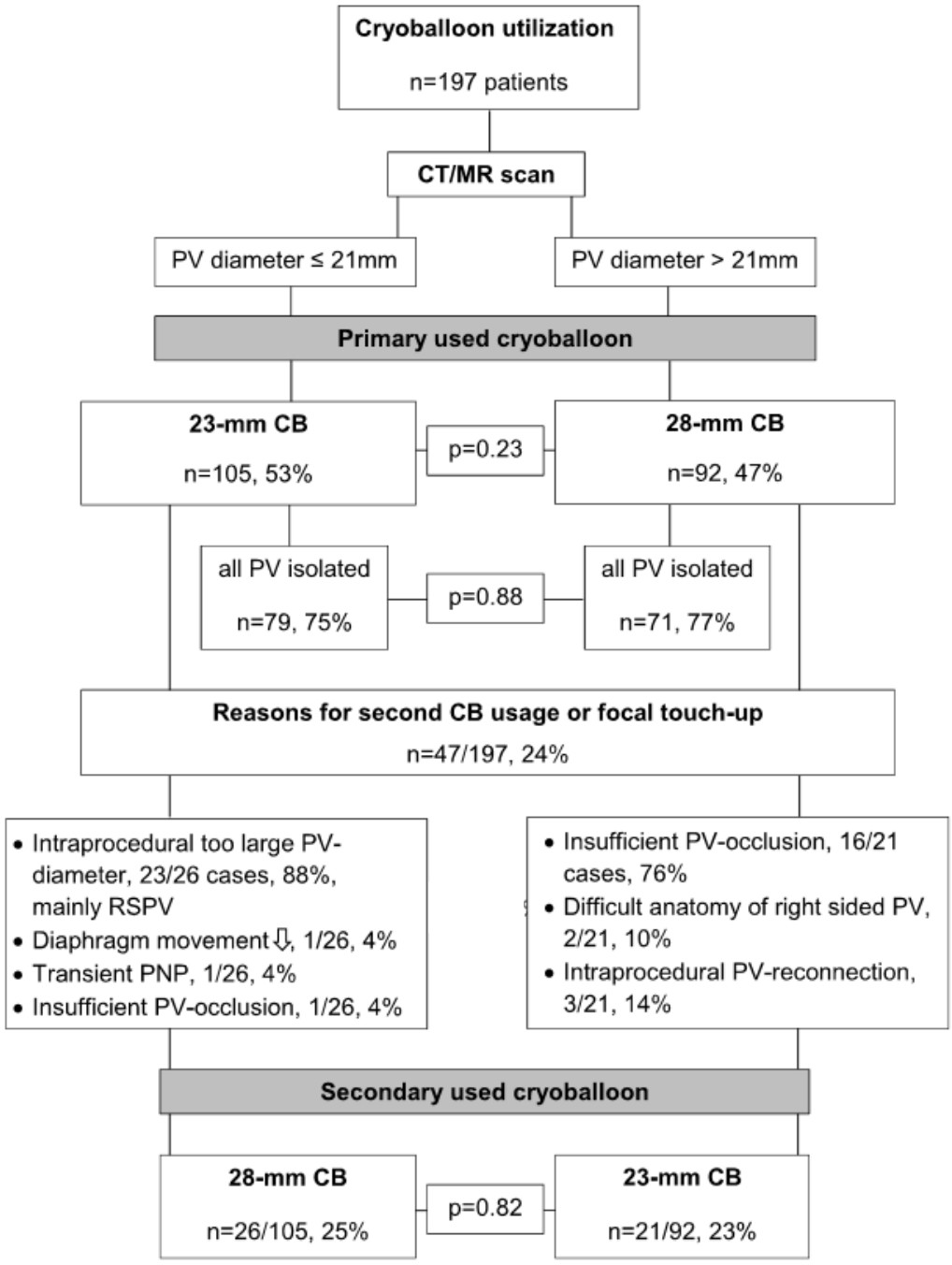

Fig. 1. Cryoballoon utilization. The graphic shows our individualized cryoballoon size selection and the reasons for additional cryoballoon insertion. CT, computed tomography; MR, magnetic resonance; PV, pulmonary vein; CB, cryoballoon; RSPV, right superior PV; PNP, phrenic nerve palsy. One focal touch-up with RF energy was performed in 1 PV (not shown) at the operator's discretion.

In univariate and multivariate analyses, no predictors for AF recurrence were identified (Table 5). However, thirty-three of 181 patients (18%) developed AF arrhythmia recurrences during the blanking period. Fourteen of 181 patients (8%) underwent a redo procedure due to repetitive symptomatic arrhythmia recurrences over time. Of those, seven patients (50%) demonstrated durable PV isolation of all veins and 11 of 59 PVs (19%) showed conduction recovery. One reconducting vein was found in three patients (21%) and two reconducting veins were found in 4 patients (29%). No patient presented with three or more reconducting veins. Right atrial arrhythmia (isthmus dependent atrial flutter) was mapped and ablated in one patient (7%) and left atrial arrhythmias were diagnosed in 3 of 14 patients (21%): two left atrial flutter and one focal left atrial tachycardia.

No major adverse cardiac or cerebrovascular events and no deaths were reported during the follow-up period.

Discussion

In this large single-center study, we investigated patients with PAF undergoing an initial CBG2-PVI based on an individualized cryoballoon sizing depending on PV diameter. Patients were treated with either the 23-mm CB, 28-mm CB, or both CB sizes in case acute PVI was not achievable with one balloon.

Table 2
Procedural data.

	Overall ($n=197$)	23-mm CB	28-mm CB	both CB	*P*-value
Total procedure time, min	146 ± 42	137 ± 45†	141 ± 34†	172 ± 38‡	<0.01
LA time, min	104 ± 35	97 ± 35†	97 ± 29†	129 ± 32‡	<0.01
Fluoroscopy time, min	25 ± 9	22 ± 8†	25 ± 9†	31 ± 9‡	<0.01
Dose area product, cGy*cm²	2481 (1586–3810)	2224† (1408–3138)	2304† (1342–3783)	2866‡ (2008–4046)	0.01
Acute PVI with cryoenergy only	778/779 (99.9)	432/432 (100.0)	346/347 (99.7)	–	0.91
Focal touch-ups per vein	1/779 (0.1)	0/432 (0.0)	1/347 (0.3)	–	0.91
Ablation duration per application, s	194 ± 37	194 ± 41	195 ± 31	–	0.61
Ablation duration per patient, s	826 ± 151	862 ± 135†	789 ± 167†	822 ± 134	<0.01
Applications per patient	12.1 ± 2.60	11.9 ± 2.43†	11.8 ± 2.57†	14.8 ± 2.42‡	<0.01
Number of applications until PVI	1.24 ± 0.60	1.18 ± 0.49†	1.21 ± 0.52†	1.57 ± 0.97‡	<0.01
Single Shot PVI, % of veins	82.7	82.9	82.4	–	0.98
Applications per PV	2.98 ± 1.18	2.70 ± 0.96†	2.86 ± 1.25†	3.98 ± 1.17‡	<0.01
Time to isolation determined*	376/779 (48)	226/432 (52)	150/347 (43)	–	0.01
Time to isolation, s	39 ± 25	35 ± 24	46 ± 28	–	<0.01

Data are presented as mean ± SD, median (IQR) or % of pulmonary veins and patients, respectively. Pairs of † and ‡ indicate significant differences.
LA, left atrium; PVI, pulmonary vein isolation; CB, cryoballoon; PV, pulmonary vein.
* Determination of "Time to isolation" was feasible in 48% of all PVs (376 of 779 PVs) with the 15-mm or 20-mm Achieve™ catheter.

Table 3
Intraprocedural differences and premature freezing-termination during 23-mm or 28-mm cryoballoon application.

Pulmonary veins ($n=779$)	23-mm CB	28-mm CB	*P*-value
Nadir CB-temperature, °C	−56 ± 7	−51 ± 6	<0.01
Lowest CB-temperature, °C	−78	−69	–
Premature termination of the application for low CB-temperature	41/434 PV (9%)	18/345 PV (5%)	0.04
Nadir esophageal-temperature, °C	+33 ± 5	+33 ± 14	0.58
Lowest esophageal-temperature, °C	+6.8	+7.1	–
Premature termination of the application for low esophageal- temperature	12/434 PV (3%)	15/345 (4%) PV	0.33

Data are presented as mean ± SD, single value or % of pulmonary veins.
CB, cryoballoon; PV, pulmonary vein.

Table 4
Periprocedural adverse event rates.

Type of complication ($n=197$ patients)	Cryoballoon				Rate (%)
	23-mm ($n=79$)	28-mm ($n=71$)	Both ($n=47$)	Total ($n=197$)	
Total major adverse events ($n=1$)		**1**	**0.5**		
Death, MI, TIA/stroke, PV stenosis				0	0.0
Transient amaurosis fugax	1			1	0.5
Tamponades				0	0.0
Total minor adverse events ($n=7$)		**7**	**3.5**		
PNP recovered at discharge		1		1	0.5
Inflammatory pericardial effusion*	1	2		3	1.5
Groin complication			1	1	0.5
Febrile airway infection		1		1	0.5
Urinary tract infection			1	1	0.5
Total adverse events ($n=8$)	**2**	**4**	**2**	**8**	**4.0**
		p = 0.63			

MI, myocardial infarction; TIA, transient ischemic attack; PV, pulmonary vein; PNP, phrenic nerve palsy.
* Asymptomatic, treated conservatively.

Decision on the primary cryoballoon size

Based on technical advantages of the 28-mm CB (increased flow rate of the refrigerant in comparison to the first-generation CB was only achieved for the 28-mm CBG2, broader cooling zone, broader lesion zone) [3] and safety concerns regarding the 23-mm CB (suspected higher risk of PV stenosis and PNP if deployed too far within the PV), a single big balloon strategy for PVI is preferred in most centers and favorable outcome results have been demonstrated [5–8]. However, individual morphologies of the LA and PVs raise the question if the pre-shaped CB can sufficiently occlude all PV ostia in every patient [13], especially small and inferior veins are often challenging to occlude with the 28-mm CB. Therefore, we investigated baseline characteristics and procedural data as well as efficacy and safety for the 23-mm, 28-mm, or both CBs after individual cryoballoon sizing. Our center is familiar with the use of the 23-mm CB because of the experience with the double balloon strategy in persistent AF with the first-generation cryoballoon [14]. Van Belle et al. suggested that the PV diameter/balloon size ratio should not exceed 0.94 to avoid CB ablation inside the veins [11]. To ensure patients' safety in this study, primary 23-mm CB usage was therefore only permitted if PV diameter was measured ≤21 mm in prior CT/MRI scan.

Outcome and safety depending on the cryoballoon sizes used

The present study demonstrates an overall 86% freedom from arrhythmia at 12 months and 71% at 18 months irrespective of the

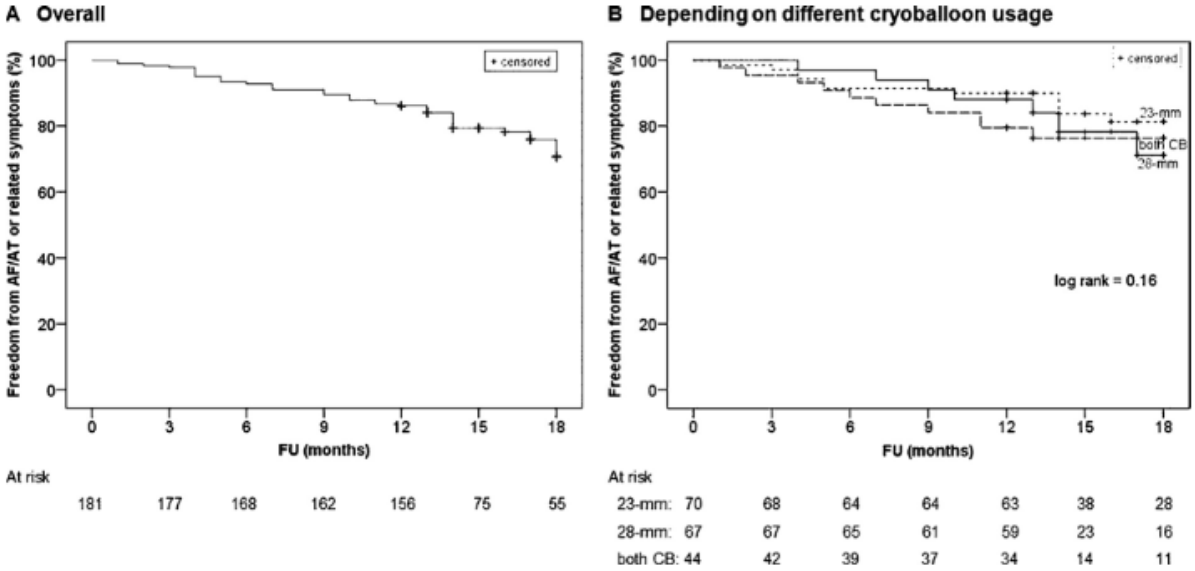

Fig. 2. Primary composite endpoint after a single procedure: Freedom from AF/AT or AF symptoms. The graphs show Kaplan–Meier estimates of freedom from documented AF/AT or related symptoms, with or without the use of antiarrhythmic medication, after a single procedure using the second-generation cryoballoon. There was no significant difference regarding the outcome of different balloon sizes or the usage of two balloons. A 3-month blanking period was considered. Four patients received re-ablation during the blanking period and were calculated as failure. Median follow-up was 13 months. AF, atrial fibrillation; AT, atrial tachycardia; FU, follow-up.

Table 5
Univariate and multivariate analyses indicating predictors for AF recurrence.

Variable	β coefficient	Hazard ratio (95% confidence interval)	*P* value
Univariate analysis			
Age (years)	−0.016	0.98 (0.96–1.01)	0.22
Female gender	−0.25	0.78 (0.44–1.37)	0.39
Ejection fraction (%)	−0.04	0.97 (0.91–1.02)	0.24
Hypertension	−0.02	0.98 (0.55–1.73)	0.94
LA diameter (mm)	0.01	1.01 (0.97–1.05)	0.71
History of AF (months)	0.001	1.00 (1.00–1.00)	0.22
Cryoballoon size			
23-mm	–	–	0.21
28-mm	−0.61	0.55 (0.27–1.09)	0.86
Both	−0.44	0.65 (0.32–1.30)	0.22
Relapses in BP	−0.43	1.54 (0.83–2.87)	0.17
Multivariate analysis			
Relapses in BP	0.62	1.86 (0.93–3.75)	0.08
LA diameter (mm)	0.02	1.02 (0.98–1.07)	0.35
Arterial hypertension	0.16	1.17 (0.63–2.20)	0.42
Ejection fraction (%)	−0.24	0.98 (0.92–1.04)	0.46

LA, left atrium; AF, atrial fibrillation; BP, blanking period.

CB size used and independently of whether PV anatomy was difficult and required second CB size insertion or not (Fig. 2). We could show that PVI with the 23-mm CB is equivalent in terms of safety and efficacy as compared to a single procedure with the 28-mm CB or cases in which both CB sizes were used (Table 4, Fig. 2). These findings compare well with recent results of the CB technique [5–8,15]. The prerequisites, however, are that 23-mm CB PVI is performed in exclusively small PV only and that an antral balloon positioning is ensured in order to prevent complications such as PV stenosis or PNP [16,17]. Due to the smaller surface of the 23-mm CB, lower nadir CB temperatures are typical in comparison to the big balloon [18]. Since the temperature is measured on the proximal part of the balloon, it does not directly reflect tissue temperature. However, higher rates of premature procedure interruptions for the 23-mm CB were preceded for safety reasons according to our general termination criteria. No PV stenosis was detected by CT scan in any patient that presented with associated symptoms after the procedure.

Indications to apply the second cryoballoon size

Our ablation procedure protocol was not restricted to a single balloon strategy and the use of a second catheter was generously allowed, if acute PVI appeared difficult and could not be achieved with the first balloon (e.g. insufficient occlusion or undersized balloon compared to PV ostium).

Challenging PV isolation: transition from big to small CB

The main reason for the transition from the 28-mm CB to the 23-mm CB was a challenging PV occlusion, especially in small and inferior veins. The 23-mm CB was then successfully used as a second catheter for PVI (Fig. 1).

Limitations of pre-procedural imaging: transition from small to big CB

We could demonstrate that pre-procedural measurements of the PV using CT/MRI scans is not always reliable. When a 23-mm CB balloon strategy was chosen because of exclusively small PV diameters in prior imaging, the actual size of at least one PV appeared too large for the small CB in almost 25% of cases during the procedure (Fig. 1). This required a change to the big 28-mm CB and led to prolonged procedure times and higher material costs. Therefore, prior imaging might be omitted if not indicated for other reasons or a shorter PV-diameter cut-off criterion has to be applied. If necessary, PV measurements can be performed during the procedure using PV angiography and/or ICE.

Indications for the 23-mm cryoballoon

According to our data, the 23-mm CB is an equivalent alternative for exclusively small veins (≤21 mm) and is an option when the 28-mm CB cannot sufficiently isolate all PVs. Interestingly, those patients treated with the 23-mm CB based on pre-procedural imaging included more females, patients with smaller body height, and patients with short LA-diameters in comparison to patients that were assigned to the 28-mm CB group. Future studies need to evaluate if the 23-mm CB could be beneficial as the

primary CB size in small females with short LA diameters without pre-procedural CT/MRI imaging.

Indications for the 28-mm cryoballoon

According to the technical benefits of the 28-mm CB over the small CB, the favorable pre-existing outcome for the single big balloon strategy and the potentially higher complication rate of a primary 23-mm CB usage, which might result in CB applications too distal in the veins, the 28-mm CB should be the primary catheter in all patients. The fact, that prior PV measurements were not always reliable in our study emphasizes this recommendation.

Economic aspects

It is unclear whether the fast and straightforward cryoballoon ablation is time- and cost-effective [19] after adjusting for personnel costs, catheter laboratory time, and expenditures on redo procedures especially when compared to the traditional RF point-by-point ablation guided by 3D-mapping. Further studies need to evaluate the time- and cost-effectiveness of cryo- versus RF-ablation. The present study follows a "proof-of-concept" strategy indicating that durable PVI is possible using the cryoenergy source only. The main aim was to show the feasibility and safety of the individualized strategy. Of course, other techniques such as RF-touch up ablations are also reasonable in those situations when the big balloon fails to isolate a vein.

Predictors for AF recurrence

We could not identify any predictors for AF recurrence. The majority of patients in this study did not suffer from severe comorbidities and it is likely that the small number of subjects with large LA diameters was not statistically powerful enough to reach significance. However, we assume low success rates in patients with large LA diameters and thus we usually do not schedule patients with LA diameters > 55 mm for CB PVI. Reduced kidney function was recently detected as a predictor for AF recurrence [20], but was not significant in our cohort.

Limitations

Our study is a non-randomized large single-center study with an observational design. Results might be biased by a co-treatment with AADs at baseline (41%) and at 12 months (6%). No continuous monitoring of arrhythmia recurrence has been performed (e.g. internal loop-recorder). Therefore, the arrhythmia recurrence rate and asymptomatic episodes might have been underestimated. The effort of our ablation procedure protocol was considerably greater than that of other groups who have reported similar outcome data following a single-balloon approach. However, no comparative long-term outcome data are available. Due to our scientific ablation procedure protocol, total procedure times might be longer compared to the literature.

Conclusions

CBG2-PVI is a successful treatment option for the index ablation of symptomatic PAF but can also be challenging due to individual PV anatomy. The 28-mm CB should be the preferred catheter in all patients undergoing cryoballoon ablation. If PV occlusion is difficult with the big balloon, the 23-mm CB is a safe and effective option to achieve PVI in small veins. Further studies need to investigate if the 23-mm CB could be beneficial as the primary CB in females with small body height and short LA diameter.

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Disclosures

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Original article

Cryoballoon ablation for persistent atrial fibrillation – Large single-center experience

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ABSTRACT

Background: Different catheter ablation (CA) strategies have been established in the treatment of persistent atrial fibrillation (persAF). Pulmonary vein isolation (PVI) only might be an option for the initial ablation procedure. There is a paucity of outcome data on second-generation cryoballoon (CBG2) PVI in persAF.

Methods: Patients with symptomatic drug-refractory persAF who underwent initial CA of AF were prospectively enrolled and PVI was performed with CBG2. The primary composite endpoint was freedom from AF, atrial tachycardia, or related symptoms after a 3-month blanking period. The secondary endpoint referred to periprocedural complications.

Results: One hundred seventy-three consecutive patients (64 ± 10 years, 29% female) with symptomatic drug-refractory persAF were identified. Acute PVI was achieved in 100% of pulmonary veins with the CB technique. The left atrial procedure time was 112 ± 30 min. Major complications occurred in 1.7% (3 of 173 patients) including two phrenic nerve palsies (1%), which resolved until discharge, and one pericardial effusion (0.6%). Follow-up ≥12 months was completed for 157 of 173 patients (91%). Median follow-up was 14 months. At 12 months, the primary composite endpoint was achieved in 129 of 157 patients (82%). However, 22 of 129 patients at risk (17%) were still on antiarrhythmic drugs. A relapse during the blanking period was identified as the only independent predictor for AF recurrence.

Conclusion: PVI using the second-generation cryoballoon is a reasonable treatment option for patients with symptomatic drug-refractory persAF with a favorable rate of freedom from AF and a low complication rate.

Introduction

Catheter ablation is established as a class II a/B recommendation in the treatment of symptomatic drug-refractory persistent atrial fibrillation [1]. Ablation strategies that target the pulmonary veins (PVs) and/or PV antrum are the cornerstone for most AF ablation procedures. When PVs are targeted, electrical isolation is the endpoint of the procedures [1]. For persistent AF, there is still an ongoing debate about the preferred ablation strategy as the initial procedure. The STAR AF II Trial Investigators recently found no benefit of either linear ablation or ablation of complex fractionated electrograms performed in addition to PV isolation (PVI) in patients with persistent AF. PVI alone resulted in a rate of 59% freedom from AF after 18 months [2].

Meanwhile, the use of cryothermal energy has obtained increasing recognition for PVI. With the second-generation of the cryoballoon (CBG2), 1-year success rates for paroxysmal AF are consistent among different centers and range from 80% to 91% [3–6]. One explanation is the durable lesion, which is created with the CBG2. Reddy et al. performed scheduled remapping 3 months after CB ablation in 21 consecutively ablated patients and demonstrated that 91% of veins were still isolated [7]. If PVI is the aim at the initial procedure for persistent AF, cryoballoon ablation could be an alternative to radiofrequency (RF) ablation. In a pilot study using the first-generation of the cryoballoon, which provides a cooling zone only around the equator, we established a double balloon strategy for persistent AF combining the small and large CBG1, which results in an ostial PVI (small 23-mm CB) followed by an antral cryolesion (large 28-mm CB). We demonstrated that this concept is feasible, safe, and associated with a favorable outcome for persistent AF [8]. The CBG2 has a broader,

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more uniform cooling zone and is more effective [9,10]. So far, outcome data after CBG2-PVI in persistent AF are sparse. Ciconte et al. recently published a non-randomized study comparing RF (n = 50) and CBG2 (n = 50). They found a success rate of 60% for CB and 56% for RF at 12 months [11]. In the present study, we evaluated the safety and efficacy of PVI with the CBG2 for consecutive patients with persistent AF undergoing the first AF ablation procedure.

Materials and methods

Objectives

The main objective was to assess the clinical outcome ≥12 months after initial CBG2-PVI in a large cohort of consecutive patients with persistent AF. Furthermore, we evaluated procedural data and periprocedural safety.

Study population

From May 2012 to February 2014, a total of 173 consecutive patients (29% female) with persistent AF underwent initial CBG2-PVI and were prospectively enrolled in our monocentric observational study. Follow-up was completed for 157 patients (91%) who were enrolled in the analysis of the primary endpoint. As recommended in the AF ablation guidelines [12], persistent AF was defined as continuous AF that is sustained beyond 7 days. Patients with episodes of AF in which a decision was made to electrically or pharmacologically cardiovert the patient after 48 h of AF, but prior to 7 days, were also classified as having persistent AF. Patients who suffered from symptomatic drug-refractory persistent AF or who had contraindications for chronic antiarrhythmic drug (AAD) treatment were included. Exclusion criteria were long-standing persistent AF, left atrial diameter >60 mm, intracardiac thrombi, severe valvular disease, progressed heart insufficiency, and previous left atrial ablation. All data were collected prospectively. All patients provided written informed consent for participating in the study prior to ablation therapy. The study was approved by the institutional review committee and complies with the declaration of Helsinki.

Ablation procedure protocol

Our standardized cryoballoon ablation procedure was previously described in detail [10] and can be summarized as follows: PV anatomy was determined with computed tomography or magnetic resonance imaging scans prior to ablation. CB procedure (CBG2: Arctic Front Advance, Medtronic Inc., Minneapolis, MN, USA) was performed with an anatomy-based individualized approach using the 28-mm CBG2 as the preferred ablation catheter and the 23-mm balloon in addition if PVI was not achieved with the 28-mm balloon and maximum PV diameter was ≤21 mm. In patients with exclusively small veins ≤20 mm, the 23-mm CB was allowed as the primary catheter. Additional touch-up lesions using RF or cryo tip-catheters were allowed to obtain PVI.

For positioning of the balloon, the spiral mapping catheter (Achieve™ 15 mm or 20 mm spiral mapping catheter with 8 poles, Medtronic Inc.) was used in an over the wire technique. The degree of vessel occlusion was determined by PV angiography. Once cryoenergy was applied, intracardiac echocardiography was used to ensure the antral balloon position and to screen for incomplete occlusion visualized by Doppler imaging. At least two freeze–thaw–freeze cycles with a standard freezing time of ≥180 and ≤240 s were applied to each vein, including a bonus application after acute PVI was achieved. PV potentials were mapped before and after each freeze cycle and again at the end of the procedure. If feasible, online PV potential mapping to determine the time to PVI during the freeze was recorded. Early PV reconduction was defined as any recurrence of PV entrance signals or demonstration of exit conduction after isolating the targeted vein until the end of the procedure. On the discretion of the treating physician, premature termination of an application and additional applications were allowed if necessary, for example in case of (a) long time to PV isolation; (b) early reconnection of the vein during the procedure; (c) ineffective first freeze; (d) low esophageal temperatures ≤+15 °C, e.g. three short freezes (e.g. ≤100 s) were allowed instead of two long cycles to avoid low esophageal temperatures; (e) if the occlusion of the vein was difficult and e.g. pull-down maneuvers were needed; (f) or if the second cryoballoon size was used and additional freezes with the alternate size were applied to the vein with the intention to create a broader lesion.

To avoid phrenic nerve palsy (PNP), PN monitoring with PN pacing (1200 ms cycle length) was performed along with manual examination of the diaphragm by the second operator after achieving −15 °C or 20 s of freezing time. If deemed necessary, intracardiac echocardiography (ICE) visualization of the diaphragmatic motion was used in addition. Refrigerant supply was immediately stopped (single stop technique) if weakening or loss of diaphragmatic movements were noticed. An esophageal temperature probe (SensiTherm™, 3 thermocouples, St. Jude Medical, Saint Paul, MN, USA) was used in all patients to detect the lowest esophageal temperature. The intraluminal esophageal temperature cut-off value for termination of the cryoapplication was set at ≤+15 °C.

During the entire procedure, an activated clotting time between 300 and 400 s was ensured by intravenous heparin administration. Before sheath removal, protamine was given intravenously. One hour after sheath removal, we administered intravenous unfractionated heparin continuously with a targeted partial thromboplastin time of 50–70 s. Oral anticoagulation was started on the day after ablation and continued for at least 3 months and afterward, depending on the CHA_2DS_2-Vasc Score. Previous AAD therapy was recommended to be discontinued 3 months after the procedure.

Follow-up

Postprocedural follow-up was performed in our clinic. Transthoracic echocardiography was accomplished to exclude pericardial effusion. Electrocardiography (ECG) and Holter studies were applied for the first 24–48 h post-ablation. Additional ECGs and Holter studies were continued up to 7 days in patients with AF symptoms. All complications were registered prospectively.

After a scheduled discharge on day 2 after ablation, routine outpatient follow-up was performed in all patients at 1, 3, 6, 12, and 18 months post-ablation and regularly, at least once a year (24 h Holter monitoring, ECG, and symptoms). Findings of collaborating institutions were requested and sent to our center to confirm the diagnosis, if any recurrence was suspected [e.g. documented AF, atrial tachycardia (AT), or related symptoms]. If patients reported typical AF symptoms without ECG documentation for this episode, this event was calculated as a recurrence.

Statistical analysis

Continuous data were expressed as means with standard deviation (SD) or as the median with interquartile range (IQR), if data were non-normally distributed in accordance with the Kolmogorov–Smirnov test. Categorical data were expressed as numbers and percentages. Event-free survival was assessed by the Kaplan–Meier method. To find predictors for AF recurrence, uni- and multivariate analyses were performed using the Cox-regression model. All p-values were calculated by two-tailed tests.

Statistical significance was defined at $p < 0.05$. Data processing and analysis were performed by Excel 2010 (Microsoft Corp., Redmond, WA, USA) and SPSS 20.0 (IBM Corp., Armonk, NY, USA).

Results

From May 2012 to February 2014, PVI was performed with CBG2 in 173 patients suffering from symptomatic drug-refractory persistent AF. Of those, 157 patients (91%) completed the follow-up ≥12 months and were considered for the analysis of the primary endpoint (age 64 ± 10 years, 29% female). Median follow-up was 14 months (IQR 12–19). Most patients were refractory to at least one AAD. The others had a contraindication for chronic AAD treatment.

Baseline characteristics

Baseline characteristics are shown in Table 1. Median history of AF until PVI was 29 months (IQR 12–67). Patients underwent a mean of 2.4 ± 1.6 electrical or pharmacological cardioversions prior to the procedure. At baseline, 103 of 157 follow-up patients (66%) were on class I/III AAD therapy, not including beta-blockers. The others had intolerance or contraindications for chronic AAD therapy. The mean left atrial diameter was measured 46 ± 7 mm, the left atrial volume index was 47 ± 13 ml/m² and the left ventricular ejection fraction was 54 ± 8%. Forty-six of 173 patients (27%) presented with a relevant structural heart disease (coronary artery disease, cardiomyopathy, or mitral valve insufficiency ≥°II).

Procedural data and acute success rates

Procedural data and acute success rates are shown in Table 2. In our cohort of 173 patients, the 28-mm cryoballoon was applied in 56% (97 patients), the 23-mm balloon in 19% (32 patients), and both balloons in 25% (44 patients). The mean procedure time was 155 ± 37 min, the mean left atrial procedure time 112 ± 30 min, and the mean fluoroscopy time was 27 ± 11 min.

In total, 673 PVs were ablated and acute PVI was achieved in 100% using cryoballoon only. No additional touch-up ablations with RF or cryotip catheters were performed. On average, 1.26 ± 0.62 cryoapplications per PV were necessary for acute PVI. A single-shot success (isolation after the initial cryoapplication) could be accomplished in 82%. After successful PVI, a bonus freeze was applied. Therefore, the average total number of cryoapplications per PV was 3.02 ± 1.19 with an average ablation duration of 198 ± 40 s per application.

Table 1
Baseline characteristics. Data are presented as mean ± SD, median (IQR) or % of patients.

Number of patients	173
Age, years	64 ± 10
Female sex	50 (29)
Ejection fraction, %	54 ± 8
LA diameter, mm	46 ± 7
LA volume[a], ml	145 ± 39
LA volume index[a], ml/m²	47 ± 13
Arterial hypertension	123 (71)
Hypertensive heart disease	41 (24)
Structural heart disease	46 (27)
Coronary artery disease	23 (13)
Mitral valve insufficiency ≥°II	12 (7)
Cardiomyopathy	11 (6)
Creatinine, mg/dl	0.98 ± 0.07
BMI, kg/m²	27.3 ± 5
History of AF, months	29 (12–67)
Number of cardioversions	2.4 ± 1.6
Basal rhythm at study entry	
Sinus rhythm, n (%)	122 (78)
Atrial fibrillation, n (%)	35 (22)
Medical treatment at baseline, n (%)	139 (89)
AAD treatment, n (%)	103 (66)
Amiodarone, n (%)	68 (43)
Dronedarone, n (%)	17 (11)
Flecainide, n (%)	11 (7)
Propafenone, n (%)	2 (1)
Sotalol, n (%)	5 (3)
Beta-receptor blockers, n (%)	36 (23)
None, n (%)	18 (11)

LA, left atrium; BMI, body mass index; AF, atrial fibrillation; PVI, pulmonary vein isolation; AAD, antiarrhythmic drug.
[a] Data based on computed tomography findings.

Table 2
Procedural data. Data are presented as mean ± SD, median (IQR) or % of pulmonary veins and patients.

	Overall (*n* = 173 patients)
Total procedure time, min	155 ± 37
LA time, min	112 ± 30
Fluoroscopy time, min	27 ± 11
Dose area product, cGy cm²	3230 (1870–5297)
Acute PVI with CB only	673/673 (100)
Focal touch-ups per vein	0/673 (0)
Cryoballoon usage	
23-mm CB only	32/173 (19)
28-mm CB only	97/173 (56)
28-mm + 23-mm CB	44/173 (25)
Ablation duration per PV, s	198 ± 40
Ablation duration per patient, s	808 ± 166
Applications per patient	12.39 ± 2.78
Applications per PV	3.02 ± 1.19
Number of applications until PVI	1.26 ± 0.62
Time to isolation, s	44 ± 37
Feasibility to determine the TTI (veins, %)	292/673 (43)
Single-shot PVI (% of veins)	82

LA, left atrium; PVI, pulmonary vein isolation; CB, cryoballoon; PV, pulmonary vein; TTI, time to isolation.

Outcome results

At 12 months, the primary composite endpoint (freedom from AF, AT, or related symptoms after a single procedure) using the second-generation cryoballoon was achieved in 129 of 157 patients (82%). At that point, 22 of 129 patients at risk (17%) were on AAD

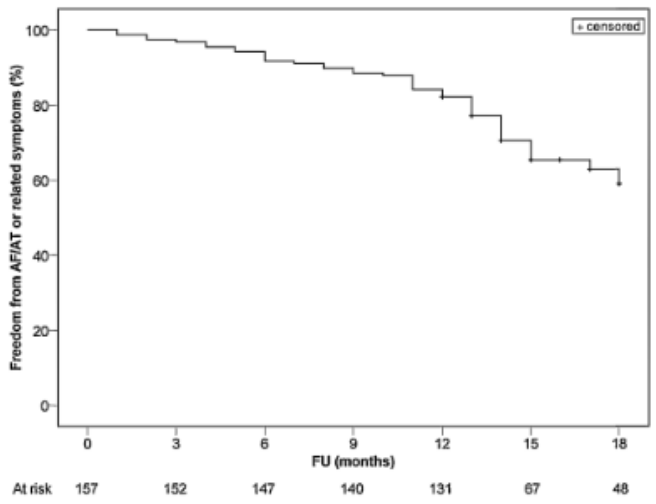

Fig. 1. Primary composite endpoint after a single cryoballoon procedure: freedom from AF/AT or AF symptoms. The graph shows Kaplan–Meier estimates of freedom from arrhythmia with or without the use of antiarrhythmic medications. A 3-month blanking period was considered. Five patients were re-ablated during the blanking period and therefore calculated as failure. Median follow-up was 14 months. AF, atrial fibrillation; AT, atrial tachycardia; FU, follow-up.

treatment. At 18 months, the estimated probability for freedom of AF/AT or symptoms was 59% and 6% (3 of 48 patients at risk) were treated with AAD. Fig. 1 demonstrates the Kaplan–Meier survival curve. Thirty-six of 157 patients (23%) suffered from AF arrhythmia recurrences during the blanking period. Uni- and multivariate analyses demonstrated that arrhythmia relapse during the blanking period was an independent predictor for AF recurrence with a 2.3-fold risk (Table 3). In total, 18 of 157 patients (12%) received further AF ablation due to arrhythmia recurrences. Of those undergoing a second electrophysiology study because of symptomatic recurrence, right atrial arrhythmias were mapped and ablated in 2 patients (11%): one isthmus dependent atrial flutter and one focal right AT. Left atrial arrhythmias were found in 5 patients (28%): four left atrial flutter and one focal left AT. In those patients undergoing a redo procedure for arrhythmia recurrence, 8 of 18 patients (44%) demonstrated durable PVI of all veins and 21 of 76 PVs (28%) showed reconduction. PV reconduction was measured in 4/18 left inferior PV (22%), 9/18 right inferior PV (50%), 6/18 right superior PV (33%) and 2/18 left superior PV (11). One reconducting vein was found in two patients (20%), two reconducting veins were found in six patients (60%), and three and four reconducting veins were found in one patient each (10%).

Adverse events

Adverse event rates are shown in Table 4. Any complications occurred in 4.0% of all patients (7 of 173 patients). Major complications were observed in 1.7% of all procedures (3 of 173 patients), and included two persistent PNPs with recovery until discharge (1.1%) and one pericardial effusion, with the necessity of a pericardial drainage (0.6%). Minor complications occurred in 2.3% (4 of 173 patients); two groin complications (1.15%) and two febrile airway infections (1.15%) were treated conservatively.

Table 3
Univariate and multivariate analyses indicating predictors for AF recurrence.

Variable	β coefficient	Hazard ratio (95% confidence interval)	p-Value
Univariate analysis			
Age, years	−0.05	0.96 (0.97–1.02)	0.70
Female sex	−0.23	0.80 (0.47–1.35)	0.40
Ejection fraction, %	−0.32	1.00 (0.97–1.04)	0.84
Hypertension	−0.04	1.00 (0.59–1.67)	0.99
LA diameter, mm	0.01	1.01 (0.98–1.05)	0.49
Number of cardioversions	−0.28	0.76 (0.54–1.05)	0.10
History of AF, months	0.001	1.00 (1.00–1.01)	0.59
Cryoballoon size			
23-mm	–	–	0.93
28-mm	0.07	1.07 (0.48–2.40)	0.86
28-mm + 23-mm	0.12	1.13 (0.59–2.16)	0.71
Relapses in BP	0.81	2.26 (1.38–3.70)	**<0.01**
Multivariate analysis			
Relapses in BP	0.84	2.31 (1.31–4.09)	**<0.01**
LA diameter, mm	0.04	1.00 (0.96–1.05)	0.86
Number of cardioversions	−0.32	0.74 (0.51–1.06)	0.10
History of AF, months	<0.01	1.00 (0.99–1.00)	0.70

LA, left atrium; AF, atrial fibrillation; BP, blanking period.
A p-Value <0.05 was considered to be statistically significant.

Table 4
Adverse event rates.

Type of complication	No. of patients, n = 173	Rate, %
Total major adverse events	3	1.73
Death, MI, TIA/stroke	0	0.00
PV stenosis	0	0.00
Persistent PNP until discharge	2	1.15
Pericardial effusion including drainage	1	0.57
Total minor adverse events	4	2.31
Groin complication	2	1.15
Febrile airway infection	2	1.15
Total adverse events	7	4.05

MI, myocardial infarction; PV, pulmonary vein; TIA, transient ischemic attack; PNP, phrenic nerve palsy.

Discussion

To date, this is the largest single-center study representing data of ≥12 months clinical follow-up of patients with persistent AF after initial PVI using the second-generation cryoballoon. The main findings of our study are: (1) at 12 months, single-procedure success without additional substrate modification was 82% (17% of patients on AAD); (2) relapse during the blanking period was an independent predictor for AF recurrence; (3) peri- and postprocedural complication rates were low.

Procedure protocol and outcome

PVI was performed with the second-generation cryoballoon. We applied an anatomy-based individualized approach using the 28-mm balloon as the preferred ablation catheter and the 23-mm balloon only in addition if PVI was not achieved and maximum PV diameter was ≤21 mm. The second-generation cryoballoon is more effective due to a broader cooling zone and an increased flow rate of the refrigerant for the 28-mm CB, which results in a decreased need for a second cryoballoon to obtain PVI in comparison to its predecessor [9]. In our cohort, a considerable number of patients were treated with both balloon sizes, which possibly creates a greater lesion and thus may increase the chance of durable PVI. In the end, we did not find any significant differences in outcome results between the 23-mm, the 28-mm, or both balloons (Table 3). This finding is reasonable as the additional usage of a second balloon was only intended if PVI could not be achieved completely with the first balloon. Nevertheless, a double balloon rate of 25% is high compared to the study of Ciconte et al. on persistent AF ablation with the CB [11]. In 50 patients, they used the 28-mm CBG2 only and published a 60% rate of freedom from AF/ATs (off AAD) after a single procedure at 12 months compared to a similar result of 82% freedom from AF/AT or symptoms (17% on AAD) at 12 months in our study. It remains unclear whether our results could be confirmed using a big balloon concept. More long-term follow-up data are needed to clarify whether a double balloon approach will play a role in the future AF treatment. In our standard procedure, one bonus freeze cycle was applied by protocol after successful PVI. Nonetheless, acute PVI could be achieved in 100% in total and in 82% of all PVs after a single cryoapplication. Whether the bonus freeze is generally required needs to be further investigated. The mean number of applications per vein was 3.02 in our study, compared to 1.7 in the study of Ciconte et al. on persistent AF with the second-generation cryoballoon. It remains unclear whether the longer total cryoapplication time itself or our individualized anatomic approach allowing the 23-mm balloon size to be used if necessary contributes to a higher rate of freedom from AF in our study.

Compared to CBG1, the rate of durable isolation of all PVs after 28-mm CB ablation in a scheduled remap study has increased from 67% to 79% of patients [7]. In our study, 18 of 157 patients (12%) underwent a second procedure for symptomatic recurrence; PV reconduction was documented in only 28% of veins and 44% of those patients demonstrated durable PVI of all veins.

To improve outcome in patients with persistent AF, the current guidelines consider PVI with additional substrate modification. The rationale is that there are more complex, substrate-based

mechanisms underlying persistent AF in comparison to paroxysmal AF (PAF), where triggers from the PVs play the major role in initiating PAF [12,13]. The STAR AF II Trial compared three different RF ablation strategies in the treatment of persistent AF: PVI alone, PVI plus linear ablation, and PVI plus ablation of complex fractionated electrograms. PVI alone was not inferior and the procedure and radiation time were significantly shorter compared to the other two strategies that were using additional substrate modification. Single-procedure success (PVI alone), with or without AADs, was 59% after 18 months. The authors assumed that more extensive ablation may induce new substrate for arrhythmogenesis [2]. Using the CBG2 in our cohort, beside the broad circumferential CB lesion, no additional substrate modification was performed and the results compare favorably with the current literature for RF ablation in persistent AF. However, there were no patients with long-standing persistent AF and only few patients with far progressed structural heart disease in our cohort.

If PVI only is the aim at the initial procedure for persistent AF, durable PVI has to be achieved. The EFFICAS I and II trials worked out that contact-force guided RF ablation for PVI increases the rate of durable PVI from 35% to 63% of patients [14,15]. For CBG2, Reddy et al. demonstrated durable PVI in 79% of patients [7]. Only recently, Squara et al. compared CBG2 and contact-force RF for paroxysmal AF and found no difference in terms of freedom from AF/AT at 18 months with more major adverse events in the contact-force RF arm (2.5% vs. 0%, $p = 0.03$) [16]. It has to be determined in a larger randomized study, if contact-force RF or CBG2 is the preferred strategy for PVI in persistent AF.

Predictors and safety profile

In our present study, we could confirm recent results [17] suggesting that arrhythmia relapses in the blanking period are associated with AF recurrences. There was no statistical significance for the size of the left atrial diameter as a predictor for recurrences. However, we still assume low success rates in patients with large left atrial diameters. In our clinic, patients with large left atrial diameters ($\geq$55 mm) are usually not scheduled for PVI, which might explain our findings. Very few serious adverse events occurred in our cohort: Two asymptomatic persistent PNPs recovered until discharge and one pericardial effusion needed pericardial drainage. No death, myocardial infarction, stroke/transient ischemic attack, or atrioesophageal fistula was observed.

Our data suggest that PVI using the second-generation cryoballoon is a safe and effective treatment option for persistent AF in a first ablation procedure. Total procedure time and fluoroscopy time were short. The radiation exposure was comparable to a complex percutaneous intervention. Nevertheless, larger patient populations and longer follow-up data are necessary to determine the best strategy for the treatment of persistent AF in the initial AF ablation procedure.

Conclusion

PVI using the second-generation cryoballoon is a safe and effective option as an ablation strategy for symptomatic drug-refractory persistent AF at the initial ablation procedure with favorable mid-term results and a low complication rate.

Limitations

Our study is a single-center study with a single-arm observational design. Results might be biased by a co-treatment with AADs at baseline (66%) and at 12 months (17%). Additionally, a considerable number of patients were treated with both balloon sizes, which might overestimate outcome results. No continuous monitoring of arrhythmia recurrence has been performed (internal loop-recorder). Therefore, the arrhythmia recurrence rate and asymptomatic episodes might have been underestimated. Symptomatic episodes without documentation were calculated as recurrences. This might overestimate the recurrence rate. Only a limited number of patients were investigated. The ongoing Freeze Cohort Study [18] (NCT01360008), including a total of 4000 patients with paroxysmal or persistent AF undergoing CB or RF ablation, will give more answers to the question of the preferred technique to perform a safe and effective AF ablation.

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Curriculum Vitae

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