Pulmonary vein isolation in treatment of atrial fibrillation using radiofrequency or cryoballoon ablation: factors associated with better clinical outcomes

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Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2022

UNIVERSITY OF BERGEN

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Date of defense: 03.02.2022

Year: 2022

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Print: Skipnes Kommunikasjon / University of Bergen

Scientific environment

The candidate is affiliated with the Department of Clinical Science, University of Bergen, Norway. The work presented in this thesis was performed at the Department of Heart Disease, Haukeland University Hospital.

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Acknowledgements

This thesis is based on several clinical studies carried out from 2016-2021 at the Department of Heart Disease, Haukeland University Hospital and also in collaboration with the Department of Cardiology, St. Olavs Hospital in Trondheim and the Department of Cardiology, University Hospital of North Norway in Tromsø.

I would like to express my deep gratitude to my main supervisor Professor Jian Chen and co-supervisor Associate Professor Ole Rossvoll for their patient guidance, enthusiastic encouragement and useful critiques of this research. Professor Jian Chen introduced me to the field of electrophysiology and relevant research. His knowledge and insight into the subject matter steered me through the research work presented here.

I would also like to acknowledge the following people, without whom I would not have been able to complete this research. My sincere thanks to Professor Ole-Jørgen Ohm, Dr Per Ivar Hoff, and the whole EP team at the Department of Heart Disease, Haukeland University Hospital for their invaluable advice, practical help and professional support. I thank the EP teams at the Department of Cardiology, St. Olavs Hospital in Trondheim and the Department of Cardiology, University Hospital of North Norway in Tromsø, for their contributions to the NO-PERSAF study. Dr Alessandro De Bortoli provided very valuable advice and took part in several studies, especially paper IV. My former colleagues at the Peking University First Hospital, Yuchuan Wang and Songyun Chu, have supported me and took part in some of the work presented here.

Finally, and most importantly, I would like to offer my special thanks to my family for their endless love and encouragement. For my kids, sorry for being even grumpier than normal whilst I wrote this thesis! And for my wife Nan Wang, thanks for all your support, without which I would have stopped these studies a long time ago.

Bergen, September 2021

Libin Shi

Contents

Abbreviations

AADs	**Antiarrhythmic drugs**
AF	**Atrial fibrillation**
AFL	**Atrial flutter**
AI	**Ablation index**
ATA	**Atrial tachyarrhythmia**
CB2	**Second-generation cryoballoon**
CBA	**Cryoballoon ablation**
CF	**Contact force**
CFAE	**Complex fractionated atrial electrograms**
CI	**Confidence interval**
CTI	**Cavotricuspid isthmus**
ECG	**Electrocardiogram**
ESC	**European Society of Cardiology**
FTI	**Force-time-integral**
HF	**Heart failure**
HPSD	**High-power short-duration**
ID	**Impedance drop**
IQR	**Interquartile ranges**
ITT	**Intention-to-treat**
LA	**Left atrium**

LPV	**Left common pulmonary vein**
LVEF	**Left ventricular ejection fraction**
NOAC	**Non-vitamin K antagonist oral anticoagulant**
PV	**Pulmonary vein**
PVI	**Pulmonary vein isolation**
QoL	**Quality of life**
RCT	**Randomized controlled trial**
RFA	**Radiofrequency ablation**
SR	**Sinus rhythm**
TTI	**Time to isolation**
WACA	**Wide antral circumferential ablation**

Abstract

Background: Electrical pulmonary vein isolation (PVI) is still regarded as a cornerstone for treatment of paroxysmal and persistent atrial fibrillation (AF). It can be achieved by different techniques. We investigated the indications and techniques of PVI using radiofrequency ablation (RFA) and cryoballoon ablation (CBA) for AF and compared the efficacy of the two techniques for persistent AF.

Methods and results: First, we conducted a prospective, randomized (1:1), open-label, multi-centre clinical trial to evaluate the effectiveness of PVI performed with CBA in comparison with contact force-sensing RFA in patients with persistent AF. A total of 101 patients (52 in CBA and 49 in RFA) were enrolled and followed up for 12 months. The CBA group showed a similar clinical outcome to RFA in terms of freedom from atrial tachyarrhythmia at 12 months (69.2% in CBA vs. 61.2% in RFA, P=0.393). In addition, CBA showed comparable complications (1 in CBA vs. 4 in RFA, P=0.353), less atrial flutter (AFL) recurrence (3.9% in RFA vs. 18.0% in CBA, P=0.020), and shorter procedure and ablation time (158.9±28.9 vs. 197.9±38.4 minutes, 35.8±6.5 vs. 55.9±16.7 minutes, respectively, both P<0.001) than RFA.

Second, we conducted an observational study in an RFA population, to investigate the impacts of procedural parameters on durability of PVI. We analysed the impacts of contact force (CF), power, and application time on ablation effect indicated by impedance drop (ID) in an RFA procedure with both conventional and high-power short-duration (HPSD) settings. We found that: (i) The minimum requirement of CF for effective ablation was 5 g. (ii) With CF ≥5 g, CF, power and application time can compensate for each other within restricted ranges, while the time to reach maximal ablation effect can be shortened by increasing CF or power output. (iii) The effect of HPSD ablation with 50 W for 10 s is equivalent to conventional ablation with 25 W for 40 s and 30-35 W for 20-30 s, in terms of ID. Changes of ID with increasing ablation index were similar at 30, 35 and 50 W. At 25 W they showed the same trend, but with smaller ID at the same ablation index.

Third, we analysed the predictive value of procedural and biophysical parameters for the durability of PVI in a CBA population in a retrospective case-control study that used the data from 241 pulmonary veins of 71 patients who underwent a repeat AF ablation procedure. Thawing plateau time ($Time_{TP}$, defined as the time from 0 to 10°C inside the balloon in the thawing period) was shown to be the strongest independent predictor for the durability of PVI. The relationship between $Time_{TP}$ and the durability of PVI presents in a dose-proportional

manner. $Time_{TP}$ <15 s predicts long-term reconnection while $Time_{TP}$ >25 s predicts durable PVI. In these two studies, we provided practical data for optimizing dose strategies for RFA and CBA to improve the durability of PVI.

Finally, we performed a retrospective cohort study to investigate the incidence and risk factors for AF in 117 patients who suffered mostly AFL and underwent an elective cavotricuspid isthmus (CTI) ablation. During a mean follow-up period of 68 ± 24 months, 89 patients (70%) developed AF, 53 patients (42%) underwent AF ablation procedures, and 10 patients (8%) developed non-fatal ischemic cerebral events. Independent predictors for additional AF ablation included a higher CHA_2DS_2-vasc score (odds ratio (OR) 0.72, 95% confidence interval (CI), 0.53–0.98), documentation of both pre- and intraprocedural AF (OR 3.81, 95% CI, 1.14–12.8), and previous use of flecainide (OR 2.43, 95% CI, 1.06–5.58). We emphasized the high risk of AF occurrence and PVI in the future for AFL patients. The findings indicate that CTI block has limited prophylactic effect for AF episodes and that prophylactic PVI may be applied in selective AFL patients.

Conclusions: (i) Compared with RFA, PVI performed by CBA offers shorter ablation time and procedure duration, with less AFL recurrence and similar freedom from atrial tachyarrhythmias at 12-month follow-up. (ii) Procedural parameters have predictive value and significant impacts on durability of PVI. (iii) Patients undergoing AFL ablation are at high risk of developing AF in the future and prophylactic PVI may be applied in selective AFL patients.

List of Publications

1. **Shi LB,** Rossvoll O, Tande P, Schuster P, Solheim E, Chen J. Cryoballoon versus radiofrequency catheter ablation: insights from NOrwegian randomized study of PERSistent Atrial Fibrillation (NO-PERSAF study). Europace 2021 (in press) https://doi.org/10.1093/europace/euab281.
2. **Shi LB**, Wang YC, Chu SY, De Bortoli A, Schuster P, Solheim E, Chen J. The impacts of contact force, power and application time on ablation effect indicated by serial measurements of impedance drop in both conventional and high-power short-duration ablation settings. Journal of Interventional Cardiac Electrophysiology 2021; Apr 23. doi: 10.1007/s10840-021-00990-4.
3. **Shi LB**, Chu SY, Wang YC, Solheim E, Schuster P, Chen J. Thawing plateau time indicating the duration of phase transition from ice to water is the strongest predictor for long-term durable pulmonary vein isolation after cryoballoon ablation for atrial fibrillation — Data from the index and repeat procedures. Submitted manuscript.
4. De Bortoli A, **Shi LB**, Ohm OJ, Hoff PI, Schuster P, Solheim E, Chen J. Incidence and clinical predictors of subsequent atrial fibrillation requiring additional ablation after cavotricuspid isthmus ablation for typical atrial flutter. Scandinavian Cardiovascular Journal 2017; 51:123-128.

1. Introduction

1. An overview of atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia with significantly impaired quality of life and increased risk of stroke and overall mortality. Substantial research effort and resources have been applied to AF for its significant social burden. However, there are still many controversies and challenges of AF mechanisms and treatments owing to their complexity.

1.1.1 Definition and classification

i. Diagnosis: According to the definition in the latest Guidelines of the European Society of Cardiology (ESC), AF is defined as "a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction"[1]. The diagnosis of AF is established based on an episode lasting over 30 seconds with surface electrocardiography (ECG) showing: 1) irregular R-R intervals (when atrioventricular conduction is not impaired), 2) absence of distinct repeating P waves, and 3) irregular atrial activations[1].

ii. Classification: The classification of AF evolves continuously. The newest classification in the guidelines takes patients' willingness for treatment into account and is more convenient for clinical practice. The five AF patterns are:

1) First diagnosed AF: AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
2) Paroxysmal AF: AF that terminates spontaneously or with intervention within 7 days of onset.
3) Persistent AF: AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥ 7 days, but shorter than 12 months.
4) Long-standing persistent AF: Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.
5) Permanent AF: AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken. This term represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF.

1.1.2 Mechanisms

AF is a heterogeneous rhythm disorder, whose mechanisms are complicated and not fully understood. Usually, AF presents in statuses of initiation (triggers) and perpetuation. Most triggers relate to the myocardial sleeve inside or close to the pulmonary veins (PVs). The critical role of ectopic atrial activity from the PV in the initiation and maintenance of paroxysmal AF was first reported by Haïssaguerre et al. in 1998[2], and was further confirmed by several subsequent studies[3-6]. Besides the PVs, ectopic sources triggering AF may also originate from extra-PV locations, such as the atrial appendages, coronary sinus, vena cava, crista terminalis, ligament of Marshall, and the inter-atrial septum[7-15]. Mechanisms responsible for AF maintenance are even more important for persistent AF. There are several theories involved, such as the multiple wavelet hypothesis and localized AF drivers (i.e., the leading circle, spiral wave reentry or "rotor", micro-anatomic, and intramural reentries). Functional and/or structural reentries, which can work as a leading circle or spiral wave, are vital for maintaining AF[16]. The perpetuation of AF is affected by multiple factors. The most important substrate for AF is atrial fibrosis, which is a hallmark of structural remodelling; AF begets AF, and the increasing AF burden leads to structural and functional remodelling, creating a substrate that favours AF propagation. Paroxysmal AF eventually progresses to persistent or permanent AF. Reverse remodelling of the left atrium (LA) with the recovery of atrial function is considered an important target of any AF treatment.

1.1.3 Epidemiology, complications and social burden

AF is the most common sustained cardiac arrhythmia and increasingly prevalent, especially in men and Caucasians. The estimated prevalence is currently about 2% to 4% in adults, with an expectation of a 2.3-fold rise in 50 years[17, 18]. The lifetime AF risk, estimated at the index age of 55, has increased to 1 in 3[19] individuals of European ancestry from 1 in 4 10 years ago[20]. Age is the strongest risk factor for AF, while other factors, such as obesity, hypertension, heart failure (HF), coronary artery disease, chronic kidney disease, diabetes mellitus, and obstructive sleep apnoea are also important. Although AF per se is not harmful, it brings serious consequences of increased mortality, disability and impaired quality of life (QoL) owing to its complications. The increase of all-cause mortality has been confirmed by a series of studies. The Framingham Study showed 1.5-fold and 1.9-fold increased cardiovascular

mortality in men and women with AF, respectively[21]. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study reported a cardiovascular mortality of 4.5% per year[22]. Stroke is the most common and lethal complication of AF. Patients with AF are 5 times more likely to suffer from ischemic stroke than their peer counterparts, with a mortality of 1.5% in those aged 50–59 years to 24% in those aged 80–89 years. It is estimated that 20% of ischemic strokes could be attributed to AF. AF is also an independent risk factor for congestive HF with an increased relative risk of 2.98 in the Manitoba Follow-Up Study[23]. Persistent AF leads to a 3-fold higher mortality[23, 24]. AF impairs the QoL of patients as measured by using the SF-36 QoL scale with different cardiovascular comorbidities[25]. QoL reduction was observed even in those with asymptomatic AF.

Finally, a vast economic burden is imposed by AF in western countries and it is likely to increase further. Kim et al. registered an elevated rate of hospitalization and in-hospital mortality of AF patients in comparison to matched non-AF controls (37.5% vs. 17.5% and 2.1% vs. 0.1%, respectively). The estimated US national incremental AF cost was reported as between 6.0 and 26.0 billion dollars[26]. AF-related annual healthcare costs in Europe were reported to account for 0.28–2.60% of total healthcare spending (€660–3,286 million)[27].

1.1.4 **Current therapy strategies**

The treatment of AF can be epitomized as the simple AF Better Care (ABC) holistic pathway: ‘A’ indicates anticoagulation or avoid stroke; ‘B’ indicates better symptom management; ‘C’ indicates cardiovascular and comorbidity optimization[1].

i. **Anticoagulation and prevention of stroke**: The current most-used stroke risk assessment for non-valvular AF is based on CHA_2DS_2-vasc [Congestive HF, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female)] score. Anticoagulation in low-risk patients (0 in male or 1 in female) is not necessary; it can be considered in intermediate-risk patients and it is recommended in high-risk patients. The HAS-BLED[28] [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly] score is the most used parameter for evaluating the risk of bleeding. Patients with a HAS-BLED score ≥3 need to be monitored during anticoagulation therapy. Although both vitamin K antagonist and non-vitamin K antagonist oral anticoagulants (NOACs) are recommended by

guidelines, NOACs are frequently used as the first-line option. Evidence supporting the benefits of occlusion or exclusion of the LA appendage for stroke prevention is not enough.

ii. **Better symptom management**: To reduce the AF-related symptoms is the primary indication of both rate control and rhythm control therapy. There is no substantial evidence that favours rhythm control in terms of clinical outcome and AF progression in the general AF population[29]. The recently published EAST-AFNET 4 Trial compared the presence of a composite primary endpoint (death from cardiovascular causes, stroke, or hospitalization with worsening of HF or acute coronary syndrome) between rhythm control and rate control in relatively young and healthy patients. It showed that fewer primary endpoints were achieved in the rhythm control group (Hazard ratio, 0.79; 95% confidence interval (CI), 0.66 to 0.94; P=0.005)[30]. This result supports the proposition that early rhythm control treatment should be conducted in young and otherwise healthy AF patients.

   A. **Rate control**: Lenient rate control (target heart rate <110 beats per minute) has a similar clinical outcome to strict rate control (target heart rate <80 beats per minute at rest and <110 during moderate exercise)[29, 31]. Rate control can be achieved with antiarrhythmic drugs (AADs, such as beta-blocker, non-dihydropyridine calcium channel blockers, digitalis glycosides and amiodarone) or atrioventricular node ablation combined with pacing (especially for patients with indication for cardiac resynchronization therapy).

   B. **Rhythm control**: As well as reducing AF-related symptoms, maintenance of sinus rhythm (SR) improves QoL. Ways to achieve rhythm control include:

      a. **Cardioversion**: In haemodynamically unstable AF, cardioversion should be performed immediately. In haemodynamically stable cases, it can be conducted within 48 hours of AF onset or after at least 3 weeks of anticoagulation. Four weeks of anticoagulation after cardioversion and long-term oral anticoagulation, evaluated on CHA_2DS_2-vasc score, are recommended by the 2020 ESC guidelines. Electrical (biphasic defibrillators) or pharmacological cardioversion (including 'pill in the pocket') are commonly used in clinical practice. Alternative drugs used for AF conversion include flecainide, amiodarone, vernakalant, dofetilide and ibutilide.

b. **Long-term pharmacological rhythm control with AADs.** The efficacy of AADs to maintain SR for 1 year was reported from 32.2 to 45.0% and it is inferior to catheter ablation[32-35]. Available AADs include amiodarone, flecainide, propafenone, dronedarone, sotalol and disopyramide.

c. **Catheter ablation**: The primary indication of catheter ablation, referring to pulmonary vein isolation (PVI), is still symptom relief in the 'general' AF population. The efficacy of catheter ablation to reduce symptoms and improve QoL is superior to AADs[36]. The reduction in all-cause mortality, stroke, or major bleeding by catheter ablation in the 'general' AF population has not been proved by randomized control trials (RCTs)[37]. In patients with HF with reduced left ventricular ejection fraction (LVEF), a reduction of mortality has been demonstrated by RCTs[38, 39]. However, the benefit for HF with preserved or mild reduced LVEF is still debated[37]. Catheter ablation was earlier used as a second-line therapy for AF patients who were refractory or intolerant to class I or III AADs. Recent RCTs supported catheter ablation as first-line therapy for patients with symptomatically paroxysmal AF using either radiofrequency ablation (RFA)[40, 41] or cryoballoon ablation (CBA)[34, 35, 42]. In the 2020 ESC guidelines, it is recommended as first-line therapy for paroxysmal AF, persistent AF without major risk factors for recurrence, tachycardia-induced cardiomyopathy, HF with reduced LVEF, and AF-related bradycardia. Complications related to procedure should be taken into consideration. Electrical PVI is fundamental for AF treatment and is recommended by guidelines for all AF ablations. RFA and CBA are the most-used techniques to achieve PVI. PV reconnection and procedure-related complications are still challenging. Other energy sources and techniques, such as laser ablation and pulsed field ablation, are also used for AF treatment. The efficacy of catheter ablation in persistent AF is worse than that in paroxysmal AF. Strategies beyond PVI, including linear ablation, complex fractionated atrial electrogram (CFAE) ablation, ganglionated plexi ablation, focal rotor or rotational activity ablation, have been investigated in persistent AF, but they have not been proved superior to 'PVI alone' in the first-time procedure[43-46].

d. **Surgery or concomitant surgery for AF**: The efficacy of maintaining SR has been verified, while the benefits of QoL improvements and mortality

reduction after surgery for AF have not been established. These techniques are mostly used in selected patients with concomitant mitral surgery or coronary artery bypass. Recently, thoracoscopic ablation was shown to be more effective in terms of SR maintenance compared with catheter ablation, although the rate of complications was higher[47, 48].

e. **Upstream therapy, interventions of lifestyle and specific cardiovascular risk factors and comorbidities:** Upstream treatments target the atrial-remodelling process with non-AADs. The RACE 3 trial compared therapy targeting underlying conditions (interventional treatment, including mineralocorticoid receptor antagonists, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and cardiac rehabilitation) and conventional therapy, with the primary endpoint of SR at 1 year in patients with early persistent AF and mild-to-moderate HF. The results favoured the interventional treatment (75% vs. 63% in SR, P=0.042)[49]. Hypertension is associated with a 1.7-fold higher risk of AF, and AF is the common manifestation of hypertensive heart disease[50]. According to the latest ESC guidelines, the treatment of hypertension in AF patients is mandatory. Additionally, diabetes mellitus and sleep apnoea are associated with development of AF. Treatments against these comorbidities showed improvement of rhythm control and hence it is recommended to treat them simultaneously.

2. Pulmonary vein isolation in AF ablation

1.2.1 PVI is the cornerstone of catheter ablation for AF

The outstanding finding of Haïssaguerre et al. in 1998, that ectopic atrial activity from the myocardial sleeve inside or close to the PVs plays a critical role in the initiation and maintenance of AF, inaugurated a new era of AF catheter ablation. Although other origins were recorded, 94% of AF triggers were located in the PVs[2]. At the beginning, the focal activities from PV were the target of ablation, while a higher incidence of PV stenosis was observed as a complication. Later, Pappone et al. developed a strategy of ablation encircling the PVs guided by 3-dimensional electroanatomical mapping[51].

This approach with ablation in the PV antrum has become the main-stream method with better outcomes and lesser PV stenosis. Proietti et al. compared ostial PVI with wide

antral circumferential ablation (WACA) in a systematic review and meta-analysis, which showed a superiority of WACA in terms of freedom from recurrence of all atrial tachyarrhythmias (ATAs) during long-term follow-up [52].

PVI has been regarded as the cornerstone of AF ablation strategy and is accepted as the standard approach by most centres for de novo ablation procedure in paroxysmal and persistent AF patients. According to the Get With The Guidelines-Atrial Fibrillation (GWTG-AFIB) registry, PVI was performed in 95.6% cases of paroxysmal AF and 93.3% of persistent AF[53].

In a meta-analysis, Sau et al. compared the efficacy of catheter ablation based on PVI to ablation without PVI in patients with AF in RCTs. PVI-based procedures demonstrated a lower risk of AF recurrence compared with those without documented PVI[54].

In paroxysmal AF, 1-year success rates for PV antrum isolation-based procedures range from 70-80% after a single procedure, and increase to 80-85% after multiple procedures[55-57]. The highest single-procedure freedom from ATAs at 12 months was recently reported as 94% by Duytschaever et al. with the application of the CLOSE protocol[58]. But in another study which was conducted in the same centre, the 6-month single-procedure freedom from ATAs after PVI using the CLOSE protocol was 90%[59], therefore the 12-month success rate would be lower than 90%. Notably, the reported success rates are affected by the monitoring methods. According to the CIRCA-DOSE study in which all patients were monitored by an implantable loop recorder, the freedom of ATAs at 1 year after PVI for paroxysmal AF using RFA or CBA were only 51.7-53.9%, while the freedom from symptomatic ATAs was 73.3-79.1%[60].

The underlying mechanisms in persistent AF are different from those in paroxysmal AF. The atrial substrates rather than triggers may be more important in maintaining AF. Fibrosis in the LA is increasingly recognized as a foundation of the pathomorphological substrate creating an electrophysiological environment for electrical conduction heterogeneities. The strategy of PVI alone is not as effective for persistent AF as for paroxysmal AF. In the STAT AF II study, the freedom of atrial arrhythmias after PVI without AADs was 41%[43]. In the randomized Alster-Lost-AF Trial, Fink et al. reported a similar 1-year success rate of 39%[45]. Tilz et al. reported that the freedom of ATAs was 35.6% at 12 months, and 20.3% after a 5-year follow-up[61]. In the CHASE-AF Clinical Trial, the 1-year success rate was also less than 40%[44]. Because of the poor clinical outcomes of PVI alone for persistent AF, many adjunctive ablation strategies, mainly

including linear ablation, CFAE ablation, and rotor ablation, have been developed for patients with persistent/long-standing persistent AF. However, the benefits of adjunctive ablation strategies in addition to PVI have not been proved by RCTs[43-45]. As shown in the STAT AF II and CHASE-AF trials, neither linear ablation nor CFAE ablation improved freedom from ATAs. Later, ablation targeting focal impulses and rotors modulation (FIRM) was developed. Data from RCTs supporting benefit of FIRM-guided ablation are lacking. In a meta-analysis, the success rate was 50% in PVI+FIRM and 58% in PVI only[46]. For now, PVI remains the standard procedure for de novo persistent AF ablation.

In the recently published PRECEPT trial, the success rate of RFA using a contact force (CF)-sensing catheter in patients with persistent AF (long-standing persistent AF was excluded) was 80.4% at 15 months[62]. In the PRAISE study, the success rate of 12 months was 80%. Besides the different study cohort (longstanding persistent AF was excluded), the higher success rate might result from more durable PVI achieved by using a contact-force-sensing catheter guided by ablation index (AI). The PRAISE trial and another AI-guided PVI study reported the relatively low PV reconnection rate of 38%[63].

1.2.2 Techniques for achieving PVI

PVI can be achieved with several energy sources, such as radiofrequency, cryo, laser, ultrasound, and pulse-field energy. In a study based on 3139 patients from 2016 to 2018 in the GWTG-AFIB registry, the most commonly used technique in persistent AF ablation was RFA with an irrigated CF-sensing catheter in a point-by-point manner (70.5% of all procedures) while CBA was a frequent alternative (23.7%)[53].

i. **PVI achieved by radiofrequency ablation**

RFA creates lesions by heating. During RFA, the surface of tissue in contact with the ablation catheter electrode is warmed immediately by resistive heating, while the deeper tissue layer is warmed by conductive heating at a later stage[64]. Lesions form because of thermal injury to the sarcolemmal membrane of the myocardium. The half-time of lesion growth ranges from 5 to 15 s after the start of energy delivery and maximum lesion size can be achieved within 60 s most of the time[65].

RFA can be adopted for AF ablation strategies beyond PVI, for example, ablation targeting focal sites or formation of lineal lesions. Operators can decide where and to some extent how deeply they want to ablate. Disadvantages of PVI achieved by RFA in a point-by-point mode include relatively long procedure time, chest pain, potentially

discontinued lesions, relatively high risk of PV stenosis, and pericardial complications associated with steam-pop and perforation.

Ablation guided by sensing CF on the catheter tip, providing real-time measurement and monitoring of CF during the procedure, is now the most frequently used technique for PVI. Force on the catheter tip is estimated by measuring the deflection of a small spring between the catheter shaft and tip or by the deformation of a deformable body in the catheter tip with three optical fibres.

Conventional RFA strategy utilises power ranging from 25 to 35 W for a duration of 20–60 s for each application. Recently, new approaches with a setting of high-power and short duration (HPSD) (50-90 W for 4-10 s) have emerged as alternatives. Bhaskaran et al. reported similar efficacy, with fewer complications, using 50/60W for 5s compared with 40 W for 30 s[66]. Bourier et al. reported larger maximum diameter and less deep lesions created by HPSD in comparison with conventional strategies[67]. In a recent meta-analysis including 15 studies and 3718 patients, HPSD showed a higher freedom from ATAs compared with conventional strategies (odds ratio (OR) 1.44; 95% CI, 1.10-1.90; P = 0.009)[68].

ii. **PVI achieved by cryoballoon ablation**

CBA creates lesions by freezing. During CBA, pressurized cryorefrigerant (nitrous oxide, N_2O) is forced into the inner balloon through an injection tube. Freezing is realized by the Joule-Thompson effect when the highly compressed gas (-80°C) expands. The cryorefrigerant absorbs heat from the tissue adhering to the surface of the balloon. The significant drop of tissue temperature leads to extra- and intra-cellular ice crystal formation and consequent cell injury. The subsequent recrystallization in the thawing phase and the later vascular stasis also play important roles in tissue necrosis and lesion formation. There are several practical and theoretical advantages of using the cryoballoon technique for AF ablation, including reduction of pain and discomfort during the procedure, improvement of catheter stability as a result of tissue-catheter adhesion, diminished risk of thrombosis due to decreased activation of platelets and coagulation cascade, uniform tissue necrosis due to lack of vascular and endothelial disruption, preservation of the connective tissue matrix, rapid contiguous circumferential lesion creation, and avoidance of steam pop. Disadvantages of CBA include higher risk of phrenic nerve injury, limited efficacy for variant anatomy (e.g.

common ostium of PV, inferior right PV, extra PVs, different angles and dimensions), and difficulty in performing additional ablation beyond PVI.

Compared with the first-generation cryoballoon, the second-generation cryoballoon (CB2) catheter has a greater freezing surface. It significantly improves ablation efficacy and PVI durability and has been widely used in clinical practice.

iii. Comparison of ablation between RFA and CBA

For paroxysmal AF, the FIRE AND ICE study[69] demonstrated the noninferiority of CBA to point-by-point RFA in terms of clinical outcomes. This conclusion was confirmed by the CIRCA-DOSE study[60]. Moreover, the RAZE-AF study[70] showed similar durability of PVI between RFA using a CF-sensing catheter and CBA using a CB2 catheter.

For persistent AF, there has not been published any RCT comparing the ablation efficacy between RFA and CBA so far. In other studies, the success rate of CBA for persistent AF ranged from 60-70% at one-year follow-up[71, 72]. According to results from the multicentre STOP Persistent AF trial, freedom from ATAs at 12 months after PVI achieved by CBA was 54.8% (95% CI, 46.7%–62.1%)[73]. Recently, Chun et al. reported a similar outcome of 78% recurrence freedom[74]. In a meta-analysis that included 917 patients who underwent CBA for persistent AF from 11 studies, after a mean follow-up of 16.7±3.0 months, 68.9% patients were free from recurrences (95% CI, 63.4-74.7%)[75]. The clinical results of AF ablation using RFA have been reviewed as abovementioned. In a non-randomized study comparing outcomes of PVI using RFA and CBA in persistent AF, CBA and RFA had similar 1-year freedom from ATAs (60% in CBA vs. 58% in RFA, P=0.71)[76].

3. Current challenges in PVI for the treatment of AF

1.3.1 PV reconnection and AF recurrence

Although durable PVI has been established as the cornerstone for AF ablation therapy, it is difficult to achieve a permanent PVI after a single procedure. Nery et al. reported that PV reconnection was detected in 85.5% of patients with AF recurrence and 58.6% of AF-free patients in a meta-analysis[77]. It has been accepted that PV reconnection plays a critical role in the recurrence of ATAs after a PVI procedure. Durable PVI is associated with a lower risk of AF recurrence, with a relative risk of 0.57 (95% CI, 0.37 to 0.86)[77]. Most centres in western countries take re-isolation of reconnected PVs as the primary

strategy in a repeated ablation procedure, and improvement of clinical outcomes has been shown in several observations[78]. In addition, clinical outcomes of repeat procedures in patients with PV reconnection are better than those without PV reconnection[79]. Technical improvements of ablation catheters have had a positive impact on the durability of PVI. In earlier years when non-irrigated, non-CF RFA catheter or first-generation cryoballoon were mainly used for PVI, PV reconnections were detected in 80-100% of patients who underwent a repeat AF ablation. Later, PVI with CB2 achieved a reduced PV reconnection rate ranging from 59 to 74%. AI-guided RFA may also improve the durability of PVI. De Pooter et al. reported the significantly lower PV reconnection rate of 38% of patients in the repeat ablation procedure after an AI-guided PVI[63].

1.3.2 Atrial tachycardia and atrial flutter after AF ablation

Atrial tachycardia and atrial flutter (AFL) were reported in 4 to 31% of patients who underwent a previous AF ablation[80, 81]. Mechanisms of AFL, comprising focal activation, microreentry, small-loop reentry, and macroeentry, have been demonstrated[82]. Extensive LA ablation, especially CFAE-based AF ablation, results in a high incidence of atrial tachycardia or AFL[83]. The impact of the energy used in the previous AF ablation on the AFL incidence is still debated. Akerström et al. reported a trend, but not statistically significant, of lower incidence of atrial tachycardia and AFL following AF ablation using CBA in comparison with RFA (2.8% vs. 4.8%, P=0.23)[84]. In another study, Chang et al. reported a higher AFL incidence linked to CBA (54.5% vs. 12.5%, P=0.027)[85]. Ablation for atypical AFL after AF ablation is challenging because of its complexity, variability, and unpredictability.

1.3.3 Complications

Peri-procedural complications are still the main challenges for AF catheter ablation. Since the primary indication for most ablation procedures is symptoms relief, the benefit can be negated by a slight increase of major complications. The incidence of overall complications ranges from 4% to 14% in prospective, registry-based studies[1, 86], and 2-3% of them are potentially life-threatening. Deshmukh et al. reported an increase of in-

hospital complications from 5.3% in 2000 to 7.5% in 2010[87], and the in-hospital mortality was reported as 0.46%. The experience of the operator and procedure volume of the hospital are highly associated with the complication risk[87]. In recently published data from GWTG-AFIB registry, the overall in-hospital complications occurred in 5.1% of the total 3139 patients. Complications occurred more frequently in persistent AF than in paroxysmal AF (6.7% vs. 3.9%, P=0.0004)[53]. Life-threatening complications were observed in 0.7% of patients. Reported complications include death (0.1-0.4%), atrial oesophageal fistula (0.02-0.11%), cardiac tamponade (2-5%), stroke and transient ischemic attack (0-2%), permanent phrenic nerve paralysis (0-0.4%), vascular complications (0.2-1.5%), PV stenosis (<1%), air embolism (<1%), asymptomatic cerebral embolism (2-15%), coronary artery stenosis/occlusion (<0.1%), gastric hypomotility (0-17%), mitral valve entrapment (<0.1%), radiation injury (<0.1%), stiff left atrial syndrome (<1.5%)[65].

Cardiac tamponade is reported as the most common (25%) cause of ablation-related death and can happen acutely during the procedure or delayed in the weeks after the procedure. It seems to be more common in RFA procedures[69]. Excessive CF and steam-pop play an important role in the presence of cardiac tamponade, but there is no evidence that the use of CF-sensing RFA catheter reduces the risk[88].

Injury to the oesophagus have been reported in both RFA and CBA procedures, and can present in three types: atrial oesophageal fistula, atrial pericardial fistula, and oesophageal haematoma. Although the reported incidence is very low, it has been paid much attention because of its high mortality[89].

PV stenosis has been reported in ablations with almost all energy sources except the laser balloon system. Arentz et al. reported a much higher incidence of PV stenosis when ablation sites were distal in comparison to ostial sites (10/13 vs. 3/13, P<0.01)[90]

Phrenic nerve paralysis can occur in all technologies of AF ablation, but it is the most common complication during CBA procedures. Incidence of transient paralysis was reported at 3.5%–11.2% while permanent paralysis is quite low. To avoid damage of the phrenic nerve while ablating the right PVs, visual inspection of diaphragmatic contraction and monitoring of the diaphragmatic compound motor action potential have become standard approaches in clinical practice.

Optimization of dose strategy for more durable PVI and fewer complications is important for clinical practice. Parameters for control of energy delivery are demanded by both RFA and CBA.

4. Coexistence of AFL and AF

Typical AFL is another common cardiac arrhythmia that may be treated with RFA aimed at the cavotricuspid isthmus (CTI), with a success rate over 90%. It often coexists with AF[91]. The association between AF and AFL has long been recognized[92-94]. Waldo et al.[81] demonstrated the role of AF in the initiation of AFL and this finding was further confirmed by Schneider et al.[95] in a prospective randomized trial. However， the benefit of prophylactic CTI ablation during PVI procedure is denied by clinical trials[96, 97]. Many patients who underwent a previous typical AFL ablation later developed AF[98, 99]. Seara et al. reported that AF after CTI ablation was associated with increased risk of stroke and mortality[100]. Some RCTs have provided evidence suggesting that prophylactic PVI after CTI ablation might be necessary for high-risk patients[95, 101, 102]. Performing an additional AF ablation procedure may increase healthcare costs and the risk of complications. It is still unclear which proportion of these AFL patients may develop symptomatic AF and require further PVI procedures. Prophylactic PVI for patients with AFL has been introduced, but favourable clinical outcomes have not been confirmed by RCTs.

2. Aims

This study aims to investigate the efficacy, safety and technical aspects of PVI in treatment of AF.

Paper I: To evaluate the effectiveness of PVI alone, performed with CBA as therapy in comparison with CF-sensing RFA catheter, in patients with persistent or longstanding persistent AF.

Paper II: To clarify the contribution and correlation of CF, power, and application duration in making an adequate lesion, based upon impedance drop (ID) as a surrogate for lesion formation.

Paper III: To investigate whether the time of phase transition, measured by thawing plateau time, may serve as a predictor for durable PV isolation after CBA.

Paper IV: To test the incidence and possible predictors of symptomatic AF and PVI procedure after a typical AFL ablation.

3. Methods

1. Study design and conduct

All studies were conducted following the Declaration of Helsinki and approved by the Ethics Committee of Western Norway.

Paper I (NO-PERSAF study, NCT03008811) is a prospective, randomized (1:1), open-label, multi-centre clinical trial; Paper II is an observational study; Paper III is a retrospective case-control study; Paper IV is a retrospective cohort study.

The main portion of paper I and the whole work of papers II to IV were conducted in Haukeland University Hospital, Bergen, Norway. Paper I was in collaboration with the Department of Cardiology, St. Olavs Hospital in Trondheim and the Department of Cardiology, University Hospital of North Norway in Tromsø.

2. Patient selection

Papers I to III enrolled patients with symptomatic AF who underwent de novo catheter ablation targeted on PVI.

In specific: Paper I enrolled 18-75 year-old patients who underwent PV isolation as the first ablation procedure for symptomatic persistent AF (lasting for >7 days, but <12 months) or long-standing persistent AF (lasting for 12-36 months) refractory to at least one antiarrhythmic drug. All patients had received at least one direct current cardioversion. Written informed consent was acquired. Exclusion criteria included any previous LA ablation or surgery, presence of an intracavitary thrombus, uncontrolled HF, severe valvular disease, LA anteroposterior diameter >60 mm confirmed by echocardiography, contraindications to systemic anticoagulation with heparin or Warfarin, severe renal dysfunction, and acute coronary syndrome. After the written informed consent had been signed, patients were randomly assigned in a 1:1 ratio to a CBA or RFA group. Paper II enrolled patients with paroxysmal AF. Paper III enrolled both paroxysmal and persistent AF patients.

Paper IV enrolled patients who underwent elective CTI ablation with the indication of symptomatic, recurrent typical AFL.

3. PVI procedure

3.3.1 Preparation before ablation

All patients had taken oral anticoagulation for at least four weeks. Transoesophageal echocardiography was undertaken in all patients and no cardiac computed tomography was performed before the procedure. The patients underwent the procedure under conscious sedation. Heparin was administered immediately after transseptal access to the LA. Activated clotting time was kept between 250 and 350 s throughout the procedure.

3.3.2 RFA procedures

The ablation procedure performed at our institution has been previously described[103, 104]. After the transseptal puncture, angiography of the PVs was performed and a long sheath (Swartz™, Abbott Medical) was placed in the LA. A circular mapping catheter was inserted in the PVs for monitoring the pulmonary potentials. All patients were treated with a contact-force-sensing irrigated ablation catheter and an electroanatomic mapping system. A point-by-point encircling ablation strategy was performed in all PVs. The procedural endpoint was electrical isolation of the PVs based on the elimination of all ostial PV potentials and both entrance and exit conduction block observed.

In Paper I, the catheters and mapping system were restricted to TactiCath™ (Quartz, Abbott Medical), Advisor™ FL (Sensor Enabled™, Abbott Medical) and EnSite Precision™ Cardiac Mapping System (Abbott Medical). Application targeted force-time-integral (FTI) of 400 g·s for every lesion.

In Paper II, the catheters and mapping system were restricted to a 3.5 mm-tip CF-sensing irrigated ablation catheter (Navistar ThermoCool SmartTouch™, Biosense Webster, Diamond Bar, CA, USA) and an electroanatomic mapping system (Carto 3, Biosense Webster, Diamond Bar, CA, USA) with the Visitag module activated during the procedure. We performed a single transseptal puncture, through which both ablation and circular mapping catheters were advanced into the LA. We carried out the procedure

without the assistance of a dedicated long sheath for the ablation catheter. To avoid the mutual effects of two RF applications and the impact of the pre-existing scar issues, we identified and enrolled the ablation points in sinus rhythm at separate sites of the PVs (distance >1 cm, local electrogram amplitude ≥2 mV) before circumferential ablation was performed. In the conventional group, RF energy was delivered in a temperature-controlled mode with a cut-off of 50°C at a cooling rate of 2-20 mL/min. An application time of 60 s with power of 25, 30 or 35 W was used respectively. In the HPSD group, energy was delivered in a power-controlled mode with a cooling rate of 2-30 mL/min and power of 50 W applied for 10 s.

3.3.3 CBA procedures

We placed a steerable 12-Fr sheath (Flexcath®, Medtronic) in the LA and performed angiography of the PVs after the transseptal puncture. A second-generation 28-mm-diameter cryoballoon catheter (Arctic Front Advance®, Medtronic) was introduced into the LA through the sheath with a circular mapping catheter (Achieve™, Medtronic) inserted in the lumen. The circular mapping catheter was advanced more distally, if necessary, to support the deployed cryoballoon stabilizing at the PV ostium. The PV occlusion after balloon inflation was confirmed by venography. Phrenic nerve stimulation at the high output (up to 20 mA), an inspection of diaphragmatic contraction, and monitoring of the diaphragmatic motor action potential were performed to prevent damage during cryoablation in the right PVs. In paper I, the dosing strategy was two cycles of 240-second application. In paper III, freezing delivery time varied from 180 to 300 s for every single application, with or without a bonus application after the PV was isolated, at the operator's discretion. Electrical PV isolation was demonstrated by the elimination of all PV ostial potentials recorded by the circular catheter, and the entrance and exit conduction block were proven by stimulation manoeuvres.

4. AFL ablation

The ablation approach of isthmus-dependent AFL has been previously described[105]. A duodecapolar catheter (Livewire™, St. Jude Medical) was looped around the tricuspid valve with the distal dipoles inserted in the coronary sinus. An irrigated tip ablation catheter (Thermocool Navistar™, Biosense Webster or CoolPath™, St. Jude Medical) was advanced to the right atrium, guided by fluoroscopy. Patients were treated either in

ongoing AFL or in sinus rhythm. An ablation line was completed between the tricuspid annulus and the inferior caval vein with a point-by-point approach. Energy was delivered with a cooling rate of 17–20 ml/min, power output cut-off of 40 W, and temperature cut-off at 50°C. The ablation endpoint was a bidirectional isthmus conduction block, as shown by change of conduction pattern on the duodecapolar catheter and differential pacing on each side of the CTI lesion. An observation time of 30 minutes was followed by a new assessment of bidirectional block.

Programmed electrical stimulation to induce AF was never performed before CTI ablation. The occurrence of intraprocedural AF was deemed to be either spontaneous or occasionally induced by catheter manipulation.

Patients presenting AF without spontaneous termination at any stage of the procedure underwent external electrical cardioversion during a short period of general anaesthesia.

5. Follow-up and endpoints

In paper I, AADs were maintained for at least three months and then discontinued at the physicians' discretion. The patients received direct current cardioversion if they suffered persistent AF during the first month after the procedure. All patients were followed up in an out-patient clinic with a 7-day ambulatory ECG monitoring at 3, 6 and 12 months after ablation. Post-procedural cardiac computed tomography was performed between 3 and 6 months. The primary endpoint was defined as documented recurrent ATAs, including AF, AFL and atrial tachycardia, lasting longer than 30 s in duration after a 3-month blanking period. Secondary endpoints were defined as procedure-related complications, including bleeding/haematoma, phrenic nerve palsy, stroke, pericardial effusion or tamponade, PV stenosis, coronary artery stenosis/occlusion, and atrioesophageal fistula.

In paper IV, Follow-up was performed on an ambulatory basis at 3, 6 and 12 months. Further follow-up depended on the clinical situation. Arrhythmia recurrence was identified from routine ECG, Holter monitoring, and device interrogation if applied. All patients were additionally followed up via telephone questionnaires.

6. Data collection

In paper II, we recorded and exported CF, impedance, temperature, and energy delivered, for analysis off-line. AI was calculated with a customized formula of $AI = \left(k * \int_0^T CF^a(t)P^b(t)dt\right)^c$ by the system[106]. Impedance drop (ID) was defined as the difference between the impedance at a certain time and the baseline value and was used as the surrogate for assessment of ablation efficacy, as the correlation between ID and lesion dimension has been shown in previous studies[104, 107-109]. The maximum ID (MaxID) for each point represented the difference between the minimum impedance value and the impedance at baseline. During an application, ID ≥10 Ω was regarded as an adequate lesion formation[104, 110, 111].

In paper III, we recorded procedural data during the index procedure and analysed data after the repeat ablation procedure. If more than one freezing was applied in a single PV, the application resulting in eventual PV isolation was included for investigation. All temperature values refer to the inner balloon temperature measured by the thermocouple inside the CB. For further analysis, the freezing stage was divided into two periods: initial freezing (IF, from freezing starts to temperature decreases to -40°C) and effective freezing (EF, from temperature reaches -40°C to end of freezing). Duration of initial freezing ($Time_{IF}$) and effective freezing ($Time_{EF}$), and nadir temperature were recorded. If -40°C was never achieved, $Time_{IF}$ was defined as the time from the start of freezing to the point of the nadir temperature. Freezing-temperature-time integral under 0°C (FTTI0) and -40°C (FTTI40) was defined as the area bounded by the temperature curve and 0°C and -40°C, respectively. The thawing stage was divided into three periods: initial thawing (IT, from the end of freezing to the temperature reaches 0°C), thawing plateau (TP, from 0 to 10°C) and late warming (LW, from 11 to 20°C when CB deflated). Duration of the corresponding stages ($Time_{IT}$, $Time_{TP}$, and $Time_{LW}$) were recorded. Initial thawing integral, thawing plateau integral and late warming integral were defined as the area bounded by the temperature curve and 0°C, 10°C and 20°C for IT, TP and LW, respectively. The accumulated values of these parameters are the corresponding sums of all PVs. Plasma level of troponin T (TnT) was determined before and 20-24 hours after the index procedure, using an electrochemiluminescence immunoassay.

7. Statistical analysis

3.7.1 The sample size for paper I

The sample size was calculated based on previously published data covering a range of ablation modalities and methodologies. We estimated that the success rate in patients with persistent AF was around 40% for RFA and 65% for CBA. In order to statistically assess the difference in success rate between these two techniques, at least 94 patients needed to be randomized in the two groups (1:1) for 80% power at a 5% of two-sided significance level. Assuming a dropout rate of 5%, we needed 50 patients in each group.

3.7.2 Data presentation and statistics

Continuous variables were presented as mean ± standard deviation if normally distributed, or as median and interquartile ranges (IQR) if skewed distributed after Shapiro–Wilk test. To compare means of continuous data, a 2-sample *t*-test and Mann–Whitney U-test were employed for normally and skewed distributed data, respectively. Categorical values were presented as percentages and analysed by the χ^2 test or Fisher's exact test as appropriate. Logistic regression analysis was performed to evaluate the effects of the procedural parameters on the presence of PV reconnection. Variables with a P-value over 0.1 in the univariate analysis were removed from the model for further analysis. The correlation was tested among continuous variables, using Pearson's correlation coefficient for normally distributed data. Otherwise, Spearman's correlation was applied as appropriate. The Kaplan–Meier method was used to estimate the survival curves for the time to first primary endpoint and was analysed by log-rank test. For paper I, the assessment of the primary endpoint was conducted by both intention-to-treat (ITT) and per-protocol analyses. Statistical analysis was performed with SPSS version 26 (IBM, USA). A P-value of <0.05 was considered statistically significant.

4. Summary of results

1. Paper I - Clinical outcomes of PVI in patients with persistent/long-persistent AF

In paper I, we enrolled a total of 101 patients (79.2% men; mean age 63.2±8.6 years) who were randomly assigned in the study: 52 in the CBA group, and 49 in the RFA group (intension-to-treat). One patient in the CBA group crossed over to RFA for technical reasons. Thus, 51 patients underwent CBA and 50 patients received RFA treatment (per-protocol). The median of duration of persistent AF before the procedure was 8.0 (IQR 0.3-12.0) months, and 24 patients (14 in CBA and 10 in RFA) had persistent AF lasting over 12 months before the index procedure. No significant difference in demographic or clinical characteristics were found between the two groups.

A total of 397 PVs were targeted. All PVs were successfully isolated by the end of the procedure. After PVI, AF was converted to sinus rhythm in 3 patients (2 in RFA, 1 in CBA). In 2 patients in the RFA group AF changed to typical AFL and was terminated after CTI block was achieved by RFA. One patient in the CBA group was converted to AFL which was not treated during the index procedure. Fluoroscopy times were similar between the CBA and RFA groups, while shorter procedure and ablation times were found in the CBA group (158.9±28.9 vs. 197.9±38.4 minutes, 35.8±6.5 vs. 55.9±16.7 minutes, respectively, both $P<0.001$).

Nine patients experienced AF recurrence before discharge and underwent direct current cardioversion. Thirty-four patients reported AF recurrence in the first 3 months. One hundred patients were followed up until 12 months after the index procedures or the primary outcome was achieved. One patient in the RFA group died 11 months after the procedure because of a serious surgical disease unrelated to the procedure. He did not have a recurrence of any ATAs and was recorded as recurrence-free. One patient underwent ablation of the atrioventricular node after recurrence of persistent AF. After a 3-month blanking period, 36 patients in CBA group and 30 patients in RFA group maintained sinus rhythm without any episode of ATA over 30 s at 12-month follow-up, while AADs were continued in 10 of them (5 in CAB and 5 in RFA). There was no difference in ATA-freedom between the groups (69.2% in CBA vs. 61.2% in RFA, $P=0.398$). No difference in ATA-free survival curves was observed between CBA and RFA groups ($P=0.393$). In a per-protocol analysis, 36 patients in the CBA group and 30 patients in the RFA group were free from ATAs (70.6% in CBA vs. 60.0% in RFA,

P=0.264). No difference of AF recurrence was found between the two groups (27.5% in CBA vs. 38.0% in RFA, P=0.258). Less AFL recurrence was documented in the CBA group compared with RFA (3.9% in RFA vs. 18.0% in CBA, P=0.020). Among those patients with recurrence, 17 patients suffered paroxysmal AF and/or AFL, and 18 were still in persistent AF. The proportion of persistent AF was significantly higher in the CBA group compared to RFA (11/15, 73.3% vs. 7/20, 35.0%, P=0.023).

Five major complications were observed in 4 patients (4%) and no difference was found between the two groups (P=0.353). One patient in the CBA group suffered phrenic palsy (2%) and recovered after 6 months. Complications presented in the RFA group included bleeding with femoral haematoma in one patient, and chest pain in another with no abnormal finding during coronary angiography. Additionally, one patient suffered a tamponade during the procedure and a mild PV stenosis during the follow-up. No further intervention was needed.

2. Paper II - The impacts of parameters on ablation effect in an RFA procedure

In paper II, a total of 787 qualified points from 38 patients (median 20 (IQR 17-22) per patient) were included in the analysis. No major complications were observed during and after the procedures. The mean CF ranged from 1.8 to 38.0 g among all applications. Four sub-groups according to mean CF value under each power setting (25, 30, 35 and 50 W) were stratified for analysis. The mean CF were 3.8±0.8 vs. 3.8±0.5 g in group CF <5 g, 7.6±1.4 vs. 7.0±1.4 g in group CF 5-10 g, 14.2±2.8 vs. 13.5±2.7 g in group CF10-20 g and 25.5±4.5 vs. 25.9±4.7 g in group CF ≥20 g (conventional vs. HPSD, p>0.05). There was no difference regarding mean CF among different conventional power settings within the same CF level (P>0.05).

MaxID over 10 Ω was reached in 301 out of 419 (71.8%) ablation points in the conventional group and 226 out of 368 (61.4%) points in the HPSD group (P<0.01). Among the conventional subgroups, higher power and CF was observed in the points with MaxID ≥ 10 Ω compared with those < 10 Ω.

Changes of CF, power and application time individually affected ID and compensated for each other in certain circumstances.

1) Effect of prolonged application time: The effect of prolonging application time depended on the underlying CF and power level. With CF <5 g, ID seldom reached 10 Ω within 60 s regardless of the power output. This was also the case for CF 5-10 g and 25 W. For CF levels beyond 5-10 g, ID increased with prolonged application under all power settings. However, ablation efficacy improved marginally after 20-30 s (P>0.05, compared to later time points).

2) Effect of increasing CF: It was observed for a given application time and power level (25, 30 and 35 W), that ID increased with higher CF. The time to reach ID ≥10 Ω and MaxID tended to be shorter with increasing CF levels. A CF ≥20 g led to an ID ≥10 Ω within 10 s at all power settings.

3) Effect of increasing power: As abovementioned, increasing power did not increase ID when CF <5 g. With CF ≥5 g, ID under the power of 30 and 35 W were significantly higher than that under 25 W (P<0.01). ID under 30 and 35 W were similar (P>0.05), except for CF 10-20 g for 20 to 40 s, where power of 35 W provided significantly higher ID than 30 W (P<0.05).

The efficacy of HPSD ablation at 10 s was compared with the conventional sub-groups at different time points. ID ≥10 Ω was achieved at 10 s in all cases with CF ≥5 g in the HPSD group, but not <5 g. With CF 5-10 g, ID in the HPSD group was higher than that under the setting of 25 W for 40 s, and lower than under 30 W for 40 s and 35 W for 30 s, respectively. With CF 10-20 g, ID in HPSD group was higher than that under 25 W for 30 s, and lower than under 30 W for 40 s and 35 W for 30 s, respectively. With CF ≥20 g, ID in the HPSD group was higher than that under 25 W for 10 s, and lower than those under 30 and 35 W for 20 s. Differences of ID values at 10 s under powers of 30, 35 and 50 W were not statistically significant.

The average of AI in the conventional group was higher than that in the HPSD group (531.7±89.8 vs. 395.8±43.1, P<0.01). Higher AI was found in ablation applications with ID ≥10 Ω than those with ID <10 Ω in both conventional (558.7±85.3 vs. 462.7±58.9, P<0.01) and HPSD groups (405.7±43.3 vs. 380.1±37.9, P<0.01), respectively.

The values of ID under various AI levels for powers of 30, 35 and 50 W were similar and the corresponding curves of ID were uniformly superimposed, whereas 25 W resulted in significantly lower ID at all AI levels (for AI 350-500 W·g·s, P<0.01).

Notably, a minimum of 450 W·g·s of AI was required to achieve ID of 10 Ω under the power of 25W, while less than 350 W·g·s was sufficient to reach the same ID level under powers of 30-50 W.

3. Paper III - The predictive value of thawing time for the durability of PVI using CBA

In paper III, we enrolled 71 patients (age 61.8±10.5, female 39.4%) with recurrent AF. The median duration from index procedure to repeat procedure was 526 (IQR, 412-675) days. Left common pulmonary vein (LPV) was observed in 12 patients. After excluding PVs with data missing, failed PVI by CBA during index procedure, or more than 3 applications, 241 PVs were analysed. Reconnection was observed in 101 (41.9%) PVs of 53 patients (74.6%). No bonus application was performed in 168 PVs (69.7%). Complete occlusion was achieved in 173 PVs (71.8%), and suboptimal occlusion with minor leakage in 68 PVs (28.2%). Successful isolation was achieved after the first freezing in 184 PVs (76.3%).

The $Time_{TP}$ in this cohort was 23.0 (11.0, 28.0) s, and it correlated with the nadir temperature (ρ=-0.742; P<0.01). Besides longer $Time_{TP}$ (P<0.01), those cryoablations leading to durable PV isolation showed lower nadir temperature (P<0.01), shorter $Time_{IF}$ and longer $Time_{EF}$ (P<0.01), higher FTTI0 and FTTI40 (P<0.01), longer total thawing time and $Time_{IT}$ (P<0.01), and higher initial thawing integral, thawing plateau integral, and late warming integral (P<0.01). Location of PV (specifically the left superior PV, P<0.01), $Time_{TP}$ (P<0.05) and thawing plateau integral (P<0.01) were shown as independent predictors for durable PV isolation.

The durability of PV isolation increased with $Time_{TP}$ in a dose-proportional manner. The cut point of $Time_{TP}$ for PV reconnection was <15 s with a positive predictive value of 82.1% (sensitivity=63.4%, specificity=90.0%), while for durable PV isolation the cut point was $Time_{TP}$ >25 s with a positive predictive value of 84.6% (sensitivity=55.0%, specificity=86.1%). For those applications with a $Time_{TP}$ between 15 and 25 s, nadir temperature lower than -45℃ was employed as a supplementary predictor for durable PV isolation with a positive predictive value of 78.4% (sensitivity=59.2%, specificity=68.0%).

The average plasma TnT after the index procedure was 835.3±244.1 ng/L. The correlation between the accumulated $Time_{TP}$ and TnT ($\rho = 0.624$, $P<0.01$) was stronger than the accumulated values of thawing plateau integral, $Time_{IT}$ and nadir temperature.

4. Paper IV - AF after AFL ablation

In paper IV, durable CTI block was achieved in all 127 patients (counter-clockwise AFL 92%) without major procedure-related complications. Clinical AF was documented in 89 patients (70%) during a mean follow-up period of 68 ± 24 months (range 33-116). More AF was recorded in patients with earlier-documented AF compared to patients without AF history (86% in 56 vs. 58% in 71, $P<0.01$). The average time to AF occurrence was 19 ± 19 months and AF was documented within two years from the index procedure in 69 (77.5%) patients.

Fifty-three symptomatic AF patients (42% of total) underwent either a single (n=39) or multiple (n=14) AF ablation procedures at an average of 26 ± 17 months after the index AFL ablation. The remaining 36 patients were managed pharmacologically (22 remained in paroxysmal AF, 14 developed permanent AF and three of these underwent atrioventricular node ablation). Fourteen patients received either a dual-chamber (n=10) or biventricular pacemaker (n=4) implantation. Fifteen patients (12%) underwent repeat CTI ablation, either because of clinical recurrence of typical AFL (n=4) or lack of bidirectional block coincidentally demonstrated during subsequent AF ablation procedures without clinical evidence of AFL (n=11).

During the follow-up period, 10 patients (8%) developed non-fatal ischemic cerebral events, with one occurring within 72 hours after aortic valve replacement surgery. The remaining nine events occurred after 44 ± 30 months from the index procedure and were classified as transient ischemic attacks (n=3) or radiologically verified ischemic strokes (n=6). The average CHA_2DS_2-vasc score in these patients was 2.6 ± 1.7 and AF was previously registered in eight of them.

Five patients were not receiving anticoagulation (three on aspirin, two without any medication) at the time of the cerebrovascular event because of relatively low CHA_2DS_2-vasc score or gastrointestinal bleeding.

At the end of follow-up, 68 patients (54%) were using oral anticoagulation (warfarin in 30%, novel oral anticoagulants in 24%), while 20 low-risk (CHA_2DS_2-vasc score ≤1) patients (16%) were managed with aspirin.

Preprocedural documentation of AF (OR 3.53), precedent use of flecainide (OR 3.33), and left atrial diameter (OR 2.96) were independently associated with clinical occurrence of AF during the follow-up period ($p<.05$).

Two-thirds of patients without AF history before the index procedure developed AF during follow-up, similar to those patients with only intraprocedural documented AF. Patients with previous documented AF developed AF more frequently and rapidly. Independent predictors for additional AF ablation included a higher CHA_2DS_2-vasc score (OR 0.72), documentation of both pre- and intraprocedural AF (OR 3.81), and previous use of flecainide (OR 2.43).

5. General discussion

1. CBA is an effective and safe alternative to RFA

RFA has emerged as a fundamental, effective treatment for AF in the past 20 years[2, 56, 112], while CBA has become the most commonly used alternative technique according to several RCTs and observational studies. In paroxysmal AF, noninferiority of clinical outcomes of CBA has been verified by the FIRE AND ICE study[69] and the CIRCA-DOSE study[60]. The similar durability of PVI has been further confirmed by the RAZE-AF study[70]. However, evidence in patients with persistent/long-standing persistent AF is still lacking. The success rate of CBA for persistent AF in early observational studies ranged from 60 to 70% at one-year follow-up[71, 72]. In the CRYO4PERSISTENT AF trial, one-year freedom from ATAs was achieved in 61% of patients[113]. The multicentre STOP Persistent AF trial demonstrated that freedom from ATAs at 12 months after PVI using CBA was 54.8% (95% CI, 46.7%–62.1%)[73]. Based on this trial, the US Food and Drug Administration approved CBA for treatment of persistent AF in June 2020. Recently, Chun et al. reported 78% recurrence freedom[74]. In a meta-analysis of 11 studies that included 917 patients who underwent CBA for persistent AF, after a mean follow-up of 16.7±3.0 months 68.9% were free from recurrence (95% CI, 63.4-74.7%)[75]. Comparisons of efficacy between CBA and RFA for PVI have been conducted in several studies. A non-randomized study in persistent AF showed a similar 1-year freedom from ATAs (60% in CBA vs. 58% in RFA, P=0.71)[76]. In another study using a propensity-score-matching algorithm in patients with persistent AF and enlarged LA, no difference of AF recurrence (34.2% vs. 28.8%, P=0.66) was found[84, 114]. Although several studies support that CBA is effective for treatment of persistent AF, the results are limited by the fact that most patients enrolled in these trials were persistent AF (duration <1 year) or early-stage persistent AF (duration <6 months), and the non-randomization design.

Our study (paper I) is the first randomized evaluation of PVI achieved by RFA or CBA in patients with persistent/long-standing persistent AF. The clinical features of the patients were comparable to those in other trials[43, 73]. Although the proportion of long-standing persistent AF was relatively low, over half of the patients had persistent AF lasting over 6 months prior to the index procedure. We found CBA was as effective as RFA regarding freedom from recurrence of ATAs. This finding is in line with published

data and further strengthens the evidence that CBA is an effective alternative to RFA in treating persistent/long-standing persistent AF. Notably, our study used 7-day ambulatory ECG monitoring to detect symptomatic and asymptomatic recurrences during follow-up in order to obtain a reliable measure of ATA-freedom.

We found that, consistent with previous reports[84, 114], less AFL was recorded in the CBA group during follow-up. Meanwhile, the proportion of AF recurrence in persistent form was significantly higher in the CBA group. These observations may be explained in part by the difficulty of creating continuous circumferential lesion lines when using point to point RFA, and in part by increased catheter stability due to freeze-mediated adhesion of the cryoballoon in CBA. This might result in creation of more homogeneous lesions with potentially less proarrhythmic effect with CBA[115]. In addition, the lesion size, depth, durability, and even lesions covering the posterior wall of the LA created by CBA may differ from RFA. These issues demand further investigation.

No statistical difference was found between the two groups with respect to procedure-related complications. Other publications have reported similar incidences of overall complications between CBA and RFA[69], finding also that phrenic nerve palsy is more likely in CBA and tamponade more common in RFA[86]. We observed one phrenic nerve palsy in the CBA group, and one tamponade and a mild PV stenosis in the RFA group. The tamponade occurred before the RFA catheter was introduced, so was not linked to RFA technique.

The essential factor for clinical outcome in this study might be the durability of PVI for both CBA and RFA The FIRE AND ICE trial[69] demonstrated a significantly lower rate of PV reconnection in RFA compared to CBA (46% vs. 64% of PVs). However, the durability of PVI has also been improved by the guidance of lesion-formation indices, such as FTI, lesion index and AI [60, 63]. In the RAZE-AF study[70], the durability of PVI achieved by RFA with CF-sensing technique and CBA with CB2 was similar. Larger-scale RCTs are required to verify these observations.

Considering the similar ATA-freedom achieved by CBA, and its shorter procedure and ablation times, our results further encourage the use of CBA as an alternative to RFA in patients with persistent/long-standing persistent AF.

2. Relationship between procedural parameters and durability of PVI

5.2.1 Procedural parameters and ablation effect in an RFA procedure

Creating transmural lesions by effective ablation is the basis of durable PVI in RFA procedures. Controllable parameters which have impacts on ablation effect include CF, power, and application time. Our study provides insight into how procedural parameters influence the ablation effect.

CF represents the contact pressure between the catheter tip and tissue. Following the development of CF-sensing techniques, real-time CF can be measured during the procedure. The essential role of CF in AF ablation has been demonstrated in a series of observational studies from basic to clinical level. However, the benefit of applying CF-sensing catheters in terms of clinical outcomes has not been supported by randomized-controlled trials[116, 117]. A meta-analysis that enrolled 9 RCTs utilizing CF-sensing catheters failed to show improvement in freedom from AF in comparison with non-CF sensing catheters (relative risk, 1.03; 95% CI, 0.95-1.11)[118]. Experimental models have shown how ablation efficacy is impacted by several parameters[109]. During RFA, the surface of tissue in contact with the ablation electrode is warmed immediately by resistive heating, while the deeper tissue layer is warmed by the conductive heating at a later stage. Passively conductive heating is time-dependent[64]. FTI takes both CF and application time into consideration and a minimum FTI of 400 g·s for creating transmural lesions was agreed in several studies[119-121]. A limitation of FTI is that it does not take power into account. Increasing current intensity or power output at the electrode-tissue interface produces higher temperature gradients and thus greater and deeper lesion.

AI was proposed based on a weighted formula integrating CF, power and application time. It has been reported that predicted lesion depth based on AI correlates well with actual lesion depth in the beating canine heart[106]. Improvement of clinical outcomes and durability of AI-guided PV isolation has been reported in observational studies based on the CLOSE protocol that targets values of 550 W·g·s in the anterior and 400 W·g·s in the posterior left atrial wall [58, 122]. Significantly fewer PV reconnections were reported in the PRAISE trial[63]. In the RAZE-AF study[70], AI-guided PVI showed fewer PV reconnections compared with the FTI-guided procedure.

Our study supports these findings by providing insight into both individual and collective impacts of CF, power and application on ablation effect. In common with a previous study conducted in an ex vivo model[67], we found that a minimum CF of 5 g is required

for effective ablation. Moreover, our study showed additional impacts of application time and power on ablation effect.

We used ID as a surrogate for ablation efficacy because the correlation between ID during ablation and lesion dimensions has been confirmed in animal studies[107-109] and ID has been widely used to monitor the acute efficacy of catheter ablation in clinical practice[123, 124]. While an increase in power output resulted in consistently higher ID, the effect of increasing ablation time was insignificant after 30 to 40 s. This is in line with various studies which reproducibly demonstrated that maximum lesion volume is achieved after 30 to 40 s of energy delivery[108, 125]. Our finding supports the idea of delivering RF energy to a target magnitude of AI rather than for a fixed duration. Outside this time window, the additional effect of prolonging application time on ID is limited, and might lead to collateral tissue damage, especially with higher CF and power levels.

It is noteworthy that our study showed that AI-guided ablation had satisfactory efficacy under power outputs ranging from 30 to 50 W, but not under 25 W, a finding supported by results from a recent in vivo study[126]. This observation might be explained by the fact that the customized formula for calculating AI was based on experiments that used power outputs of 30-50 W. In clinical practice, the interpretation of AI needs caution when sometimes 25 W is applied because of pain or other reasons.

In the CLOSE protocol, AI ≥400 W·g·s is applied at the posterior wall. Yet 14% of oesophageal thermal injury (3% of severe oesophageal thermal ulcer) was reported when ablation with AI ≤350 W·g·s was applied at posterior wall[127]. Interestingly, our data showed that the AI of 350 W·g·s might be sufficient to reach the ID goal of 10 Ω under powers of 30-50 W. This finding may support a lower AI target at the posterior wall to reduce complications.

Recently, HPSD ablation has emerged as a new option for AF ablation. Animal studies have shown the efficacy and safety of the strategy with several combinations of power (50 to 90 W) and application time (4 to 8 s)[66, 128]. Similar AF-freedom and complication rates of AF ablation using HPSD protocol with 45-50 W for 5-15 s compared with conventional strategy have been demonstrated by clinical studies[129, 130]. In an experimental study using porcine thigh muscle, Bourier et al. reported that HPSD ablation resulted in a similar lesion volume, but with a larger maximum diameter and a smaller lesion depth. The lesion volume made by ablation using 50 W for 13 s was equal to that using 30 W for 30 s[67]. These findings were confirmed by our data which showed that ablation with 50 W for 10 s resulted in a similar ID to the conventional 30 W for 30

s. However, the ID was lower than that achieved using 30 W for 40 s. Additionally, we found that a lower proportion of ablations achieved ID ≥10 Ω in the HPSD than in the conventional group. This may be explained by a reduction of the conductive heating phase due to the shorter application duration in HPSD ablation with power-controlled mode[66]. Thus, in order to get durable lesions under the setting of 50 W for 10 s, sometimes longer application time or increased power may be considered. Recently published data have shown new information supporting this hypothesis[131].

5.2.2 Predictors for the durability of PVI in a CBA procedure

The conventional dosing strategy of two or more cryoenergy applications of at least 240 s in each PV was based on the data from the first-generation cryoballoon. It has since been challenged, as the cooling efficiency of the second-generation cryoballoon is improved by the increase in freezing surface. In a study using real-time magnetic resonance imaging-guided cryoablation of the PVs on canines, Lichter et al. reported that PVI could be achieved by one freezing cycle of 3-minute duration[132]. Several pilot studies with fixed duration or patient-tailored strategies were conducted to confirm the efficacy and safety of lower-dose strategies. The data from these studies were encouraging as they achieved similar clinical outcomes to the conventional approach but with reduced procedural time and fewer complications[133-135]. However, it is also reported that the efficacy of cryoablation is impaired by over-reduction of dosage[136, 137].

To optimize the dose strategies for CBA, bio-physiological and procedural parameters with potential predictive value for the durability of PVI were evaluated in a series of studies, including balloon temperature, time-to-isolation (TTI) and thawing time. The balloon temperature during freezing has been studied in an earlier animal study, demonstrating that a rapid temperature drop to below -40°C was associated with maximal tissue damage[138]. Fürnkranz et al. reported an association between nadir temperature at -51°C and acute PV isolation in patients [139]. Unfortunately, the predictive value of the nadir temperature during freezing for long-term durability of PV isolation has not been confirmed by clinical trials. In an analysis of PV reconnection in patients who underwent a repeat AF ablation procedure, the nadir balloon temperature during freezing failed to show an independent predictive value[140]. Our findings further support their arguments. Lower nadir temperature was associated with better durability of PVI, but it was not an independent predictor. A possible explanation may be that the balloon temperature measured by the thermocouple inside the balloon is remote from the tissue and not

accurate enough. It is influenced by the pressurized cryorefrigerant injection and the warming of blood flow.

TTI indicates the time from start of freezing to the point when signals in PVs disappear. During freezing, cardiac cells sustain electrical dormancy (20℃ to 25℃) and lethal injury (-20℃ to -50℃). TTI represents the time when the electrical dormancy of the myocardial sleeve is achieved. Shorter TTI implies better energy conduction, or a more superficial myocardial sleeve[141]. TTI is considered as a predictor for durability of PVI and an association of TTI longer than 60 s with PV reconnection has been confirmed by studies[140, 142, 143]. Several patient-tailored dosing strategies based on TTI showed similar clinical outcomes to the conventional 240-second procedure[144, 145]. But TTI has its shortcomings. First, TTI indicates electrical dormancy rather than non-viability. The real duration from TTI to achievement of durable PVI is not easy to obtain in a clinical study. The regimen of two-minute freezing after TTI remains an empirical strategy. Second, TTI may be affected by previous freezing. In clinical trials based on a TTI-guided strategy, plans for applications following previous freezing with unsatisfactory TTI were often fixed-dose[144, 145]. Third, it is somehow difficult to compare approaches based on different TTI criteria. Finally, TTI is not always available because sometimes it is necessary to advance the circular recording catheter further distally into the PVs to better support a stable PV occlusion during freezing. We did not analyse the relationship between TTI and the durability of PV isolation in this study because of the non-availability of data and fixed regimen.

Thawing time has been suggested as a predictor for the durability of PV. Ghosh et al. reported that a thawing time of ≥25 s between -30°C and +15°C may predict permanent PV isolation[146]. Aryana et al. indicated a thawing time that reached 0°C (equals $Time_{IT}$ in our study) of ≥10 s may offer greater sensitivity and specificity to predict the durability of PV isolation[140]. However, the usefulness of thawing time is limited in clinical practice. It is not available before the end of an application and so cannot be used for adjusting the ongoing delivery of cryorefrigerant. We also proved that thawing time is an independent predictor for the durability of PVI, but more importantly, we demonstrated that the most decisive part in the thawing period is the thawing plateau stage and further that $Time_{TP}$ is linked to the durability of PV isolation in a dose-proportional manner. Moreover, we found that $Time_{TP}$ <15 s and >25 s can predict 82.1% of reconnection and 84.6% of durable PV isolation, respectively.

Multivariable regression analysis demonstrated that $Time_{TP}$ was the strongest biophysical predictor among those that were shown to be significant in the univariate investigation. This might be explained by the following facts and observations. First, $Time_{TP}$ represents the size of frozen tissue created by the CBA, as abovementioned. Second, the balloon temperature at the thawing plateau is closer to the tissue temperature than at other stages[147]. Third, recrystallization frequently takes place at this stage and even prolongs the duration[138, 148]. Finally, the rate of thawing has a significant effect on osmotic stress, and slow thawing, in general, is more likely to cause fluid shifts and increase osmotic trauma to the cells[138, 148]. This hypothesis was further supported by the correlation between $Time_{TP}$ and TnT. Although TnT is not a predictor for the clinical outcome of CBA for AF, it precisely quantifies the magnitude of myocardial injury[149]. In the present study, $Time_{TP}$ positively correlated with the elevation of TnT after the index procedure, which suggested $Time_{TP}$ may serve as a parameter to estimate lesion size. As indicated by other investigations, $Time_{IT}$ may also reflect the degree of freezing. The main difficulty is that $Time_{IT}$ is usually short and hard to measure the differences.

Based on our results, $Time_{TP}$ may be not only a predictor for the durability of PVI but also a parameter that reflects the actual freezing effect received by tissue. Therefore, it could be used for evaluating applications without information of TTI. For application with $Time_{TP}$ <15 s, an extra bonus freezing might be needed, while $Time_{TP}$ >25 s indicates durable PVI without further freezing.

3. High incidence of AF and PVI therapy after ablation for typital AFL

CTI ablation has been established as the standard therapy for typical AFL with a success rate of over 90% if the bidirectional block is achieved. Unfortunately, the freedom from ATAs is relatively low due to concomitant AF. The association between AF and AFL has been recognized, showing that AF plays a critical role in the initiation of typical AFL [81]. Clinical studies in both animal and human models have shown that AF occurs often before the onset of AFL[92, 93]. An intercaval line of block induced by variable length bursts of AF is the basis of AFL[80]. Previous studies investigating long-term outcomes of elective CTI ablation reported an incidence of AF in up to 70% of AFL patients[94, 99, 100]. The reported AF incidence increased with longer follow-up duration and more intensive monitoring. Our results are consistent with previous publications although as our follow-up duration was longer than most previous studies and we recorded a higher incidence

of AF. In addition, 42% of patients in our study underwent a PVI ablation for AF during follow-up. Initial clinical trials showed that prophylactic PVI reduced the occurrence of AF in patients with only clinical documentation of AFL[95, 101, 102]. The EAST-AFNET 4 trial reported a lower risk of adverse cardiovascular outcomes with early rhythm-control therapy in patients with early AF and cardiovascular conditions, implying that early intervention for AF might benefit patients. Demographic and clinical characteristics of patients in our study were comparable to the EAST-AFNET 4 trial. It therefore seems reasonable to consider including a PVI procedure during elective AFL ablation for those patients. However, the risk of complications and extra costs need to be taken into consideration. How to select patients for this type of procedure is still unclear. Our study showed a lower CHA_2DS_2-vasc score (OR 0.72), documentation of both preprocedural and intraprocedural AF (OR 3.81), and previous use of flecainide (OR 2.43) were independent predictors for additional PVI ablation. This finding might help to identify candidates for prophylactic PVI.

Besides AF, we also recorded a high incidence of non-fatal ischemic cerebral events. This agreed with other studies showing an increased rate of stroke in patients who developed AF after AFL ablation[100, 150]. The increased risk of ischemic cerebral events might be due to the coexistence of AF. Our results support more active anticoagulation in these patients.

4. Limitations

Most studies in this thesis are single-centre studies with a limited sample size. Because of the variety of catheters, settings and mapping systems, application of the results elsewhere should be interpreted with caution.

In paper I, the sample size was estimated based on the available outcomes of earlier investigations. With the wide use of CF-sensing catheters guided by parameters representing ablation power, such as lesion size index and AI, the efficacy of RFA for persistent AF seems improved. Large-scale randomized clinical trials are required to further confirm the conclusions of this study. We did not analyse the radiation exposure because we had observed a large variation of radiation dosage from one lab to another due to different devices/systems. Since the fluoroscopy time was similar between the two groups, the radiation exposure might be higher in the CBA group given that cine

angiography of the PVs was carried out before every cryoablation, which was not necessary in the RFA group.

Paper II focused on the effect of each single RF application without a mutual effect. The results could not be simply generalized to clinical outcomes. We used ID as surrogate for ablation effect, based on both animal and clinical studies. Impedance is measured in clinical practice with different techniques. This may influence the interpretation of optimal ID for an adequate lesion. Few points with high CF were involved in this study as catheter stability was more challenging in such situations without the support of a steerable long sheath. Power settings were selected following clinical practice. Thus, no further information was available on other power levels.

In paper III, TimeTP should be accurately measured by the precise interval of the thawing plateau. However, the beginning and end of the plateau on the curve are difficult to define in practice and variation exists even for a single observer. We employed the thawing time between 0 and 10°C to standardize and simplify the measurement. Since the plateau always lies in this narrow range, the difference is little and acceptable. The impacts of TTI and freezing dosage/duration were not analysed because of the non-availability of data or identical regimen. We could not conduct subgroup analysis of a single PV due to the limited sample size. There were no major complications observed among study patients, therefore we could not verify the predictive value of $Time_{TP}$ for complications.

Paper IV was a single-centre, retrospective study. The retrospective nature of this investigation might have an impact on the interpretation of the data. During extended follow-up (>12 months) ECG and Holter monitoring were performed only in the presence of symptoms. We acknowledge therefore that asymptomatic AF may have gone unrecognized. However, the long duration of follow-up (averaging over five years) increases the likelihood that most of our patients with AF occurrence were identified.

5. Future perspectives

Since several studies have reported similar freedom from ATAs for RFA and CBA during long-term follow up, a noninferiority trial in a large patient population of persistent AF is called for. Ablation strategies and techniques have recently advanced in RFA and CBA for AF treatment. Lesion-formation-guided RFA has improved outcomes with more durable PVI.

HPSD settings for RFA and reduced dosage in CBA have produced similar clinical results with shorter procedure times. A large-scale trial for comparison of RFA and CBA using alternative strategies is demanded.

Less AFL was recorded following CBA compared with RFA. The mechanisms have not been clarified. Investigations into the distribution of scar tissue and form of the ablation area created by CBA and RFA could provide new information and further explanation. Since AFL is often more symptomatic than AF, the QoL of patients undergoing CBA and RFA might differ. We found a large proportion of patients who underwent AFL ablation later also needed AF ablation, suggesting that indications for PVI should be considered during AFL ablation. This needs to be confirmed by RCTs.

6. Conclusions

1. PVI achieved by CBA was as effective as RFA for treatment of persistent or long-standing persistent AF in terms of ATA-freedom at 12-month follow-up, with less AFL recurrence and shorter procedure and ablation times.

2. CF of at least 5 g is required for effective ablation. With CF ≥5 g, CF, power and application time can compensate for each other within restricted ranges. The time to reach the maximal ablation effect can be shortened by increasing CF or power output. The effect of HPSD ablation with 50 W for 10 s is equivalent to conventional ablation with 25 W for 40 s or 30-35 W for 20-30 s in terms of ID. ID and AI correlate well at power outputs between 30 and 50 W, and with lower ID values at 25 W.

3. $Time_{TP}$ is an independent predictor for the durability of PV isolation, and it presents in a dose-proportional manner. $Time_{TP}$ <15 s predicts long-term reconnection while $Time_{TP}$ >25 s predicts durable PV isolation. These findings may guide the regulation of further CBA regimens.

4. After long-term follow-up, AF occurred in the majority of patients after elective CTI ablation and often required an additional AF ablation procedure. Pre- and intraprocedural documentation of AF together with previous use of flecainide, independently predicted the occurrence of AF and the need for additional AF ablation.

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I

Cryoballoon versus radiofrequency catheter ablation: insights from NOrwegian randomized study of PERSistent Atrial Fibrillation (NO-PERSAF study)

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Brief running title: Cryoballoon versus radiofrequency catheter ablation

The total word count: 3567

Funding: This study was partly supported by Helse Vest, Norway (LBS).

Conflict of interest: Dr. Jian Chen serves as a consultant for Biosense Webster, Johnson & Johnson, and has received research grant from Medtronic and Abbott Medical. Otherwise, there are no conflicts of interest to be disclosed for other co-authors.

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Abstract

Aims: Pulmonary vein isolation (PVI) is still regarded as a cornerstone for treatment of persistent atrial fibrillation (AF). This study evaluated the effectiveness of PVI performed with cryoballoon ablation (CBA) in comparison with radiofrequency ablation (RFA) in patients with persistent AF.

Methods and results: A total of 101 patients with symptomatic persistent AF were enrolled and randomized (1:1) to CBA or RFA groups and followed up for 12 months. The primary endpoint was any documented recurrent atrial tachyarrhythmia (AT) lasting longer than 30s following a 3-month blanking period. Secondary endpoints were procedure-related complications, procedure and ablation duration, and fluoroscopy time. The AT-free survival curves were estimated by Kaplan–Meier method and analysed by log-rank test. According to intention-to-treat analysis, freedom from AT was achieved in 36 out of 52 patients in the CBA group and 30 out of 49 patients in the RFA group (69.2% vs. 61.2%, P=0.393). No difference of AT recurrence was found between the two groups (27.5% in CBA vs. 38.0% in RFA, P=0.258), and less atrial flutter recurrence was documented in the CBA group compared with the RFA group (3.9% vs. 18.0%, P=0.020). The procedure and ablation duration were significantly shorter in the CBA group (160±31 vs. 197±38 minutes, P<0.0001; 36.7±9.5 vs. 55.3±16.7 minutes, P<0.0001). There was no difference regarding fluoroscopy time (21.5±7.8 vs. 23.4±11.2 minutes, P>0.05).

Conclusions: Compared with RFA, PVI performed by CBA led to shorter procedure and ablation duration, with less atrial flutter recurrence and similar freedom from AT at 12-month follow-up.

Keywords: persistent atrial fibrillation, pulmonary vein isolation, cryoballoon, radiofrequency ablation, randomized trial.

Introduction

It has been demonstrated that catheter ablation is effective and safe for treatment of paroxysmal atrial fibrillation (AF), but long-term outcome is poor for patients with persistent or long-standing persistent AF[1-3]. Although a variety of additional ablation strategies have been attempted, electrical pulmonary vein isolation (PVI) is still regarded as a cornerstone of treatment for persistent AF[1, 3, 4]. Radiofrequency ablation (RFA) by point-by-point mode is the most common method to achieve PVI, while cryoballoon ablation (CBA) has emerged as an alternative technique. Similar clinical outcomes and durability of PVI in ablation of paroxysmal AF have been demonstrated by randomized controlled trials[5-7]. For persistent AF, the success rate of CBA ranged from 60-70% at one-year follow-up[8-11], while a relatively low success rate of 35.6-41.0% for RFA was reported from earlier studies[1-3, 12]. Hoffmann et al. reported a similar recurrence rate of atrial tachyarrhythmia (AT) for RFA and CBA in patients with persistent AF in a prospective multicentre and multinational observational cluster cohort study[13]. Randomized controlled trials are called for to compare CBA and RFA for PVI in treatment of persistent AF.

We aimed to evaluate the effectiveness of PVI performed with CBA in comparison with contact-force-sensing RFA in patients with persistent or long-standing persistent AF.

Methods

Study design

NO-PERSAF study (ClinicalTrials.gov number, NCT03008811) is a prospective, randomized (1:1), open-label, multi-centre clinical trial to compare clinical outcomes of PVI achieved using cryoballoon and contact-force-sensing RFA catheter in persistent or long-standing persistent AF. All patients were recruited in three Norwegian centres. This study was conducted following

the Declaration of Helsinki and approved by the Regional Ethics Committee of Western Norway.

Study participants and randomization

This study enrolled patients who underwent PV isolation as the first ablation procedure for symptomatic persistent AF (lasting for >7 days, but <12 months) or long-standing persistent AF (lasting for >12months) refractory to at least one antiarrhythmic drug. All patients had received at least one direct current cardioversion. Eligibility criteria were 18 to 75 years old and able and willing to give informed consent. Exclusion criteria were any previous left atrial (LA) ablation or surgery, presence of an intracavitary thrombus, uncontrolled severe heart failure, severe valvular disease, LA anteroposterior diameter >60 mm confirmed by echocardiography, AF lasting longer than 36 months, contraindications to systemic anticoagulation with heparin or Warfarin, severe renal dysfunction, and acute coronary syndrome. After the written informed consent had been signed, patients were randomly assigned in a 1:1 ratio to the CBA group or RFA group.

Ablation procedure

All patients had taken oral anticoagulants for at least four weeks. Transoesophageal echocardiography, but not cardiac computed tomography, was performed on all patients before the procedure. The patients underwent the ablation procedure under conscious sedation. Heparin was administered immediately after transseptal access to the LA. Activated clotting time was kept between 250 and 350 s throughout the procedure. Angiography of the PVs was performed after the transseptal puncture. The procedural endpoint was defined as electrical isolation of the PV demonstrated by the elimination of PV potentials in the ostium.

Cryoballoon ablation: After the transseptal puncture, a steerable 12-Fr sheath (Flexcath®, Medtronic) was placed in the LA. All patients were treated with a 28-mm diameter cryoballoon

(Arctic Front Advance®, Medtronic). A circular mapping catheter (Achieve™, Medtronic) was inserted through the lumen of the cryoballoon and was advanced more distally to stabilize the cryoballoon at the PV ostium. Occlusion of the PV by the balloon was confirmed by venography. The ablation regimen consisted of two freezing applications of 240 s in each PV. To prevent damage of the phrenic nerve while ablating the right PVs, visual inspection of diaphragmatic contraction and monitoring of the diaphragmatic compound motor action potential were performed during phrenic nerve pacing with another diagnostic catheter at a high output (up to 20 mA and 2 ms duration).

Radiofrequency ablation: After the transseptal puncture, a long sheath (Swartz™, Abbott Medical) was placed in the LA. A circular mapping catheter (Advisor™ FL, Sensor Enabled™, Abbott Medical) was inserted in the PVs for monitoring the pulmonary potentials. All patients were treated with a contact-force-sensing irrigated ablation catheter (TactiCath™ Quartz, Abbott Medical) with support of a deflectable long sheath (Agilis™, Abbott Medical). An encircling ablation strategy was performed in all PVs, with targeting force-time-integral of 400 g·s for each lesion.

A 3-dimensional mapping system (EnSite NavX, Abbott Medical) was employed to reconstruct the LA geometry in all patients, and bipolar voltage mapping was performed with the circular mapping catheter in AF before ablation and in sinus rhythm after PVI. If the procedure started with sinus rhythm, we induced AF with burst atrial pacing. If the patient was still in AF after PVI, direct current cardioversion was conducted to resume sinus rhythm.

Patients without complications were discharged from the hospital within 1-2 days of the procedure. Oral anticoagulation was continued for at least three months.

Follow-up and endpoints

Antiarrhythmic drugs were maintained for at least three months and then discontinued at the physicians' discretion. The patients received direct current cardioversion if they suffered persistent AF during the first month after the procedure. All patients were followed up in an out-patient clinic with a 7-day ambulatory ECG at 3, 6 and 12 months after ablation. Post-procedural cardiac computed tomography was performed between 3 and 6 months. The primary endpoint was defined as any documented atrial tachyarrhythmia, including atrial fibrillation, atrial flutter, and atrial tachycardia, lasting longer than 30 s in duration after a 3-month blanking period. Secondary endpoints were defined as procedure and ablation duration, fluoroscopy time, and procedure-related complications, including bleeding/haematoma, phrenic nerve palsy, stroke, pericardial effusion or tamponade, PV stenosis, coronary artery stenosis/occlusion, and atrioesophageal fistula.

Statistical analysis

The sample size was calculated based on previously published data covering a range of ablation modalities and methodologies. We estimated that the success rate in patients with persistent AF was around 40% for RFA and 65% for CBA. In order to statistically assess the difference in success rate between these two techniques, at least 94 patients needed to be randomized in the two groups (1:1) for 80% power at a 5% of two-sided significance level. Assuming a dropout rate of 5%, we needed 50 patients in each group.

The Shapiro–Wilk test was used for testing normality. Continuous variables were presented as mean ± standard deviation if normally distributed, otherwise presented as median and interquartile ranges (IQR). To compare means of continuous data, a 2-sample *t*-test and Mann-Whitney U test were employed for normally and skewed distributed data, respectively. Categorical values were presented as percentages and analysed by χ^2 test or Fisher's exact test as appropriate. The Kaplan–Meier method was used to estimate the survival curves for the time to first primary endpoint and was analysed by log-rank test. Logistic regression analysis was

performed to evaluate predictors for the recurrence of AT. Variables with a P-value over 0.1 in the univariate analysis were removed from the model for subsequent multivariate analysis. A P-value of <0.05 was considered statistically significant.

Assessment of the primary endpoint was conducted by both intention-to-treat (ITT) and per-protocol analysis.

Results

Population characteristics

A total of 101 patients (79.2% men; mean age 63.2±8.6 years) were randomly enrolled in the study: 52 patients were assigned to the CBA group and 49 to the RFA group (ITT). The patient flow diagram is shown in Figure 1. One patient in the CBA group did not receive the allocated treatment because of a technical problem and underwent RFA treatment instead (crossover). Thus, 51 patients underwent CBA and 50 patients received RFA treatment (per-protocol). One patient in the RFA group suffered cardiac tamponade during the transseptal puncture, after which the procedure was interrupted without ablation. This patient received a new RFA procedure 3 months later and was followed up for 12 months after the second procedure. The median duration of persistent AF before the procedure was 8.0 (0.3, 12.0) months, and long-standing persistent AF presented in 24 patients (14 in CBA and 10 in RFA). Seven patients had a history of earlier cavotricuspid isthmus ablation for typical atrial flutter (AFL). No significant differences in clinical characteristics were found between the two groups (Table 1).

Clinical results

A total of 397 PVs were targeted. Left common PV was found in 7 patients (2 in CBA and 5 in RFA). Four PVs (2 left inferior and 2 right inferior) from 3 patients in the CBA group were not isolated by the cryoballoon so a cryo (Freezor™, Medtronic) or RFA catheter (TactiCath™ Quartz, Abbott Medical) had to be employed. All PVs were successfully isolated by the end of

the procedure. After PVI, AF was converted to sinus rhythm in 3 patients (2 in RFA, 1 in CBA). In two patients in the RFA group, AF changed to typical AFL and was terminated after cavotricuspid isthmus block. One patient in the CBA group was converted to AFL which was not further treated during the index procedure. Fluoroscopy times were similar between the CBA and RFA groups, while shorter procedure and ablation times were found in the CBA group ($P<0.001$) (Table 2).

Primary endpoint during follow-up

Nine patients experienced AF recurrence before discharge and underwent direct current cardioversion. Thirty-four patients reported AF recurrence in the first three months. One hundred patients completed 12-month follow-up. One patient in RFA group died 11 months after the procedure because of a serious surgical disease unrelated to the procedure. He had not experienced any ATs. One patient underwent atrioventricular junction ablation 4 months after CBA due to intolerable fast AF and heart failure associated with AF recurrence. After the 3-month blanking period, 36 patients in the CBA group and 30 patients in the RFA group maintained sinus rhythm without any episode of AT over 30 s at 12-month follow-up. No difference in AT-freedom was found between the groups (69.2% in CBA vs. 61.2% in RFA, $P=0.398$) after ITT analysis. AT-free survival curves are shown in Figure 2. Ten patients (5 in CBA and 5 in RFA) who were free from ATs continued with antiarrhythmic drugs. In a per-protocol analysis, 36 patients in the CBA group and 30 patients in the RFA group were free from ATs (70.6% vs. 60.0%, $P=0.264$). No difference of AF recurrence was found between the two groups (27.5% in CBA vs. 38.0% in RFA, $P=0.258$). Less AFL recurrence was documented in the CBA group compared with RFA (3.9% in RFA vs. 18.0% in CBA, $P=0.020$). Among those patients with recurrence, 17 patients suffered paroxysmal AF and/or AFL, and 18 were still in persistent AF. The proportion of persistent AF was significantly higher in the CBA group compared to RFA (11/15, 73.3% vs. 7/20, 35.0%, $P=0.023$).

Risk factors were analysed and compared between the AT-free and recurrence groups (Table 3). Multivariable analysis showed that AT recurrence was related to longer duration of persistent AF before the procedure (OR 1.08, 95% CI 1.02-1.15, P=0.008), long-standing persistent AF (OR 3.24, 95% CI 1.11-9.47, P=0.032), and early recurrence of AF in the blanking period (OR 6.43, 95% CI 2.35-17.59, P=0.000). Among 34 patients who experienced early AF recurrence in the blanking period, ATs were recorded in 22 patients (64.7%) during long-term follow-up, and no difference was observed between the two groups (64.7% in each group).

Procedure-related complications

Five major complications were observed in 4 patients (4%) and no difference was found between the two groups (P=0.353). One patient in the CBA group suffered phrenic palsy (2%) and recovered after 6 months. Complications presented in the RFA group included bleeding with femoral hematoma in one patient, and chest pain in another with no abnormal finding during coronary angiography. Additionally, one patient suffered a tamponade during the procedure and a mild PV stenosis during the follow-up. No further intervention was needed.

Discussion

This trial was a randomized evaluation of PVI achieved by RFA or CBA in patients with persistent/long-standing persistent AF in Norwegian centres. We investigated the efficacy, safety, and procedural profiles of the two most-used ablation techniques. The clinical features of the patients were comparable to those in other trials[1, 11]. We found the efficacy of CBA to be similar to that of RFA with regard to the primary endpoint. Moreover, a similar procedure-related complication rate, less AFL recurrence, and shorter procedure and ablation times were observed in the CBA group.

RFA has emerged as an important, effective treatment for AF in the past 20 years[14, 15]. For paroxysmal AF, noninferiority of clinical outcomes of CBA has been verified by the FIRE AND

ICE study[5] and the CIRCA-DOSE study[6], while the similar durability of PVI has been confirmed by the RAZE-AF study[7]. The success rate of CBA for persistent AF ranged from 60 to 70% at one-year follow-up[8, 9]. Recently, Chun et al. reported a similar outcome of 78% recurrence freedom[16]. In a meta-analysis[10] which included 917 patients who underwent CBA for persistent AF from 11 studies, after a mean follow-up of 16.7±3.0 months 68.9% were free from recurrences (95% CI 63.4-74.7%). According to the results from the multicentre STOP Persistent AF trial, freedom of ATs at 12 months after PVI achieved by CBA was 54.8% (95% CI 46.7–62.1%)[11]. The results of CBA from the present study were in line with that of other investigations. However, the success rate of RFA in this trial was 61.2%, which seemed higher than that from earlier studies[1, 17]. The freedom rate of documented ATs after PVI without antiarrhythmic drugs was only 41% in the STAR AF II study[1]. This difference was probably due to the employment of a contact-force-sensing RFA catheter in our study, which may significantly improve ablation effect. This conjecture was supported by the recently published EARNEST-PVI trial, which showed a success rate of RFA using a contact-force-sensing catheter in patients with persistent AF of 71.7% at 12 months. In addition, similar atrial arrhythmia recurrence rates between RFA and CBA, with a trend favouring CBA in persistent AF, was reported in a prospective multicentre and multinational observational cluster cohort study based on the FREEZE cohort[13]. Our study further strengthens these results, but with a randomized design, by demonstrating a comparable efficacy of CBA to RFA in terms of freedom from ATs. Another factor which may have contributed to the higher success rate observed in this study was the lower proportion of long-standing persistent AF compared to earlier investigations[2, 3, 12]. Even so, still over half of patients had persistent AF lasting > 6 months before the procedure.

Although no difference in AF recurrence was observed, less AFL was recorded in the CBA group during follow-up. This was also in line with previous reports[18]. These observations may

be explained in part by the difficulty of creating continuous circumferential lesion lines when using point to point RFA, and in part by increased catheter stability due to freeze-mediated adhesion of the cryoballoon in CBA, resulting in creation of more homogeneous lesions with potentially less proarrhythmic effect.[19] Remarkably, the proportion of AF recurrence in persistent form was significantly higher in the CBA group. The lesion size, depth, durability, and even lesions covering the posterior wall of the LA created by CBA may differ from RFA and lead to different presenting of AF. These issues demand further investigation.

The procedure and ablation times in this study were significantly shorter in the CBA group. This finding was in line with other published data. Hoffmann et al. reported a shorter procedure time and higher radiation exposure in the CBA group[13]. Several features of our study design should be taken into account. First, we performed 3-dimensional mapping both before and after PVI according to the study protocol, which is seldom performed routinely in clinical practice with CBA. Second, we did not perform a computed tomography scan before procedures to avoid patient selection based on the anatomy. These features could lead to longer procedure and ablation times for CBA. Finally, we used a fixed freezing regimen of two applications of at least 240 s each time in each PV. This strategy has been challenged in later years with reduced application numbers and durations. Therefore, the procedure duration and ablation time of CBA can be even shorter.

Phrenic nerve palsy was observed in one patient (2%) in the CBA group, while PV stenosis was observed in one patient (2%) in the RFA group. This finding of complication is consistent with previous reports[20]. Notably, we found that both the duration of persistent AF before the ablation procedure and early AF recurrence during the blanking period were related to AT recurrence during follow-up. This is in line with the findings of other studies and suggests that these risk factors could serve as predictors for AF recurrence after ablation. In particular, unlike

paroxysmal AF, early AF episodes during the blanking period are highly associated with recurrence during long-term follow-up and should be managed without delay.

Limitations

This study was a national study in Norway with a limited sample size, which was calculated based on the available outcomes of earlier investigations when the study was designed. The success rate of RFA has increased while the catheters and techniques have been improved. Due to the difficulty of anticipating clinical incidence precisely, similar sample sizes have been applied to several clinical trials[21, 22]. Although the interpretation of the data is limited, these findings still show the real outcomes of daily ablation practice and confirm the results of previous trials. Large-scale randomized clinical trials are demanded to further confirm the conclusions of this study. A measure of combined ablation power, time and contact force, such as lesion size index, was not available when this study started. We employed force-time-integral over 400 g·s as the target for each application. This may have an impact on procedural data, but probably not much on clinical results since this criterion had been applied in practice for years. We did not compare the radiation exposure because we had observed a large variation of radiation dosage from one lab to another due to different devices and systems. Since the fluoroscopy time was similar between the two groups, the radiation exposure might be higher in the CBA group given that cine angiography of the PVs was applied before every cryoablation, which was not necessary for the RFA group.

Conclusions

PVI achieved by CBA was as effective as RFA for treatment of persistent or long-standing persistent AF in terms of AT-freedom at 12-month follow-up, with less AFL recurrence and shorter procedure and ablation times.

Funding: This study was partly supported by Helse Vest, Norway (LBS).

Conflict of interest: Dr. Jian Chen serves as a consultant for Biosense Webster, Johnson & Johnson, and has received research grant from Medtronic and Abbott Medical. Otherwise, there are no conflicts of interest to be disclosed for other co-authors.

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Table 1 Patient characteristics based on intention-to-treat groups

	CBA group (n=52)	RFA group (n=49)	P value
Age (years)	62.4±8.4	64.0±8.7	0.363
Male, n (%)	45 (86.5%)	35 (71.4%)	0.061
Body mass index, kg/m^2	29.6±4.7	28.8±4.5	0.368
Hypertension, n (%)	29 (55.8%)	28 (58.0%)	0.889
Diabetes mellitus, n (%)	1 (1.9%)	4 (8.2%)	0.148
Coronary heart disease, n (%)	4 (7.7%)	6 (12.2%)	0.444
Obstructive sleep apnoea, n (%)	5 (9.6%)	3 (6.1%)	0.516
$CHADS_2VASC_2$ Score			0.294
0	14 (26.9%)	7 (14.3%)	
1	11 (21.2%)	12 (24.5%)	
≥2	27 (51.9%)	30 (61.2%)	
Serum creatinine (umol/L)	89.2±15.8	87.0±16.3	0.478
History of AF, n (%)			0.518
< 1 year	6 (11.5%)	10 (20.4%)	
1 - 2 years	20 (38.5%)	17 (34.7%)	
> 2 years	26 (50.0%)	24 (44.9%)	
Duration of persistent AF before procedure (months)	8 (1, 14)	8 (0, 12)	0.689
Sinus rhythm before procedure, n (%)	7 (13.5%)	10 (20.4%)	0.351
< 6 months, n (%)	15 (28.8%)	13 (26.5%)	0.795
6-12 months, n (%)	16 (30.8%)	16 (32.7%)	0.839
> 12 months, n (%)	14 (26.9%)	10 (20.4%)	0.490
History of previous cavotricuspid ablation, n (%)	3 (5.8%)	4 (8.2%)	0.710
Left atrial diameter (cm)	4.6±0.6	4.4±0.7	0.110
Left ventricular ejection fraction (%)	56.0±7.2	56.8±8.1	0.679
Basal medication			
Beta-blocker	36 (69.2%)	30 (61.2%)	0.398
Amiodarone	14 (26.9%)	13 (26.5%)	0.617
Dronedarone	28 (53.8%)	17 (34.7%)	0.053
Flecainide	3 (5.8%)	3 (6.1%)	1.000

AF, atrial fibrillation; CBA, cryoballoon ablation; RFA, radiofrequency ablation.

Table 2 Procedural information and outcomes of recurrence during follow-up

	Total (n=101)	Intention-to-treat analysis			Per-protocol analysis		
		CBA group (n=52)	RFA group (n=49)	P value	CBA group (n=51)	RFA group (n=50)	P value
Procedure started in sinus rhythm	17(16.8%)	7(13.5%)	10(20.4%)	0.351	7(13.7%)	10(20.0%)	0.399
AF terminated during ablation	5(5.0%)	1(1.9%)	4(8.0%)	0.205	1(2.0%)	4(8.0%)	0.162
Ablation time (minutes)	45.6±16.3	36.7±9.5	55.3±16.7	0.000	35.8±6.5	55.9±16.7	0.000
Fluoroscopy time (minutes)	22.4±9.6	21.5±7.8	23.4±11.2	0.317	21.2±7.6	23.6±11.2	0.208
Procedure time (minutes)	178.2±39.1	160.4±30.6	197.2±38.4	0.000	158.9±28.9	197.9±38.4	0.000
Recurrence before discharge	9(8.9%)	5 (9.6%)	4(8.2%)	0.704	4(7.8%)	5(10.0%)	0.704
Recurrence in the blanking period	34(33.7%)	18(34.6%)	16(32.7%)	0.835	17(33.3%)	17(34.0%)	0.943
Recurrence during follow-up	35(34.7%)	16(30.8%)	19(38.8%)	0.398	15(29.4%)	20(40.0%)	0.264
Persistent AF	18	11	7	0.049	11	7	0.023
Paroxysmal AF alone	6	2	4		2	4	
Paroxysmal AF with AFL	9	2	7		1	8	
AFL alone	2	1	1		1	1	

Presented as mean±SD, or n (%). AF, atrial fibrillation; AFL, atrial flutter; CBA, cryoballoon ablation; RFA, radiofrequency ablation.

Table 3. Predictors for recurrence of atrial arrhythmias

	Recurrence (n=35)	Atrial arrhythmia free (n=66)	P value
Age (years)	63.7±8.4	63.0±8.7	0.704
Male, n (%)	28 (80.0%)	52 (78.8%)	0.886
Body mass index, kg/m^2	29.1±4.8	29.5±4.3	0.699
Hypertension, n (%)	22 (62.9%)	35 (53.0%)	0.343
Diabetes mellitus, n (%)	2 (5.7%)	3 (4.5%)	0.797
Coronary heart disease, n (%)	6 (17.1%)	4 (6.1%)	0.076
Obstructive sleep apnoea, n (%)	2 (5.7%)	6 (9.1%)	0.550
CHA_2DS_2VASC score			0.139
0	8 (22.9%)	13 (19.7%)	
1	4 (11.4%)	19 (28.8%)	
≥2	23 (65.7%)	34 (51.5%)	
Serum creatinine	88.2±16.6	88.1±15.8	0.974
History of AF			0.105
< 1 year	2 (5.7%)	14 (21.2%)	
1 - 2 years	13 (37.1%)	24 (36.4%)	
> 2 years	20 (57.1%)	28 (42.4%)	
Duration of persistent AF before procedure (months)	12 (5, 24)	6 (0, 12)	0.004
Long-standing persistent AF, n (%)	13 (37.1%)	11 (16.7%)	0.021
History of previous cavotricuspid isthmus block, n (%)	1 (2.9%)	6 (9.1%)	0.240
Left atrial diameter (cm)	4.7±0.6	4.5±0.6	0.175
Left ventricular ejection fraction (%)	54.8±7.4	57.1±7.6	0.236
Basal medication, n (%)			
Beta-blocker	25 (71.4%)	41 (62.1%)	0.350
Amiodarone	8 (22.9%)	19 (28.8%)	0.666
Dronedarone	14 (40.0%)	31 (47.0%)	0.502
Flecainide	2 (3.0%)	4 (11.4%)	0.089
Procedure started in sinus rhythm, n (%)	3 (8.6%)	14 (21.2%)	0.106
AF terminated during procedure, n (%)	2 (5.7%)	3 (4.5%)	0.797
AF recurrence in the blanking period, n (%)	22 (62.9%)	12 (18.2%)	0.000

AF, atrial fibrillation.

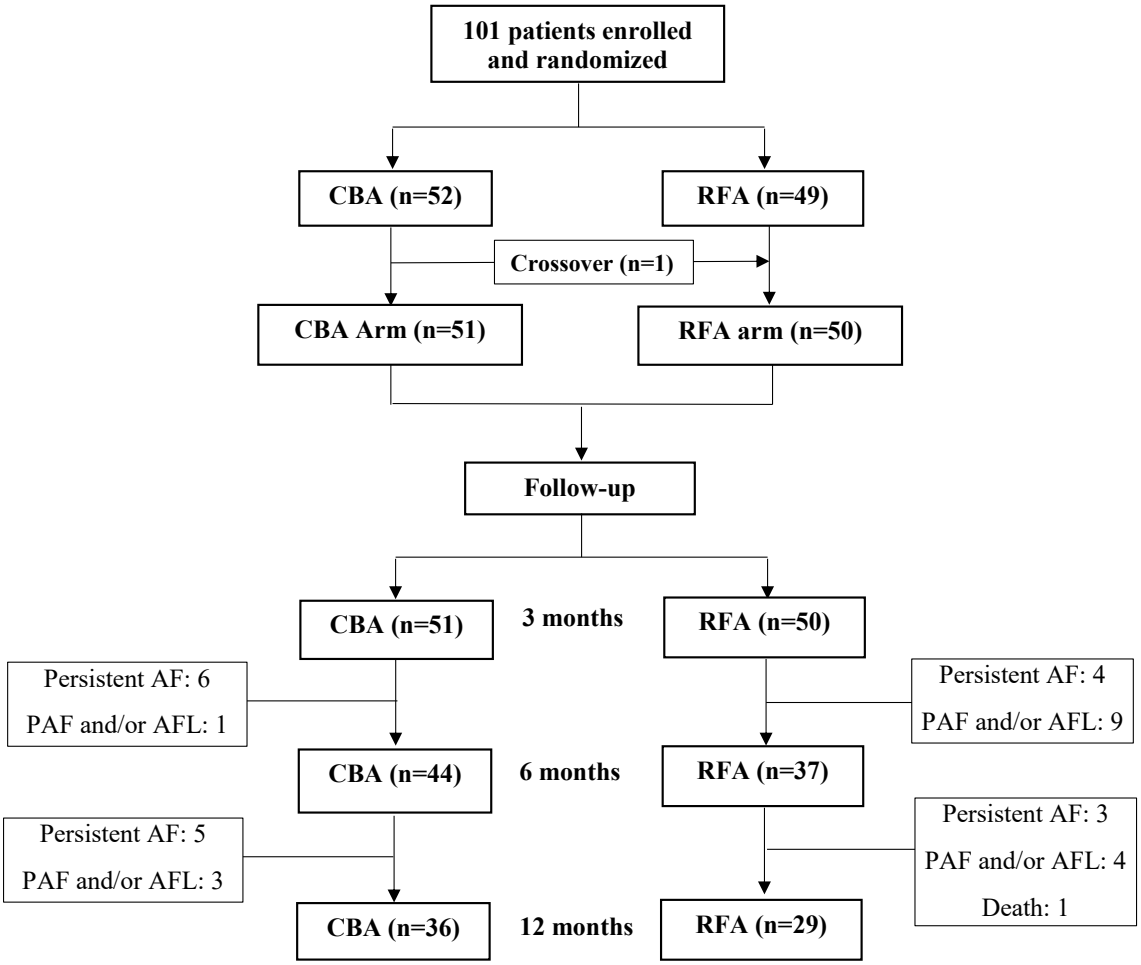
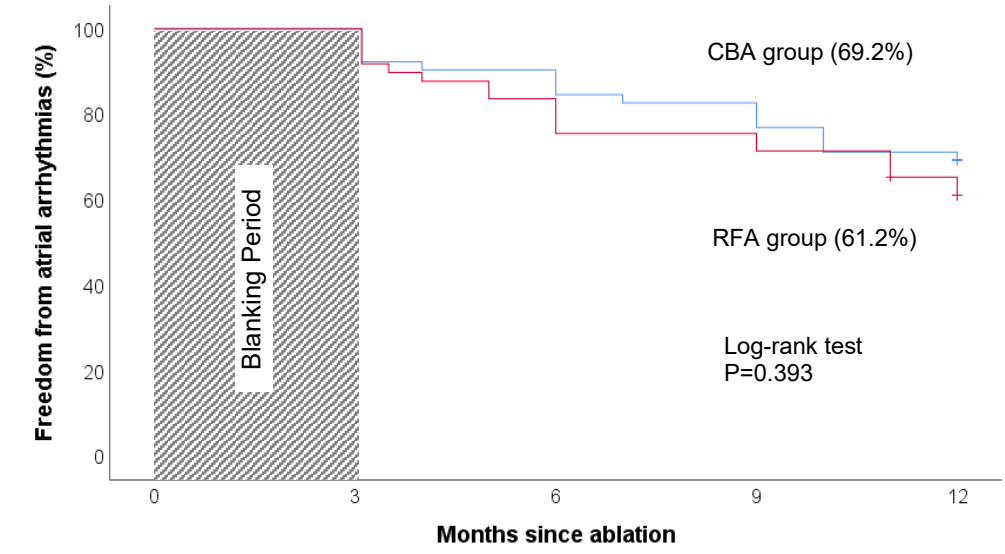


Figure 1. Randomization and patient flow for NO-PERSAF study. The number of patients with AF recurrence and recurrence-free during follow-up was based on per-protocol analysis. The crossover patient suffered AF recurrence. AF, Atrial fibrillation; AFL, atrial flutter; CBA, cryoballoon ablation; PAF, paroxysmal atrial fibrillation; RFA, radiofrequency ablation.



No. at risk					
CBA group	52	52	44	40	36
RFA group	49	49	37	35	29

Figure 2. Kaplan-Meier survival curve of freedom from atrial arrhythmias. There is no difference of freedom from atrial tachyarrhythmias between CBA (blue) and RFA (red) groups during a 12-month follow-up. CBA, cryoballoon ablation; RFA, radiofrequency ablation.

II

Journal of Interventional Cardiac Electrophysiology
https://doi.org/10.1007/s10840-021-00990-4

The impacts of contact force, power and application time on ablation effect indicated by serial measurements of impedance drop in both conventional and high-power short-duration ablation settings of atrial fibrillation

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Received: 31 January 2021 / Accepted: 5 April 2021

Abstracts

Background This study aimed to clarify the interrelationship and additive effects of contact force (CF), power and application time in both conventional and high-power short-duration (HPSD) settings.

Methods Among 38 patients with paroxysmal atrial fibrillation who underwent first-time pulmonary vein isolation, 787 ablation points were collected at the beginning of the procedure at separate sites. Energy was applied for 60 s under power outputs of 25, 30 or 35 W (conventional group), or 10 s when using 50 W (HPSD group). An impedance drop (ID) of 10 Ω was regarded as a marker of adequate lesion formation.

Results ID ≥ 10 Ω could not be achieved with CF < 5 g under any power setting. With CF ≥ 5 g, ID could be enhanced by increasing power output or prolonging ablation time. ID for 30 and 35 W was greater than for 25 W ($p < 0.05$). Ablation with 35 W resulted in greater ID than with 30 W only when CF of 10–20 g was applied for 20–40 s ($p < 0.05$). Under the same power output, ID increased with CF level at different time points. The higher the CF, the shorter the time needed to reach ID of 10 Ω and maximal ID. ID correlated well with ablation index under each power, except for lower ID values at 25 W. ID with 50 W for 10 s was equivalent to that with 25 W for 40 s, but lower than that with 30 W for 40 s or 35 W for 30 s.

Conclusions CF of at least 5 g is required for adequate ablation effect. With CF ≥ 5g, CF, power output, and ablation time can compensate for each other. Time to reach maximal ablation effect can be shortened by increasing CF or power. The effect of HPSD ablation with 50 W for 10 s is equivalent to conventional ablation with 25 W for 40 s and 30–35 W for 20–30 s in terms of ID.

Keywords Pulmonary vein isolation · Contact force · Power · Ablation index · High-power short-duration

1 Introduction

Radiofrequency (RF) ablation targeting ectopic atrial activities originating from the pulmonary veins (PV) has emerged as a standard approach for treating atrial fibrillation (AF) [1]. Electrical PV isolation is unanimously regarded as a cornerstone for both paroxysmal and persistent AF ablation [2, 3]. However, achieving durable PV isolation remains challenging during AF ablation, and PV electrical reconnection is frequently observed after AF recurrence, even after employing a contact-force sensing catheter [4–6].

Animal studies using both irrigated and non-irrigated ablation catheters [7–10] have shown a positive correlation between catheter-tip-tissue contact force (CF) and lesion dimensions. Although several observational studies found improvement of clinical outcomes using CF-sensing catheters, further randomized controlled studies did not confirm these initial findings [11]. Other controllable parameters, such as power and application time, also have a critical impact on ablation effectiveness. During low or standard power and long duration ablation, the power is conventionally set at 25–40 W for a

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Published online: 23 April 2021

duration of 20–60 s. Ablation index (AI), which integrates CF, ablation time, and power in a weighted formula, has been employed as a lesion-related indicator for guiding the ablation procedure. However, the interaction of the controllable parameters and the contribution of each to ablation efficacy have not been clearly elucidated. Recently, a new ablation strategy using high-power and short-duration (HPSD) has emerged as an option for PV isolation. The differences of efficacy between HPSD and conventional ablation settings in clinical practice though have not been demonstrated.

This study aimed to clarify the contribution of CF, power, and application duration and their interrelationship for making an adequate lesion based upon impedance drop as a surrogate for lesion formation and to compare various settings of power, contact force, and ablation duration with regard to ablation effect.

2 Methods

We enrolled in this study 38 patients (24 men, mean age 65.4 ± 8.9 years) who underwent their first RF ablation procedure (PV isolation) for symptomatic paroxysmal AF. This study was approved by the Ethics Committee of Western Norway. All patients provided informed consent.

The ablation procedure performed at our institution has been previously described [12, 13]. Particular to this study, we performed a single transseptal puncture through which both ablation and circular mapping catheters were advanced into the left atrium. We carried out the procedure without the assistance of a dedicated long sheath for the ablation catheter. PV isolation was performed in all patients by ablating circumferentially at the PV antrum. To avoid mutual effects of two RF applications and the impact of the pre-existing scar issues, we identified and enrolled the ablation points in sinus rhythm at separate sites of the PVs (distance > 1 cm, local electrogram amplitude ≥ 2 mV) before circumferential ablation was performed. Ablations with visually evident displacement of the ablation catheter, stream popping, or overheating with a sudden significant impedance increase were excluded from the analysis. A 3.5-mm-tip CF-sensing irrigated ablation catheter (Navistar ThermoCool SmartTouch™, Biosense Webster, Diamond Bar, CA, USA) was employed in all the procedures. In the conventional group, RF energy was delivered in a temperature-controlled mode with a cut-off of 50 °C at a cooling rate of 2–20 mL/min. An application time of 60 s with power of 25, 30 or 35 W was used, respectively. In the HPSD group, energy was delivered in a power-controlled mode with a cooling rate of 2–30 mL/min and power of 50 W applied for 10 s.

An electroanatomic mapping system (Carto 3, Biosense Webster, Diamond Bar, CA, USA) was used and the Visitag module was activated during the procedure. Real-time CF, impedance, temperature and energy delivered were automatically updated and recorded every 20 ms and analyzed off-line. AI was calculated with a customized formula of $AI = \left(k \times \int_0^T CF^a(t)P^b(t)dt\right)^c$ by the system [14]. Impedance drop (ID) was used as the surrogate for assessment of ablation efficacy as correlation between IDs and lesion dimensions has been shown in previous studies [7, 9, 13, 15]. ID was defined as the difference between the impedance at a certain time and the baseline value. The maximum ID (MaxID) for each point represented the difference between the minimum impedance value and the impedance at baseline. Considering the variability in impedance between patients, we also calculated the maximum ID percentage (MaxID%), which was expressed by MaxID/impedance at baseline. During an application, ID ≥ 10 Ω was regarded as an adequate lesion formation [13, 16, 17].

2.1 Statistical analysis

Continuous variables were presented as mean ± standard deviation if normally distributed; median and interquartile ranges (IQR) were used if the data were skewed according to the Shapiro–Wilk test. For comparison between groups, the analysis of variance (ANOVA) and post hoc test according to the method of Tukey's honestly significant differences were performed. Categorical values were presented as percentages and analysed by using chi-square test or Fischer's exact test as appropriate. The correlation among continuous variables was tested using Spearman's rho coefficient. Statistical analysis was performed with SPSS version 24 (IBM, USA). A p value of < 0.05 was considered statistically significant.

3 Results

A total of 787 qualified points from 38 patients (median 20 [IQR 17–22] per patient) were included in the analysis. No major complications were observed during and after the procedures. Using temperature-control mode, target power was reached after 4 s, while it took only 1 s for HPSD ablation with power-control mode. The mean CF ranged from 1.8 to 38.0 g among all applications. Four sub-groups according to mean CF value under each power setting (25, 30, 35 and 50 W) were stratified for analysis. The distribution of application points grouped for different CF level and power setting is presented in Table 1. The mean CF was 3.8 ± 0.8 vs. 3.8 ± 0.5 g in group CF < 5 g, 7.6 ± 1.4 vs. 7.0 ± 1.4 g in group CF 5–10 g, 14.2 ± 2.8 vs. 13.5 ± 2.7 g in group CF 10–20 g and 25.5 ± 4.5 vs. 25.9 ± 4.7 g in group CF ≥ 20 g (conventional vs. HPSD, $p > 0.05$). There was no difference regarding mean CF among different conventional power settings within the same CF level ($p > 0.05$).

The IDs recorded every 10 s under different power settings at different CF levels are shown in Fig. 1. We found a strong

Table 1 Number of applications at different levels of power and contact force and distribution of points reaching an impedance drop of 10 Ω (number and percentage in parenthesis)

		Mean contact force				
		CF < 5 g	CF 5–10 g	CF 10–20 g	CF ≥ 20 g	Total
Power	25 W	31 (7, 22.6%)	53 (25, 47.2%)	44 (35, 79.5%)	13 (13, 100%)	141 (80, 56.7%)
	30 W	16 (5, 31.3%)	55 (42, 76.4%)	55 (49, 89.1%)	14 (14, 100%)	140 (110, 78.6%)
	35 W	22 (10, 45.5%)	60 (45, 75.0%)	44 (44, 100%)	12 (12, 100%)	138 (111, 80.4%)
	50 W	16 (2, 12.5%)	157 (78, 49.7%)	157 (114, 72.6%)	38 (32, 84.2%)	368 (226, 61.4%)
Total		85 (24, 28.2%)	325 (190, 58.5%)	300 (242, 80.7%)	77 (71, 92.2%)	787 (527, 67.0%)

CF contact force

linear correlation ($\rho = 0.978$, $P < 0.0001$) between MaxID and MaxID%, which suggested that individual variability in impedance had little effect on the interpretation of our results. MaxID over 10 Ω was reached in 301 out of 419 (71.8%) ablation points in the conventional group and 226 out of 368 (61.4%) points in the HPSD group ($p < 0.01$). The proportion of ablation points in which ID reached 10 Ω is presented in Table 1. Among the conventional subgroups, a higher power and CF was observed in the points with MaxID ≥ 10 Ω compared with those < 10 Ω.

Changes of CF, power and application time individually affected ID and compensated for each other in certain circumstances.

(1) Effect of prolonging application time: The effect of prolonging application time was dependent on the underlying CF and power level. With CF < 5 g, ID seldom reached 10 Ω within 60 s regardless of the power output. This was also the case for CF 5–10 g and 25 W. For CF levels beyond 5–10 g, ID increased with prolonged application under all power settings (Fig. 1). However, ablation efficacy extended marginally after 20–30 s ($p > 0.05$, compared to later time points, Fig. 1, Table 2).
(2) Effect of increasing CF: It was observed for a given application time and power level (25, 30 and 35 W) that ID increased with higher CF (Fig. 1). As shown in Table 2, the time to reach ID ≥ 10 Ω and maxID tended to be shorter with increasing CF levels. A CF ≥ 20 g led to an ID ≥ 10Ω within 10 s in all power settings (Fig. 1).
(3) Effect of increasing power (Fig. 1): As abovementioned, increasing power did not enlarge ID when CF < 5 g. With CF ≥ 5 g, ID under the power of 30 and 35 W were significantly higher than under 25 W ($P < 0.01$). ID under 30 and 35 W were similar ($P > 0.05$), except for CF 10–20 g for 20 to 40 s, where power of 35 W provided significantly higher ID than 30 W ($P < 0.05$).

The efficacy of HPSD ablation at 10 s was compared with the conventional sub-groups at different time points. ID ≥ 10 Ω was achieved at 10 s in all cases with CF ≥ 5 g in the HDSP group, but not < 5 g. With CF 5–10 g, ID in the HDSP group was higher than that under the setting of 25 W for 40 s, and lower than under 30 W for 40 s and 35 W for 30 s, respectively. With CF 10–-20 g, ID in HDSP group was higher than that under 25 W for 30 s and lower than under 30 W for 40 s and 35 W for 30 s, respectively. With CF ≥ 20 g, ID in the HDSP group was higher than that under 25 W for 10 s, and lower than under both 30 and 35 W for 20 s. Notably, differences of ID values at 10 s under powers of 30, 35 and 50 W were not statistically significant.

The average of AI in the conventional group was higher than that in the HPSD group (531.7 ± 89.8 vs. 395.8 ± 43.1, $P < 0.01$). Higher AI was found in ablation applications with ID ≥ 10 Ω than those with ID < 10 Ω in both conventional (558.7 ± 85.3 vs. 462.7 ± 58.9, $P < 0.01$) and HPSD groups (405.7 ± 43.3 vs. 380.1 ± 37.9, $P < 0.01$), respectively.

The relationship between AI and ID under different power setting is presented in Fig. 2. The values of ID under various AI levels for powers of 30, 35 and 50 W were similar and the corresponding curves of ID were uniformly superimposed, whereas 25 W resulted in significantly lower ID at all AI levels (for AI 350–500 W/g/s, $P < 0.01$). Notably, a minimum of 450 W/g/s of AI was required to achieve ID of 10 Ω under the power of 25 W, while less than 350 W/g/s was sufficient to reach the same ID level under powers of 30–50 W.

4 Discussion

In this observational study, we evaluated the additive impacts of CF, power and application time on the ablation efficacy based on ID level in patients undergoing AF ablation procedures in both conventional and HPSD settings. These three parameters compensated for each other in a CF ranging from 5 to 20 g. However, with low CF (< 5 g), ID seldom reached the threshold of 10 Ω even when power or application time was increased. The effect of HPSD ablation indicated by ID was equivalent to that of applying of 25 W for 40 s, 30 W for 30 s or 35 W for 20 s.

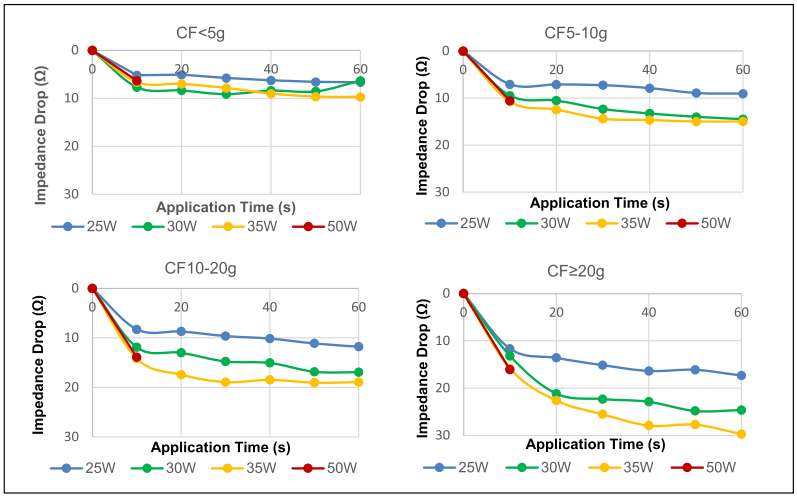

Fig. 1 Additive impacts of contact force, power and application time on impedance drop. With CF < 5 g, ID does not reach the threshold of 10 Ω within 60 s at any power setting. When CF ≥ 5 g, power and application time compensate for each other within restricted ranges. Compared with the conventional sub-groups at different time points, ID levels at 10 s of HPSD ablation lie between those of the 25 and 30W sub-groups under the same CF level. ID, impedance drop; CF, contact force; HPSD, high power short duration; †P < 0.05 compared to 25 W, ‡P < 0.01 compared to 25 W, *P < 0.01 compared to 50W

Level	Power (W)	Impedance drop (Ω) measured at ablation time of every 10 seconds					
		10 s	20 s	30 s	40 s	50 s	60 s
CF(<5g)	25	5.2±2.7	5.1±2.3	5.8±2.8	6.3±3.2	6.6±3.8	6.7±4.1
	30	7.7±5.2	8.4±6.0	9.1±6.3	8.4±6.4	8.6±6.1	6.6±3.9
	35	6.6±5.6	7.0±5.8	7.8±6.9	9.0±7.2	9.6±7.5	9.7±7.9
	50	6.4±4.1					
CF(5-10g)	25	7.1±2.2*	7.1±2.7*	7.3±3.1*	7.9±3.4*	8.9±3.6	9.0±3.8
	30	9.5±5.3†	10.5±5.8‡	12.3±6.8‡	13.3±6.7‡*	14.0±6.9‡*	14.5±7.9‡*
	35	10.7±6.3‡	12.5±8.4‡	14.4±9.4‡*	14.7±9.4‡*	15.0±9.2‡*	15.0±8.8‡*
	50	10.6±6.6					
CF(10-20g)	25	8.3±3.0*	8.7±3.7*	9.6±3.3*	10.1±4.3	11.1±4.7	11.8±5.2
	30	11.9±6.2‡	13.0±7.4‡	14.7±8.8‡	15.0±8.1‡*	16.8±9.3‡*	16.9±8.8‡*
	35	14.2±7.7‡	17.4±8.4‡	18.9±9.8‡*	18.5±9.8‡*	19.0±9.0‡*	18.9±8.9‡*
	50	13.9±6.1					
CF(≥20g)	25	11.7±2.6*	13.6±3.6	15.1±4.4	16.4±4.2	16.1±5.8	17.3±6.2
	30	13.2±4.0	21.1±6.9‡*	22.3±8.6†*	22.9±12.8†*	24.8±10.4†*	24.6±12.0*
	35	15.8±7.5	22.6±9.0‡*	25.5±11.5†*	27.9±12.0†*	27.7±9.7‡*	29.7±11.5‡*
	50	16.1±5.0					

The essential role of CF in AF ablation has been demonstrated in a series of observational studies from basic to clinical level. However, no improvement of clinical outcomes with CF-sensing catheter was demonstrated in randomized-controlled trials [4, 18]. Experimental models have shown how ablation efficacy is dependent on several parameters [9]. During RF ablation, the surface of tissue in contact with the ablation electrode is warmed immediately by the resistant heating, while the deeper tissue layer is warmed by the conductive heating at a later stage. Passively conductive heating is time-dependent [19]. Increasing current intensity or power output at the electrode-tissue interface produces higher temperature gradients and thus greater lesion size and depth. Impedance drop is often used as a surrogate for evaluating effect of ablation as supported by earlier animal and clinical investigations [7, 9, 15, 20, 21], and previous studies have suggested an ID ≥ 10 Ω to be a reliable indicator for an adequate lesion formation [16, 17, 22]. Avitall et al. demonstrated clearly on a dog model that impedance could slightly decrease (0–10 Ω) during RF delivery even when catheter tip was 5 mm away from the tissue surface and no lesion was created. Furthermore, they found that better contact led to higher ID, and both temperature increase and ID correlated with lesion diameter and depth when ID > 10 Ω [15]. Ikeda et al. confirmed that the impedance drop during the RF application correlated well with lesion size [10]. Another clinical study conducted by Chinitz et al. showed that ID < 10 Ω accounted for 89% of sites with conduction recovery and regions with

Table 2 Time (in seconds) to reach impedance drop of 10 Ω and to the maximal impedance drop (in parentheses)

		Mean contact force			
		CF < 5 g	CF 5–10g	CF 10–20 g	CF ≥ 20 g
Power	25 W	—	—	40 (60)	10 (40)
	30 W	—	20 (50)	10 (50)	10 (20)
	35 W	—	10 (20)	10 (20)	10 (20)
	50 W	—	10[a]	10[a]	10[a]

CF contact force

[a] Total application time 10 s

adjacent ablation with ID < 10 Ω were associated with a higher rate of conduction recovery (37% versus 1.5%) [23].

Various studies reproducibly demonstrated that a maximum lesion volume is achieved after 30 to 40 s of energy delivery and the half-time of lesion growth is around 8 s [7, 24]. In this study, the initial rapid fall of impedance was within 10 s, and the time to reach the heating plateau was in line with earlier studies. Ablation settings with power of 25, 30 and 35 W for 20 to 60 s are widely used for AF ablation. In most cases with poor CF (< 5 g), neither increasing power output nor prolonging application time enhanced the ablation effect. This result is consistent with a previous study conducted in an ex vivo model [25]. However, the study conducted by Winkle et al. showed that 14.5% impedance drop was achieved by contact force < 5 g [26]. This observational difference might be explained by several reasons. Firstly, that study used the TactiCath™ open irrigated-tip CF sensing catheter with EnSite™ Velocity™ system (St. Jude Medical). The methods of CF and impedance measurement are different from those employed in our study and the values of ID cannot be compared directly between two distinct systems. Secondly, the average application duration in that study was 12.5 s, which was longer than ours. Our study showed that application time and power had an additional effect on ID as long as CF was at least 5 g. While increase in power output resulted in consistently higher ID, the effect of increasing ablation time was insignificant after 30–40 s. This finding supports the idea of delivering RF energy to a target magnitude of AI rather than for a fixed duration. Outside this time window, the additional effect of prolonging application time on ID is limited, and indeed might lead to collateral tissue damage, especially with higher CF and power level.

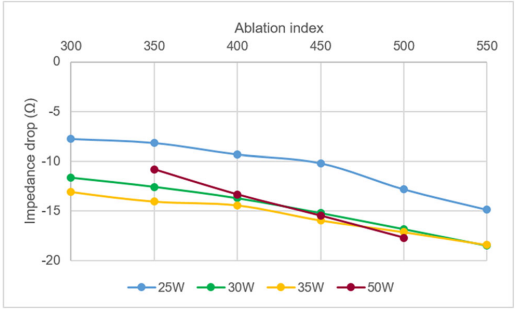

Fig. 2 Correlation between impedance drop and ablation index under different power settings. Changes of ID with increasing AI values are similar at settings of 30, 35 and 50 W. At 25 W, they show the same trend, but with lower ID at the same AI level ($P < 0.01$)

Recently, more attention has been paid to the HPSD ablation strategy. Animal studies have shown the efficacy and safety of this strategy with several combinations of power (50 to 90 W) and application time (4 to 8 s) [27, 28]. Similar AF-freedom and complication rates of AF ablation using HPSD protocol with 45–50 W for 5–15 s compared with conventional strategy have been demonstrated by clinical studies [29, 30]. Bourier et al. reported that HPSD ablation, compared with standard RF application, resulted in similar lesion volumes, but with a larger maximum diameter and a smaller lesion depth. The lesion volume made by ablation using 50 W for 13 s was equal to that using 30 W for 30 s [25]. These findings were confirmed by our data which showed that ablation with 50 W for 10 s resulted in similar ID to the conventional 30 W for 30 s. However, the ID was lower than that achieved using 30 W for 40 s. Additionally, we found that a lower proportion of ablations achieved ID ≥ 10 Ω in the HPSD than in the conventional group. This may be explained by a reduction of the conductive heating phase due to the shorter application duration in the HPSD ablation with power-controlled mode [27]. Thus, for the setting of 50 W and 10 s, there might be advantage in titrated prolongation of ablation and cautious increasing of power to ensure durable lesion formation. Recently published data have shown new information supporting this hypothesis [31].

AI is a parameter integrating CF, power and application time in a weighted formula. It has been reported that predicted lesion depth based on AI correlated well with actual lesion depth in the beating canine heart. It was noteworthy that the patterns of ID responding to AI were uniform under power outputs ranging from 30 to 50 W, but not under 25 W, a finding supported by results from a recent in vivo study. This observation could be explained by the fact that the customized formula for calculating AI was based on experiments that used power outputs of 30–50 W. The improvement of clinical outcomes and durability of AI-guided PV isolation has been reported in observational studies when target values of 550 W/g/s in the anterior and 400 W/g/s in the posterior left atrial regions were employed [32, 33]. Interestingly, our data showed that the AI of 350 W/g/s might be sufficient to reach the ID goal of 10 Ω under powers of 30–50 W.

Finally, CF, power and application time contribute individually to AI by different weight. According to our results, adequate CF is an essential prerequisite. Below the CF threshold of 5 g, no significant enhancement of ablation effect can be

made by increasing power or prolonging ablation time, even if total AI value has reached the recommended target value. On the other hand, with CF ≥ 5 g, the time to reach maximal ID can be reduced by increasing either CF or power. Our results showed that ablation effect could be simply enhanced about 33–88%, 49–100% and 125–227% by increasing application time from 10 to 60 s, or power from 25 to 35 W, or mean CF from 4.8 to 25.5 g, respectively (Fig. 1). Our results suggested that optimizing CF should be the first step to enhance ablation effect, and followed by adjusting power or application time, while also considering the limit of effectiveness of time (after maxID) and the restriction of power in the locations for high risk of complications (the posterior wall and thoracic veins).

4.1 Limitations

This investigation was a single-centre non-randomized study. It focused on the effect of each single RF application without a mutual effect. Inevitably, the results could not be simply generalized to clinical outcomes. Impedance drop is a widely used parameter to monitor ablation effect but as a surrogate is flawed by several limitations as discussed previously [34, 35]. Also, impedance is measured in clinical practice with different techniques. This may influence the interpretation of optimal ID for an adequate lesion. Few points with high CF were involved in this study as catheter stability was more challenging in such situations without the support of a steerable long sheath. The ablation effect with steerable sheath may need further investigations. Power settings were selected following clinical practice, and therefore, no further information on other power levels was available. No analyses of complications with increasing CF, power and application time were performed because of extremely low incidence under the current settings.

5 Conclusions

CF of at least 5 g is required for effective ablation. With CF ≥ 5 g, CF, power and application time can compensate for each other within restricted ranges. Time to reach maximal ablation effect can be shortened by increasing CF or power output. The effect of HPSD ablation with 50 W for 10 s is equivalent to conventional ablation with 25 W for 40 s and 30–35 W for 20–30 s in terms of ID. The ID versus AI increase matches well at power outputs between 30 and 50 W, but with lower ID values at 25 W.

Funding Open access funding provided by University of Bergen (incl Haukeland University Hospital). This study was partly supported by Helse Vest, Norway and the Research Council of Norway.

Declarations

Conflict of interest The authors declare no competing interests.

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Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230851777 (print)
9788230854464 (PDF)